835-P

Depression in Older Adults With Type 2 Diabetes Mellitus: Is there any Relationship With Glycemic Control, Gender and Habits?

EVA LOPEZ GONZALEZ, ALICIA B. GARCIA, ANGELA LUONGO, SILVANA MILRAD, MARIA L. RUIZ MOROSINI, MARIA C. VARELA, MARINA KHOURY, DECOYDI, *Buenos Aires, Argentina*

The prevalence of depression is higher in Diabetic patients; it is still controversial the association between depression and poor glycemic control. 17 centers Specialized in Diabetes in Argentina was assessed the frequency of depression in Type 2 Diabetic (DM2) patients older than 65 years and its relationship with glycemic control, gender, habits and DM2 complications. Depression was considered in those with prior diagnosis and Geriatric Depression Scale of Yesavage with a score >9 points. Physical activity >150 minutes/week. Included 427 DM2 patients, female 55.3%, age 71.8 ± 5.6 years, duration of diabetes 11.8 ± 9.2 years, glycemia 128 ± 42.2 mg/dl, A1c 7.15 ± 2.73 %, carotid disease 13.1%, nefropathy 15.2%. The frequency of Depression was 18.5%, 21,8% of them had family history of depression (FHD) (p<0.003).10.8% had previous diagnosis and 36.7% were under pharmacological treatment. Depression was associated with: female gender (rough OR:2.81, p 75 years (OR:2.71, p <0.002), living alone (OR: 2.56,p <0.001), FHD (OR: 2.58, p <0.004), nefropathy (OR:1.92, p7% (OR:1.32, p<0.29), insulin treatment (OR:1.01, p<0.94). Protective factors:working (OR:0.51, p<0.03) and physical activity (OR: 0.49, p<0.005).Forward Stepwise Logistic regression was used to identify the risk factors for depression: female gender (OR: 2.81; IC:1.53 - 5.17, p<0.001), FHD (OR:3.10; IC:1.55-6.17, p75 years (OR:3.22; IC:1.63-6.36, p<0.001), living alone, (OR: 2.37,CI: 1.27-4.44, p< 0.006), and carotid disease (OR: 2.32,CI: 1.13-4.74 p<0.02).The protective variable was physical activity (OR: 0.58 CI:0.34-0.99, p<0.04).In conclusion the presence of depression was a common occurrence in this sample of older diabetic individuals. Female gender, age >75 years, family history of depression, living alone, carotid disease were predictors of depression. Physical activity was a protective factor. In this population poor glycemic control was not associated with depression.

Supported by: Argentine Society of Diabetes

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—GLUCOSE MONITORING AND SENSING

Guided Audio Tour: Glucose Monitoring *(Posters 836-P to 843-P), see page 13.*

836-P

Accuracy of a Blood Glucose Monitoring System at Low Blood Glucose Levels: Analysis of Seven Clinical Studies

SRIKANTH BELLARY, HILARY CAMERON, KIRSTY MACLEOD, PRAVEEN RAJA, JOHN M. ELLISON, *Birmingham, United Kingdom, Inverness, United Kingdom, Milpitas, CA*

For individuals with diabetes detection of hypoglycemia is crucial, and blood glucose monitoring systems (BGMSs) must be accurate in hypoglycemic ranges. Collecting sufficient data at low blood glucose (BG) levels is difficult; therefore evidence of BGMS performance during hypoglycemia is lacking. This analysis evaluated the accuracy of 5 performance-equivalent BGMSs using OneTouch® Verio® test strips at BG levels of < 70 mg/dL in 7 separate clinical studies.The studies were conducted between June 2009 and June 2011. BG testing was performed by trained staff in 2 clinical centers in the UK. All studies were conducted in accordance with standard ISO 15197:2003 testing guidelines. Each study included 100 participants with diabetes. For each participant, duplicate BGMS tests were performed using 3-4 test strip lots per study, resulting in a total of 5,400 measurements. Of these, 674 (12.5%) were at a BG level of < 70 mg/dL; BG reference values were obtained using a YSI 2300 STAT Glucose Analyzer before and after BGMS testing. The number and percentage of results within ± 15 mg/dL and ± 10 mg/dL were calculated at BG levels < 70 mg/dL, < 60 mg/dL, and < 50 mg/dL (Table).Compared with analysis based on a single study, using data from 7 studies, 5 BGMSs, and 15 different test strip lots provides a robust depiction of test strip accuracy at BG levels < 70 mg/dL. The results indicate that OneTouch Verio test strips are highly accurate in the hypoglycemic range.

OneTouch Verio accuracy at BG levels < 70 mg/dL

	BG < 70 mg/dL	BG < 60 mg/dL	BG < 50 mg/dL
Within ± 15 mg/dL, % (n/N)*	100.0 (674/674)	100.0 (358/358)	100 (270/270)
Within ± 10 mg/dL, % (n/N)	98.8 (666/674)	100.0 (358/358)	100 (270/270)

*ISO 15197:2003 accuracy limits for BG levels < 75 mg/dL.

837-P

Structured SMBG Improves HbA_{1c} Through Targeted Changes in Diabetes Therapy in Patients With Non-Insulin Treated Type 2 Diabetes: The PRISMA Study

EMANUELE BOSI, MARINA SCAVINI, ANTONIO CERIELLO, DOMENICO CUCINOTTA, ANTONIO TIENGO, ERMINIO BONIZZONI, FRANCESCO GIORGINO, FOR THE PRISMA STUDY GROUP, *Milano, Italy, Barcelona, Spain, Messina, Italy, Padova, Italy, Bari, Italy*

The beneficial effect of self monitoring of blood glucose (SMBG) in non insulin treated (NIT) type 2 diabetes (T2D) is under debate. Aim of this study was to test whether structured SMBG (intensive structured monitoring, ISM) compared to discretionary, unstructured SMBG (active control, AC), was able to improve HbA_{1c} through optimization of diabetes therapy in patients with NIT T2D. We recruited 1,024 patients (age 60±8.5 SD yrs, 40% females, BMI 30.5±5.4) with NIT T2D (duration 6.2±3.8 yrs; baseline HbA_{1c} 7.4±0.7%) in 39 diabetes centers in Italy. All patients participated in a standard education program and were then randomized to either ISM (n=501; 4 SMBG measurements 3 days/week, including fasting, pre-prandial, 2 h post-prandial and post-absorptive assessments) or AC (n=523; 50 measurements over 3 months). During a 12 months follow-up patients were assessed quarterly with diabetes medications prescribed on the basis of HbA_{1c} and SMBG values to target fasting and/or post-prandial hyperglycemia and to avoid hypoglycemia in the ISM group or of HbA_{1c} values only in the AC group. During the study ISM patients performed a median of 512 (IQR 373 to 512) SMBG measurements and AC patients a median of 107 (IQR 61 to 182) (p<0.0001). HbA_{1c} decreased significantly more in ISM than AC patients [between-intervention difference in HbA_{1c} at month 12: -0.12% (95% CI -0.210 to -0.024), p=0.013, intention-to-treat population, n=951; -0.21% (-0.331 to -0.089), p<0.001, per-protocol population, n=553]. Changes in prescription of diabetes medications occurred more often in ISM (54.3%) than AC patients (45.7%) (p<0.001). No changes in BMI were observed in both groups, with a very low incidence of severe hypoglycemia (< 2 events) in both ISM and AC patients. Therefore, in patients with NIT T2D and close-to-target HbA_{1c} the use of structured SMBG to optimize medications and lifestyle changes improved HbA_{1c} with no increase of severe hypoglycemia or weight gain.

Supported by: Roche Diagnostics

838-P

Association Between Obstructive Sleep Apnea (OSA) Severity and Glycemic Control in Patients With Type 2 Diabetes Mellitus

NARESH M. PUNJABI, JONATHON SHAW, GREG FULCHER, MATTHEW NAUGHTON, PETER CISTULLI, RICHARD M. BERGENSTAL, PAUL ZIMMET, *Baltimore, MD, Melbourne, Australia, Sydney, Australia, Minneapolis, MN*

OSA is common in patients with type 2 diabetes mellitus (T2DM) and may alter glycemic control. Using baseline data from an ongoing international clinical trial, the current analysis examined the relationship between OSA severity and glycemic control in a sample of patients with T2DM.The GlyCOSA study is an ongoing randomized multi-center study evaluating the effects of positive airway pressure for OSA in non-insulin treated patients with T2DM. Participants were enrolled after a positive sleep study [Apnea

For author disclosure information, see page 797.

Hypopnea Index (AHI) >5] and were classified as having mild, moderate or severe OSA based on the AHI and the Oxygen Desaturation Index (ODI). Baseline glycemic control was assessed using HbA1c and self-monitored 7-point capillary glucose profiles.Data were available for 314 participants. There was no association between OSA severity and baseline HbA1c, 7 point profile average glucose, pre meal glucose values or with the change in glucose 90 minutes after breakfast or lunch. However, after adjusting for age, sex, BMI, and study site, there was an association between OSA severity and the change in glucose 90 minutes after the dinner meal. Compared to T2DM participants with an ODI < 5 events/hr, patients with progressively more severe sleep apnea as measured by an ODI of 5.0-14.9, 15.0-29.9, and ≥30.0 had a significantly greater change in glucose values 90 minutes after dinner of 18.4 mg/dL, 23.5 mg/dL, and 76.9 mg/dL, respectively ($p < 0.037$ for linear trend).In conclusion, in a cohort of T2DM patients with OSA, there was little relationship found between OSA severity and most indices of glycemic control, but T2DM patients with frequent oxygen desaturations had a significantly larger increase in post-dinner plasma glucose.

Supported by: ResMed

839-P

Is the Admission HbA1c Level a Predictor of Glycemic Control and Hospital Complications in General Surgery Patients With Type 2 Diabetes?

FARNOOSH FARROKHI, SAUMETH CARDONA, FRANCISCO PASQUEL, CHRISTOPHER NEWTON, DAWN SMILEY, LIMIN PENG, GUILLERMO UMPIERREZ, *Atlanta, GA*

Inpatient hyperglycemia is associated with increased risk of surgical complications. It is, however, unclear if chronic hyperglycemia, indicated by high admission HbA1c, is associated with hospital complications independent of glycemic control in general surgerypatients. Accordingly, we analyzed the association between admission HbA1c, inpatient glycemic control and complications in general surgery patients. A total of 211 patients with T2DM and admission BG 140-400 mg/dl were randomized to basal bolus regimen with glargine once daily and glulisine before meals (n= 104) or sliding scale insulin (SSI, n=107). The admission BG was 190±92 mg/dl and HbA1c 7.72±2.2% (±SD). Compared to SSI, patients treated with basal bolus had a lower daily BG (145±32 vs 172±47 mg/dl, p<0.01), higher % BG readings <140 mg/dl (53±30% vs 31±28%, p<0.001), and a lower rate of a composite of complications including pneumonia, bacteremia, wound infection, acute renal and respiratory failure [24.3% vs. 8.6%; OR 3.39 (95% CI 1.50-7.65), p=0.003]. Patients with HbA1c≥7% had a higher admission BG (233±103 vs 151±60 mg/dl, p<0.001) and mean daily BG (171±45 vs 148±38 mg/dl, p<0.001) compared to HbA1c <7%; however, the admission HbA1c as a continuous variable was not associated with length of stay (LOS) or with hospital complications (p=0.49 and p=0.36, respectively). Multivariate analysis adjusted for admission HbA1c, DM duration, BMI, and type of insulin treatment indicated that treatment with basal bolus was the single independent predictor of surgical complications.In summary, admission HbA1c level, an indicator of chronic hyperglycemia, correlated with inpatient glycemic control but was not associated with increased LOS or hospital complications in general surgery patients. Treatment with basal bolus regimen, independent of HbA1c level, was the best predictor of complications in general surgery patients.

Supported by: sanofi-aventis

840-P

First-Trimester Maternal Serum Biomarkers for Prediction of Gestational Diabetes

JUHA P. RASANEN, SRINIVASA R. NAGALLA, CARYN A. SNYDER, CHARLES T. ROBERTS, VISHNU PATURI, *Portland, OR, Beaverton, OR*

Gestational diabetes (GDM) confers an increased risk for pregnancy complications and development of subsequent type-2 diabetes. In this case-control study, we evaluated glycoproteins as alternative GDM biomarkers based on the hypothesis that increased hexosamine biosynthetic pathway flux secondary to hyperglycemia in GDM may affect the levels of serum analyte glycosylation. Maternal serum samples were collected between 9-11 and 16-27 gestational weeks from 150 Finnish women participating in a prospective observational cohort. GDM was diagnosed by a standard oral glucose tolerance test. Fibronectin glycosylation associated with Sambucus nigra lectin binding (FN-SNA), adiponectin, SHBG, and CRP levels were determined by immunoassay and analyzed using Receiver Operating Characteristic (ROC) curves from logistic regression modeling. First-trimester FN-SNA, adiponectin, and CRP levels were all significantly associated with subsequent development of GDM in 50 GDM subjects compared to 50 trimester-matched controls. The mean FN-SNA concentration was greater in participants who later developed GDM than in controls (102+30 mg/L vs. 56+15 mg/L; p<0.0001). At a false-positive rate of 4%, FN-SNA alone detected 84% of 1st-trimester GDM cases. The detection rate increased to 92% with addition of adiponectin and CRP. FN-SNA, adiponectin, and SHBG were all significantly associated with GDM in the 2nd trimester (p<0.01). The area under the ROC curve for FN-SNA alone was 0.92 (95% CI: 0.86, 0.98), which increased to 0.99 (95% CI: 0.98, 1.00) with the addition of adiponectin and SHBG. Similar discrimination was achieved with Aleuria aurantia lectin-reactive pregnancy-specific glycoprotein (PSG-1). Our data demonstrate that maternal serum FN-SNA represents a promising single-marker test for early identification of women at risk for GDM. Reliable early diagnosis using maternal serum glycoprotein biomarkers can facilitate new intervention strategies to prevent the complications of GDM.

841-P

Evaluation of Performance of A1c and FPG Tests for Screening Prediabetes and Newly Diagnosed Diabetes Defined by an OGTT Among Tuberculosis Patients—A Study from India

VIJAY VISWANATHAN, SATYAVANI KUMPATLA, VIGNESWARI ARAVINDALOCHANAN, RAJESWARI RAJAN, ANIL KAPUR, *Chennai, India, Gentofte, Denmark*

In the light of limitations associated with OGTT and with the recent advance of using A1c as a diagnostic criterion for diabetes, the performance of A1c and fasting plasma glucose (FPG) tests for screening prediabetes and newly diagnosed diabetes (NDD) defined by OGTT was evaluated among tuberculosis (TB) cases in India.A total of 904 subjects aged ≥18 years with TB were selected from 5 TB units, 2 urban, 2 rural and 1 semi-urban areas of Tamil Nadu, India, during August 2010-March 2011. Screening for prediabetes and diabetes was carried out by 2-hr 75 g OGTT. Classification of glucose intolerance status was based on WHO criteria. HbA1c was measured by high performance liquid chromatography using Bio-Rad turbo machine. HbA1c% ≥47.5mmol/mol was used for diagnosis of diabetes. FPG was estimated by glucose-oxidase method. Known cases of subjects with diabetes were excluded and final analysis was done using data of 779 individuals. The performance of A1c and FPG tests was evaluated against the results of OGTT using receiver operating characteristic curve analysis.Prevalence of NDD and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) was 10.8% and 29.4%, respectively. The areas under the curve (AUC) were 0.754 [95% confidence interval (CI) 0.68-0.83] (p<0.001) for A1c and 0.662 (95% CI 0.58-0.74) for FPG (p<0.001) in NDD subjects, whereas for prediabetes, the AUC were 0.535 (95% CI 0.49-0.58) (p=0.035) for A1c and 0.577 (95% CI 0.53-0.62) (p<0.001) for FPG. The HbA1c cut-off point of ≥47.5mmol/mol gave a sensitivity of 59.1% and specificity of 91.7%, and the respective values were 34.8% and 97.5% for FPG in subjects with NDD. HbA1c cut-off point of 38.8mmol/mol to 46.4mmol/mol gave a sensitivity of 64.7% and specificity of 28.1%, and the respective values were 7.6% and 76.8% for FPG in subjects with prediabetes.HbA1c performed better than FPG as a screening tool for NDD and prediabetes among subjects with TB.

Supported by: Prof. M. Viswanathan Diabetes Research Centre and World Diabetes Foundation

842-P

First User Experience of a Comprehensive Monitoring System to Facilitate Self-Management of Diabetes

KIT YEE AU-YEUNG, LORENZO DICARLO, ARNA IONESCU, JESSIE DUONG, GREG MOON, GWEN LITTLEWORT, SARA BROWNE, *Redwood City, CA, San Diego, CA*

Diabetes self-management requires medication adherence, diligent monitoring of blood glucose, weight, and physical activity. A system is being developed to directly confirm medication ingestion and monitor physiologic metrics.The initial system consists of ingestion markers co-ingested with oral medication and an adhesive monitor worn on the user's body. A mobile phone may be used for data communication. Once ingested, each marker communicates a unique ID to the monitor, which records the ID, time, and date of ingestion. It also records sleep and activity. Data from a telemetric weight scale and a glucometer are acquired; all data streams are periodically uploaded to a secured server for mobile phone or computer display to the user.The system was assessed in a pilot study of 5 patient subjects (2 females, 3 males age 43 - 61) with Type 2 diabetes for 42 days. Subjects were instructed to co-ingest a marker whenever metformin was taken, and to take 1 weight and 1 pre-prandial glucose measurement daily. On average, the cohort took 78±12% of prescribed metformin; 77±26% was taken within the prescribed 4-hour time window. The mean cohort weight was 92±19 kg. Large variability was seen in mean cohort activity (6386±2377 steps) and glucose (11.7±3.5 mmol/L). Two adverse events were reported as mild skin irritation at the monitor site in 1 subject.The system appears safe and capable of integrating multiple data streams (Fig. 1). Integration of ingestion

markers with pharmaceuticals is in progress and may, in combination with already available metrics, enable comprehensive monitoring and facilitate patient self-management.

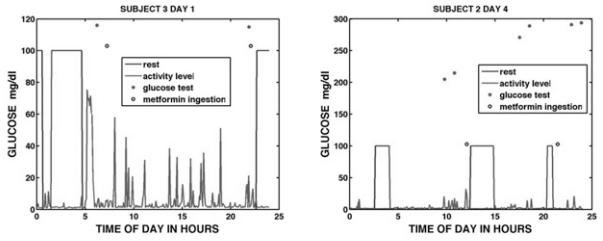


Figure 1: Example of adequate (left) and inadequate (right) self-management.

843-P

Prevention of Inpatient Severe Hypoglycemia With a Real-Time Informatics Alert

ELIZABETH PRATT, MICHAEL ELLIOTT, STEPHEN J. SCHAFERS, MARY CLARE BLACKBURN, RACHEL KILPATRICK, KEVIN HEARD, MARK THOELKE, JOHN LYNCH, JANET MCGILL, GARRY S. TOBIN, *St. Louis, MO*

Inpatient severe hypoglycemia (SH), blood glucose (BG)<40 mgs/dl, is associated with morbidity. We previously developed a predictive model to identify inpatients at risk for SH, and sought to test whether a targeted intervention could prevent SH. A 3-month prospective cohort- intervention study involving 6 intervention and 6 control acute medicine floors was performed at Barnes-Jewish Hospital in St. Louis. An alert process is triggered when a patient exceeded a specified informatics generated risk score and experienced a BG ≤90 mg/dl in the setting of active diabetes therapy. Fourteen charge nurses (CN) on intervention floors were trained to review the alert, with risk factors and orders, and collaborate with the MD. Alerts generated on the control floors were reviewed after the patient was discharged by a CDE RN to assess whether the MD's recognized the risk and made order changes consistent with the CN training. CN's and MD's completed a collaboration scale to evaluate their satisfaction with the collaborative process.The study groups were comprised of patients receiving alerts. The mean risk-alert score on the intervention floor was similar to the control floor (52 vs. 54; p=0.407). Diabetic therapy orders were changed in 51% of intervention patients compared to 23% in control patients. SH occurred in 2.7% (3/111) of the intervention patients versus 10.9% (14/128) of control patients (p=0.014). This reflects a 75% reduction in SH attributable to the alert intervention process. A blood glucose value <60mg/dl was seen in 14.4% (16/111) of the patents on intervention floors compared to 25.0% (32/128) of control patients (p=0.042). Rates of hyperglycemia (BG > 299) were similar on intervention and control floors (p = 0.331). Collaboration scores and appropriate order changes were positively correlated (F=7.72 P=0.001).Conclusion: A real-time informatics alert plus trained nurse responders significantly decreased SH in at risk hospitalized patients and merits further study with expansion.

Supported by: Barnes Jewish Hospital Foundation

844-P

Sickle Cell Trait Leads to Under Diagnosis of Glucose Intolerance by A1C

ALFRED N. ROTIMI, SOPHIA S. YU, MADIA RICKS, SAMUEL DAGOGO-JACK, DAVID SACKS, JAY LOZIER, ANNE E. SUMNER, *Baltimore, MD, Bethesda, MD, Memphis, TN*

As microvascular complications are more severe in diabetics with sickle cell trait (SCT) - early diagnosis of diabetes is important. With A1C assay standardization, ADA recommends A1C≥5.7% to diagnose glucose intolerance. A1C represents non-enzymatic glycation of HbA at the N-terminus of the β-chain. But in SCT, one β-chain is mutated, and so less HbA is available for glycation. Hence, it is unclear whether A1C will reflect hyperglycemia in individuals with SCT. To determine if A1C≥5.7% was diagnostic in the presence of SCT, we studied 116 Africans (age: 34±9y, BMI: 27.1±4.7 kg/m^2). SCT and A1C were determined by HPLC (Bio-Rad Variant II). Glucose tolerance was assessed by OGTT. SCT was present in 20% of Africans. With SCT, hemoglobin was similar but MCV lower and bilirubin higher (Table). Fasting and 2h glucose as well as prevalence of glucose intolerance did not vary by SCT status (Table). However, SCT was associated with lower A1C (*P*=0.03) (Figure). Further, in the diagnosis of glucose intolerance, sensitivity of A1C was 72% without SCT but only 43% with SCT. Hence, even though the prevalence of glucose intolerance was similar, A1C was lower and less able to identify glucose intolerance in Africans with SCT. Therefore, use of A1C may not be appropriate in the presence of SCT.

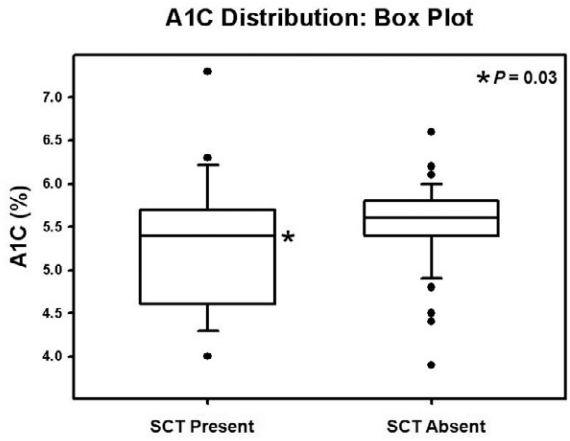


Table: Characteristics

	SCT Present (n=23)	SCT Absent (n=93)	P-value
Hemoglobin (g/dL)	14.0±1.2	13.9±1.3	0.89
MCV (fl)	81.7±4.6	85.4±5.13	<0.01
Total Bilirubin (mg/dL)	0.85±0.54	0.65±0.34	0.03
0 h Glucose (mg/dL)	90±11	89±8	0.46
2 h Glucose (mg/dL)	131±45	122±27	0.22
Glucose Intolerance (%)	30%	27%	0.73

845-P

Biological Variables Impact on the HbA1c Level: An Algorithm to Help Individualise HbA1c Targets

ALBERT HSIEH, MARGARET MCGILL, LYNDA MOLYNEAUX, MARIA CONSTANTINO, DENNIS YUE, STEPHEN TWIGG, *Camperdown, Australia, Sydney, Australia*

To aid development of personalised HbA1c targets, we examined biological variables that may predict HbA1c level during type 2 diabetes routine care. Analysis of a serial 2893 Diabetes Centre patients seen within a 5 year period was performed. The cohort had HbA1c level of 7.3±1.5% (mean±SD), age 62.3±11.5 years, diabetes duration 9.9±8.0 years, BMI of 31.4±6.5 kg/m2 and 56% were male. Biological variables potentially associated with the HbA1c value were examined: age at diagnosis, diabetes duration, gender, diabetes family history (FHx), smoking status, BMI and ethnicity. By univariate analysis, all of these variables were significantly associated with HbA1c; age of diabetes diagnosis had the strongest correlation (r = -0.28, P<0.0001), followed by diabetes duration (r = 0.26, P<0.0001). Age of diabetes onset was significant even when stratified by duration (Table). Linear multivariate regression analysis showed significant relationships of HbA1c value and all study variables except gender and ethnicity. By the multivariate regression model, a person aged 50 with diabetes duration of 15 years, active smoker, BMI of 35 and diabetes FHx would on average have an HbA1c of 7.9%. In contrast, a person aged 65 with 5 years duration, BMI 27, non-smoker and no FHx would have a much lower mean HbA1c of 6.7%. This data indicates that individualised realistic HbA1c targets could include key biological variables affecting chronic glycaemia. It also has implications in assessing efficacy of diabetes health care systems, as age of diabetes onset for a patient mix must be considered rather than just a uniform HbA1c threshold.

Table — Median HbA1c grouped by Age diagnosed and duration of diabetes

	Age diabetes diagnosed (yrs)					
Duration of Diabetes (yrs)	≤30	30.1-40	40.1-50	50.1-60	>60	P value
<5	7.3	6.8	6.4	6.5	6.3	P<0.0001
5-9.9	9.4	7.6	7.3	7.0	6.8	P<0.0001
10-14.9	8.9	8.0	7.8	7.4	6.9	P<0.0001

The provisional multivariate regression model: HbA1c (%) = 7.83+ [- 0.03 x (age of diabetes diagnosis) + - 0.03 x (diabetes duration in years) + 0.16 x (presence of a first degree family history of diabetes) + 0.22 x (current smoker) + 0.02 x (BMI) + 0.001 x (diabetes duration in years) x (age at diabetes diagnosis)].

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

846-P

The Subjective Experience of CGM-RT Use: Comparing Current Users With Ex-Users

DANIELLE HESSLER, WILLIAM POLONSKY, FARAH BOWMAN, DAVID PRICE, *San Francisco, CA, San Diego, CA*

It is unclear what distinguishes patients that continue using CGM from those that discontinue use. 2791 insulin-using adults (> 18 y) who had begun using the Dexcom CGM 6 - 12 months prior to study initiation were invited to complete an online questionnaire that examined their CGM attitudes (perceived QOL benefits due to CGM use, CGM device satisfaction), confidence regarding CGM data usage, and physician involvement. After 11 days, the survey site was closed. Completed surveys were received from 877 current users (CU) and 102 ex-users (XU), and CU were compared to XU.CU and XU demographics: type 1 DM (93% vs. 92%); gender (46% vs. 44% male); mean age (42 vs. 40); mean years since diagnosis (21in both groups); CSII users (72% vs. 78%). CU and XU differed significantly in ethnic background (90% vs. 82% non-Hispanic White; p = .02) and education level (65% vs. 53% college graduates; p = .02).More CUs than XUs reported that CGM had helped (moderately or a great deal) improve their quality of life (QOL) (79% vs. 34%; p < .001). They also reported higher rates of satisfaction with the device, in regards to accuracy (82% vs. 51%, p < .001), ease of use (95% vs. 62%, p < .001), and cost (44% vs. 28%, p < .001), and had higher rates of confidence in their ability to use the CGM data (94% vs. 65%; p < .001). More CUs than XUs also noted that their physician downloaded and reviewed their CGM data at most or every visit (59% vs. 47%; p = .02).We utilized logistic regression analysis to examine how demographics, confidence regarding CGM data and physician involvement were linked to continued use or discontinuation. Significant independent predictors of continued use were higher educational level (OR = 1.17, p = .05), more frequent data review with one's physician (OR = 1.18, p = .05) and greater confidence in using CGM data (OR = 2.67, p < .001). These data suggest that persistent CGM use is more likely when patients have ongoing physician support as well as the personal resources and confidence to use the CGM data effectively.

Supported by: Dexcom

847-P

Evaluation of a Structured Protocol for Initiating Basal/Prandial Insulin in Type 2 Diabetes (T2D) Patients in Primary Care With Adjunct Continuous Glucose Monitoring (CGM)

DAVID N. O'NEAL, JOHN FURLER, LOUISE GINNIVAN, HANAN DERRAZ, IRENE BALACKBERRY, ALICIA J. JENKINS, NEALE COHEN, GLENN WARD, DANIEL LIEW, JAMES D. BEST, DORIS YOUNG, *Fitzroy, Australia, Parkville, Australia, Prahran, Australia*

The T2D epidemic, and limited specialist resources, require increased primary care insulin initiation. We aim to evaluate a structured protocol guiding teams of Family Physicians and Practice Nurses in the initiation of basal +/- prandial insulin with Diabetes Nurse Educator and endocrinologist support. Changes in HbA1c at 12 and 24 weeks are benchmarked against specialist care in ambulatory T2D patients. We also aim to evaluate retrospective-CGM in guiding insulin dosing in primary care. To date 20 primary care sites have commenced basal insulin (glargine, sanofi-aventis) in 60 T2D patients inadequately controlled on maximal oral therapy randomized to either self monitoring of blood glucose (SMBG) alone or with adjunct retrospective-CGM (iPro 2/ Enlite sensor, Medtronic). 32 subjects at the 12 week study point were evaluated and compared to a reference group (n=61) seen by specialists. Statistical analysis was by paired t test and ANOVA.Insulin initiation was associated with significant improvements in HbA1c (Table) comparable to specialist care; Primary Care: 9.4 (1.2) to 7.6 (0.78)% vs Specialist: 9.6 (1.8) to 8.3 (1.3)% p=0.22. Glycemic parameters in CGM and SMBG randomized patients were not significantly different. Prandial insulin (Glulisine, sanofi-aventis) was initiated more often in the CGM than with SMBG (CGM: 8 vs. SMBG 3; p<0.01). There were no major hypoglycemic events. An interim analysis suggests insulin can be safely and effectively initiated in primary care. CGM use enhanced recognition of the need for prandial insulin.

Glycaemic Parameters Pre and 12W Post Insulin Initiation

Monitoring Modality	CGM (n=16)	CGM (n=16)	P	SMBG (n=16)	SMBG (n=16)	P	P
	Pre-Insulin	12W	Baseline vs 12W	Pre-Insulin	12W	Baseline vs 12W	SMBG vs CGM
HbA1c (%)	9.6(1.3)	7.7(0.8)	<0.0001	9.1(1.0)	7.5(0.7)	<0.0001	0.30
%Time 4.0-10 mmol/L	43.6(31.9)	73.9(13.2)	0.001	32.0(24.1)	58.4(27.6)	0.02	0.43
%Time>10.0mmol/L	54.7(32.3)	20.6(14.7)	0.0004	66.4(23.3)	38.7(29.2)	0.0013	0.54
% Time	1.7(3.6)	5.5(6.8)	0.07	1.6(3.3)	2.9(4.2)	0.47	0.36

848-P

Glycemic Profile Assessment Using Continuous Glucose Monitoring in Patients With and Without Hypoglycemia After Gastric Bypass Surgery

JANET CHUANG, LESLIE BAUM, DAVID D'ALESSIO, MARZIEH SALEHI, *Cincinnati, OH*

Roux-en-Y gastric bypass (GB) alters postprandial glucose homeostasis partly due to rapid intestinal glucose flux into circulation. While prior studies have shown earlier glucose peaks and lower nadir values in response to a fixed amount of ingested carbohydrate after GB, the glucose profile of GB subjects particularly those with hypoglycemia in free living condition has not been well characterized.In this study, the effect of GB on the glycemic profile measured during a 3-hour meal tolerance test (MTT, 325 kcal Ensure plus), and during free living assessed by 4-day continuous glucose monitoring system (CGM) was compared in 15 GB patients with postprandial symptoms of hypoglycemia (Sym), 8 asymptomatic GB subjects (Asym), and 12 healthy non-surgical controls (non-GB).BMI and A1C levels were comparable among groups, but controls were younger than GB subjects. Time and weight loss since surgery and presurgery rate of diabetes were similar in GB groups. During MTT, both GB groups had similar glycemic peaks that were higher compared to the non-GB (p<0.05). In 10 of the 15 Sym subjects, but in none of the Asym, glucose nadir was <50mg/dl. During CGM, fasting glucose profiles (1am-6am) were identical among all groups. GB subjects had higher non-fasting peak glucose values (188±9 vs. 149±6 mg/dL, p<0.05) and standard deviation (22±2 vs. 14±2 mg/dL, p<0.01) compared to non-GB. The lowest non-fasting CGM glucose values were similar between Asym and non-GB, but lower in Sym compared to Asym (54±3 vs. 68±5 mg/dL, p<0.05). No hypoglycemia was noted on CGM in 5 of the 10 subjects with hypoglycemia during MTT, while 3 of those who were euglycemic during MTT had glucose <50 mg/dl during free living conditions.Gastric bypass increases non-fasting glucose variability as well as peak values. Evaluation of the glycemic profile during free living condition can miss diagnosis of hypoglycemia in 50% of affected subjects, and does not appear to be as sensitive as MTT for detection.

849-P

Continuous Glucose Monitoring (CGM) Accuracy, Real-Time vs. Retrofitted: Why We Need Both

MARC D. BRETON, BORIS P. KOVATCHEV, *Charlottesville, VA*

CGM is becoming mainstream in T1D research and treatment. While CGM accuracy is still debated, here we distinguish accuracy of real-time CGM supporting instantaneous patient decisions from accuracy of retrofitted CGM used by researchers, clinicians, and patients to assess study or treatment outcomes. We argue that the latter greatly increase by introducing anchor data points.To illustrate the retrofitting procedure, we use 84 traces of SMBG-calibrated CGM from 31 T1D patients (adult and adolescent) who had frequent blood glucose (BG) references over 22h (4262 data pairs). Anchor points were obtained in 7-point daily profile (pre-meals, meals+2h, bedtime, and when CGM is below 70mg/dl). Retrofitting implied smoothing the CGM signal, computing a multiplicative coefficient at each anchor point, and applying the interpolated coefficients to the smoothed CGM.Retrofitting increased the percentage in the Clarke Error-Grid A zone from 68% to 90%, reduced extreme errors 3 fold (zones C, D, E), and increased more than 2 fold the MARD and MAD of the CGM traces. The deviation of several outcome metrics from their reference values (Table 1B) was reduced at least 2 fold. In addition, CGM-based detection of hypoglycemic events improved from 68% to 78% overall with 29% vs. 10% false alarm (FA), and from 67% to 93% (FA 34.6% vs. 10%) overnight.Retroactive adjustment of CGM data results in very accurate traces and outcome metrics. Thus, use of CGM data for judging research study outcomes and clinical treatment is justified with appropriate retrofitting. Therefore we argue that real-time and posteriori accuracy is key to optimal use of CGM in T1D.

Improvements of CGM accuracy and CGM based outcome metrics

Accuracy and Outcome Measures	Raw CGM	Retrofitted CGM
MARD	18.2%	8.70%
MAD	24.8 mg/dl	11.8 mg/dl
Clarke Error-Grid A zone	68%	90%
Mean Absolute Deviation of percent time within target 70-180 mg/dl	13.20%	4.30%
Mean Absolute Deviation of percent time within target 80-140 mg/dl	11.90%	5.20%
Mean Absolute Deviation of Mean BG	0.9 mg/dl	0.5 mg/dl
Mean Absolute Deviation of Low Blood Glucose Index (LBGI)	0.89	0.24

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

850-P

Assessing the Comparative Effectiveness (CE) of Basal-Bolus vs. Premix Insulin Using Continuous Glucose Monitoring (CGM) Summary Measures

DONALD C. SIMONSON, JASVINDER K. GILL, MAXWELL SU, LOUISE TRAYLOR, MARCIA A. TESTA, *Boston, MA, Bridgewater, NJ, Wellesley, MA*

CGM is an effective management and diagnostic tool that also can be used to assess the CE of diabetes regimens. We analyzed CGM data collected from type 2 diabetes (T2DM) patients in 52 US centers during a randomized, open-label, cross-over (12 wk phases) trial (NCT00135941) of daily insulin glargine plus premeal insulin glulisine (GG) or premix insulin 75/25 or 70/30 bid (PM) requiring titration to HbA1c < 7.0% to evaluate the utility of CGM in CE research. Three-day CGM (288 glucoses/day), HbA1c and patient-reported satisfaction were obtained at wks 0, 12 and 24 in 306 patients [45.1% men; mean (SD) age = 56.1 (9.3) y; HbA1c = 7.8 (0.7) %; diabetes duration = 14.5 (8.1) y]. Data were analyzed using longitudinal linear mixed models. Mean (SE) HbA1c decreased by 0.6 (0.1) for GG and 0.3 (0.1) % for PM ($P < 0.0001$). There was a more favorable CGM profile for GG compared to PM (Table). Measures of low blood glucose risk (AUC < 70 mg/dL) and Low Blood Glucose Index were not different. After adjusting for treatment, period, sequence, week, baseline satisfaction, BMI, age, HbA1c < 7.0%, mean daily insulin dose and duration of diabetes, each CGM measure proved to be an independent predictor of treatment satisfaction (all $P < 0.0001$). Changes in CGM summary measures differentiated GG and PM regimens in terms of glycemic variability and risk independent of changes in HbA1c, and predicted patient-reported treatment satisfaction. CGM summary measures can enhance comparative effectiveness research in diabetes by providing information on daily glucose variability that cannot be obtained from HbA1c alone.

CGM Summary Measure [Mean (SE)]	GG	PM	*P*
24-hr glucose change from baseline (mg/dL)	-28.8 (3.7)	-11.9 (3.9)	0.002
Within-Day SD (mg/dL)	46.3 (1.1)	49.7 (1.1)	0.019
AUC > 180 mg/dL (hrs x mg/dL)	16.3 (1.2)	20.0 (1.2)	0.033
Time within 70 to 130 mg/dL (hrs)	8.8 (0.3)	7.7 (0.3)	0.007
Glycemic Risk Assessment Diabetes Equation	8.3 (0.2)	9.2 (0.3)	0.013
High Blood Glucose Index	6.8 (0.3)	7.9 (0.3)	0.018

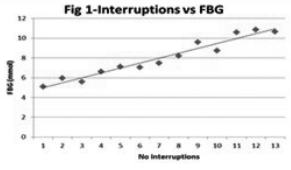
Supported by: sanofi-aventis

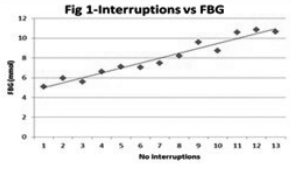
851-P

Sleep Disturbances and Glucose Variability

PATRIZIO TATTI, DESIDERIO PASSALI, *Marino, Italy, Siena, Italy*

Aim of this study is to evaluate the relationship of sleep fragmentation with the level and the variability of the fasting blood glucose values (FBG). We used the Armband, an instrument that records the number and the duration of the awakenings during sleep (AW), for six consecutive days in 60 obese type 2 diabetic subjects on diet alone or oral hypoglycemic agents and with a history of sleep disturbance (37 M, 23 F); age 61.6+5; BMI=28+1.3 kg/m2. All of them recorded their blood glucose level in duplicate upon awakening with the same brand of glucometer using an interference free electrochemical method throughout the observation period. The values were downloaded, and the Standard Deviation (SD) was calculated as an index of variability. All the data were log transformed. The correlation coefficients were for the FBG .76 (p=.000) and the SD .81 (p=.000) and the ANOVA <.001 for both. With the partial correlation, after removing the effect of BMI, Age and HbA1c the correlation of AW with the FBG was p= .001 and with the SD p=.049.We conclude that in this series the number of awakenings was significantly correlated with the fasting blood glucose and the glucose variability as represented by the SD. The total sleeping time did not have any significant interaction with both the FBG and the SD.



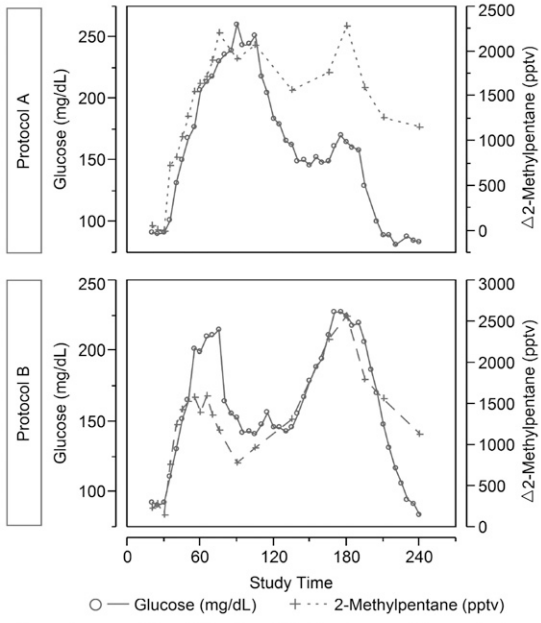


852-P

Exhaled 2-Methylpentane, a Potential Novel Biomarker of Glycemia

TIMOTHY D. MINH, SIMONE MEINARDI, HEATHER SOPHER, MATTHEW K. CARLSON, MILA IBARDOLAZA, DONALD R. BLAKE, PIETRO R. GALASSETTI, *Irvine, CA*

Breath analysis is increasingly considered a potential noninvasive alternative to measure key aspects of metabolism, simplifying diagnosis/management of conditions like obesity and diabetes. Noteworthy, several exhaled volatile organic compounds (VOCs) were previously used to estimate plasma glucose, lipids, and insulin, albeit only during single experiments (i.e. without both training and testing components). To confirm the viability of these studies, it is crucial to document stability of VOC responses to similar metabolic perturbations over time. Therefore, 6 subjects (3F; 29±1 yrs) underwent 2 4-hr glucose clamp studies, ~3 months apart, following two protocols (A and B; each included two hyperglycemic peaks induced by iv infusion of 20% dextrose). Simultaneous blood, breath, and room air samples were collected at 20 time points. Concentrations of ~100 VOCs were determined by gas chromatography. Among several VOC responses similar across both visits, 2-methylpentane (2MP; range: 86-2634 pptv breath, 34-108 pptv room air) most strongly correlated with plasma glucose (r=0.78), especially when glycemia was rapidly increasing. 2MP was previously shown to potentially arise endogenously as a by-product of oxidative stress, which is acutely increased during hyperglycemia. De-gassing of infusates and tubing ruled out the possibility that 2MP had been infused. Our findings therefore underscore the viability of breath-based metabolic tests by demonstrating the stability over time of some of its key components, and support the notion that its further refinement will lead to the rapid development of clinically applicable testing devices.



Mean glucose and 2-methylpentane delta (breath-room air) concentrations of 6 subjects during 4hr of induced glycemic fluctuations. Each subject participated in both Protocols A (top) and B (bottom) within a 3-month span.

Supported by: NIH (UL1 RR031985); NIH (F30 DK088401)

853-P

Evaluation of the Health Monitoring System on Clinical Closed-Loop Data

REBECCA A. HARVEY, EYAL DASSAU, HOWARD ZISSER, DALE SEBORG, LOIS JOVANOVIC, FRANCIS J. DOYLE III, *Santa Barbara, CA*

Continuous health monitoring has been used with cardiac patients and elderly people with great success over the last decade. In that vein, the Health Monitoring System (HMS), a safety layer for type 1 diabetes therapy, has been designed for use in parallel to an artificial pancreas (AP) control algorithm or as part of a continuous glucose monitoring (CGM) system. The Low Glucose Prediction (LGP) module is a robust alert system for hypoglycemia that uses CGM data to forecast trends and automatically alert the user and an emergency contact list to imminent hypoglycemia.The goal of the LGP is to consistently produce necessary alerts with minimal false positive alarms. The LGP predicts hypoglycemia by pre-processing CGM data for

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

missing points and sensor noise, followed by extrapolation and prediction of imminent hypoglycemia. The LGP was designed using ambulatory data and tested with the FDA-accepted UVA/Padova metabolic simulator.The system performance was evaluated against published clinical data that contained hypoglycemia episodes and/or rescue treatments. By assessing these data with the LGP, hypoglycemia treatment decisions made by physicians were compared to the alerts produced by the LGP. In closed-loop operation, the LGP must detect unavoidable hypoglycemia while allowing the controller to prevent avoidable hypoglycemia without producing false alarms. The LGP has been applied to the bihormonal closed-loop studies (20 studies, 26 hours on average) performed by El-Khatib et al. (STM 2010) The LGP predicted 91% of 22 hypoglycemia episodes within 1 hour of onset, with 81 of 99 alarms confirmed by an episode, administration of glucagon (at least 5% of rescue dose in last 15 minutes), or a meal. The LGP alerted all 17 treatments, an average of 22 minutes before.The HMS with LGP is a versatile tool for use in CGM and the future AP in alerting for imminent hypoglycemia. It is effective in predicting hypoglycemia with clinical closed-loop data before treatment is given, while maintaining a very low false positive rate.

Supported by: DP3DK094331-01 and R01DK085628

854-P

Post-Prandial Glycemic Contribution to Overall Hyperglycemia and Glycemic Variability in Obese Non Diabetic Patients With Normal or Subnormal HbA1c

MARINOS FYSEKIDIS, ISABELA BANU, REZKI AMEL, CHANTAL CYRIL, EMMANUEL COSSON, PAUL VALENSI, *Bondy, France*

The contribution of post-prandial glycemia (ppg) to overall hyperglycemia has been shown to be predominant in fairly controlled type 2 diabetic patients. The aim of this study was to examine in a series of obese non diabetic patients with normal or subnormal HbA1c the association of HbA1c levels with glycemic variability and the contribution of ppg to overall "hyperglycemia".Sixty-three obese patients, BMI = 35.0 ± 6.7 kg/m², 7 men, without known dysglycemia and free of diabetes according to the Oral Glucose Tolerance Test and an HbA1c < 6.5%, were included. HOMA-insulin resistance index and Matsuda index were calculated. A 24 hour Continuous Glucose Monitoring was used under a 1800 Kcal diet with a standardised 75 gr carbohydrate breakfast and fixed meal times. Patients were separated according to HbA1c quartiles.Higher HbA1c was associated with age (p=0.001) but not with BMI, waist circumference, HOMA-IR or the Matsuda index. Higher HbA1c was associated with higher daily mean glucose level (p=0.006) and with parameters of glycemic variability: Mean Amplitude of Glycemic Excursions (p=0.024), daily standard deviation (p=0.011), Coefficient of Variation (p=0.004), Continuous Overlapping Net Glycemic Action (p=0.005), High Blood Glucose Index (p=0.013). Ppg contribution to the relative hyperglycemia, estimated by the formula [100 x (3 hour Area Under the Curve (AUC) post prandially - 3h AUC for a constant 5.5 mmol/L glycemia) / (24h AUC- 24h AUC 5.5 mmol/L)], decreased from the lowest to the highest HbA1c quartile (97%, 73%, 59%, 57%; p< 0.001).In conclusion, in obese non diabetic patients with a normal or subnormal HbA1c level, higher HbA1c is associated with lower ppg contribution to the overall hyperglycemia and greater glycemic variability. These findings support the relevance of ppg control as a major target in the early diabetes prevention.

855-P

No Effect of Periodic CGM on HbA1c in Poorly Regulated Type 1 Patients

HENRIK ULLITS ANDERSEN, MAJBRITT KJELMANN, MINNA WITTRUP, THOMAS P ALMDAL, *Gentofte, Denmark*

In adults, only one randomised study has been performed using periodic CGM as a tool to lower HbA1c, this study showed no effect. 3000 type 1 diabetes patients are followed at Steno Diabetes Center, Denmark, and 15 - 20 % of these are poorly controlled with a HbA1c > 74 mmol/mol. The purpose of this study was to assess whether the use of periodic CGM (Guardian, Medtronic) lowers HbA1c in poorly controlled patients, defined as HbA1c > 74 mmol/mol in 3 consecutive measurements. Patients with type 1 diabetes not treated with insulin pumps are cared for by 3 teams of doctors and nurses. This study was undertaken among patients attached to one of the teams. Following CGM for 6 days the patients were seen by a senior diabetologist and diabetes nurse at start and again after 6 months. CGM was used for adjustment of basal and bolus insulin doses. In between, patients were seen at 3 months and offered to mail SMBG to a nurse for advice at 1.5 and 4.5 months. Patients in the two other teams served as controls. Primary endpoint: HbA1c at 6 months. Secondary endpoint: Patient satisfaction, evaluated by questionnaire.124 patients were eligible, 48 accepted. 43 (20M / 23 F) started the study. They had a median age of 49 (23-80) years and DM duration of 18 (4-45) years. 33% had experienced hypoglycemic comas within 2 years and 5 % suffered from unawareness. 35 completed the first 6 months. 17 patients had a lower HbA1c after 6 months. Results: Intervention team: start 78 (67-109), 6 months: 77 (51-98). Control teams: start 82 (58-169), 6 months: 80 (48-121). Only 25% (0-100%) emailed SMBG between consultations. Total insulin dose was 52 (12-120) i.u. at start, 54 (16-122) i.u. at 6 months. 70% expressed that they gained knowledge on their diabetes by using CGM. 75% used the CGM curves a lot during the trial, but only 15% made many adjustments of insulin doses. In conclusion, an intensive program based on CGM did not reduce HbA1c in poorly regulated type 1 diabetes patients. Patient satisfaction with CGM was high.

856-P

Structured Self-Monitoring of Blood Glucose (SMBG) Improves Glycemic Control in Type 2 Diabetic Veterans on Insulin

CHRISTOPHER S. WENDEL, GREGORY FOTIEO, ELENA V. PLUMMER, JAYENDRA H. SHAH, GLEN H. MURATA, *Tucson, AZ, Albuquerque, NM, Phoenix, AZ*

This group-randomized clinical trial evaluated whether structured SMBG and standard treatment orders improve glycemic control in type 2 diabetic veterans on insulin. Thirty-seven primary care providers (PCPs) at 3 southwestern VA medical centers were randomly assigned to Intervention (IG) or Control Groups (CG), stratified by provider type and practice site. Their patients were eligible if they were on insulin for type 2 diabetes and had a baseline hemoglobin A1c (A1c) ≥ 7.5%. Both PCP groups received the same diabetes training except IG providers were additionally taught how to interpret 7-point glucose profiles. Patients of IG providers performed SMBG 7 times daily for 3 consecutive days prior to each PCP visit using a paper record (Accu-Chek 360 View). IG PCPs were free to choose any treatment but had the option of using structured order sets in which they could specify the target glucose reading, insulin type, and up to 11 other parameters. Orders were executed by a research coordinator. CG patients received routine care which included ad libitum SMBG and access to certified diabetes educators. Patients visited their PCPs every 3 months. The study sample (47 IG and 47 CG) was 97% male and 35% minority. The mean (± SD) age was 64.5 ± 7.6 yrs and duration of diabetes 11.5 ± 5.7 yrs. The IG and CG had similar demographic and clinical features at entry. At 3 months, the decrease in A1c from baseline was greater for IG than CG subjects (-0.76 ± 1.17% vs -0.22 ± 0.92%; P=0.01). Multiple linear regression showed that structured SMBG had a favorable effect on A1c (-0.52 ± 0.22%; P=0.02) after adjusting for age, gender, minority status, BMI, number of oral hypoglycemic agents, and daily insulin dose at entry. In addition, the IG tended to have fewer subjects who developed hypoglycemia in the first 3 months compared to the CG (12.8% vs 26.1%, respectively; P=0.10). Structured SMBG is associated with rapid improvement in glycemic control without a high risk of hypoglycemia in insulin-treated veterans.

Supported by: Roche Diagnostics Corporation

857-P

Relationship between Fasting Glucose and Minimal Glucose Levels in 24 hours in Well-Controlled Patients With Type 2 Diabetes Treated With Metformin or Insulin Glargine

ELENA HENKEL, FRANK PISTROSCH, FRANK SCHAPER, CARSTA KOEHLER, MARKOLF HANEFELD, *Dresden, Germany*

In clinical practice basal insulin for HbA1c control to target is based on fasting glucose (FG). But FG can change corresponding to circadian fluctuations, including the dawn phenomenon and may be strongly affected by counter regulation after nocturnal hypoglycemia (H). The aim of this randomized controlled comparative study was to evaluate the relationship between FG and glucose minima in 24 hours.75 drug naive T2D patients, treated with glargine (GLA) at bedtime (n=39) vs metformin (MET) 1000 mg bid (n=36), (45/30, m/f, age 60.7±9,2yrs) with T2D duration <5 yrs, HbA1c 6.5-8.5%. GLA was adjusted with target FG<5.6 mmol/l. This evaluation is based on interstitial glucose (iG) measured with Continuous Glucose Monitoring at 36 weeks follow-up. The following minimal (min) glucose levels were measured: between midnight and breakfast (min_iGN), breakfast and lunch (min_iGBL), lunch and dinner (min_iGLD), dinner and midnight (min_iGDN). The corresponding times of m glucose were averaged. T-Test for min averaged iG values was performed to compare FG and min_iG-levels.GLA treatment resulted in a more pronounced reduction of FG (6.1±1.1 vs 7.2±1.0 mmol/l) and HbA1c (7.2 to 6.4% vs 6.9 to 6.3%) than MET. H events (time periods of iG<3.9 mmol/l) occurred equally in both groups. The min_iG-levels at all studied periods except min_iGDN were signif. lower than FG (p<0.05)The min glucose levels at day and night in both study groups were lower than FG. FG used as

parameter for treatment to target of HbA1c has little relevance to predict risk of critical glucose minima.

Minimal Glucose Levels in 24 hours and times of minima

min_iG Met	min_iGN GLA	min_iGBL Met	min_iGBL GLA	min_iGLD Met	min_iGLD GLA	min_iGDN Met	min_iGDN GLA
4.7±1.1 mmol/L	4.6±1.2 mmol/L	5.6±1.1 mmol/L	5.3±1.3 mmol/L	5.5±1.3 mmol/L	5.2±1.3 mmol/L	5.7±1.5 mmol/L	6.1±1.2 mmol/L
03:10±02: a.m.	03:26±01:5 8 a.m.	11:49±01:1 0 a.m.	11:11±02:1 3 a.m.	04:12±01:1 1 p.m.	04:31±01:4 8 p.m.	10:11±01:3 8 p.m.	10:17±01:5 8 p.m.

858-P

Increased Continuous Glucose Monitoring (CGM) Receiver Interaction is Associated With Glycemic Benefit in Pediatric Patients

LUCAS BOHNETT, JAIME REALSEN, PETER CHASE, BRUCE BUCKINGHAM, DAVID PRICE, *San Diego, CA, Denver, CO, Palo Alto, CA*

Increased CGM screen views have been associated with improved glycemic outcomes in adult patients. Whether this association holds in pediatric patients has not been reported. We looked at frequency of CGM receiver button pushes in 72 youth age 7-17 with an average baseline A1C of 8.3 at 3 US centers that were subjects in a home use performance study of a prototype Dexcom 7 day CGM system. Subjects were scheduled for three consecutive 7-day wear periods. In the initial period, subjects were blinded from glucose information. In the subsequent two periods, glucose data was un-blinded and CGM was used real-time (rt). In this retrospective analysis (Table), we independently assessed daily glycemic measurements during the un-blinded time period with CGM receiver screen views. We considered the daily frequency of button pushes that result in presentation of glucose information on the CGM receiver to reflect CGM receiver screen views. Repeat button pushes within a minute were not counted in duplicate.Correlation analyses show increasing CGM receiver screen view frequency is associated with a statistically significant improvement in the time spent within a target glucose range (70-180 mg/dL), time spent high (> 200 mg/dL), and also in mean of CGM glucose (all $p < 0.05$). Neither time spent low (< 60 mg/dL) nor standard deviation of CGM glucose was found to have a significant association. Similar to adult patients, an increased frequency of receiver interaction in pediatric subjects using rt-CGM demonstrated association with glycemic improvement.

Correlation Analyses between Daily Glycemic Measuresand the Number of CGM Receiver Screen Views

Glycemic Measurement	Pearson Correlation Coefficients	p-value
Mean of CGM Glucose *	-0.09	< 0.01
Standard Deviation of CGM Glucose	-0.04	= 0.19
Time Spent within a Target Glucose Range [70, 180] *	0.07	< 0.01
Time Spent Low (<60)	0.0003	= 0.99
Time Spent High (>200) *	-0.1	< 0.01

*statistical significance at p = 0.05

859-P

Comparison of A1c Measurements from a Home Test Device to a Hospital Laboratory

JESSICA T. THUERINGER, AREEF ISHANI, THOMAS RECTOR, NANCY GREER, NACIDE ERCAN-FANG, *Minneapolis, MN*

In patients with diabetes mellitus, improved glycemic control is associated with significantly reduced rates of microvascular complications. Nurse case management has been shown to significantly improve glycemic control. However, patients must come to the hospital laboratory for HbA1c testing, which is time consuming and costly. We wanted to determine whether home HbA1c test results can be utilized by patients and case managers to guide therapy. The availability of a point-of-care device marketed for both professional and home use (A1cNow+) provided an opportunity to compare test results.The current study is nested within a randomized control trial to determine if case management with home telemonitoring would result in improved glycemic control compared to usual case management. At the initiation of the trial, patients performed a HbA1c test with the A1cNow+ device. At the same study visit, a venous blood sample was collected and analyzed by the hospital laboratory using HPLC (Bio-Rad Variant II). The primary objective was to compare the two sets of test results using a Bland-Altman plot, Pearson's correlation coefficient and Student's paired t-test.Paired samples from 50 individuals were compared. The mean value of HbA1c obtained by laboratory testing was 9.9% ± 1.0% (range 8.6-12.9%). The mean HbA1c value obtained by the A1cNow+ was 9.6% ± 1.1% (range 7.3-12.7%). The differences between the tests were not significantly related to the mean values (r =-0.19; p = 0.18). Overall, the HbA1c results from patient testing on the A1cNow+ device were significantly lower than the results obtained from laboratory testing (mean difference = 0.3% ± 0.7%; p=0.003).Due to the lack of agreement between HbA1c values obtained by patients on the A1cNow+ device compared to those obtained in the laboratory, we do not currently recommend use of the A1cNow+ device for home monitoring of HbA1c by patients or use of home test values by case managers to advance treatment.

860-P

Incorrect Strip Filling Impairs the Performance of Many Glucose Meters for Patient Self-Testing

FRANK FLACKE, PETRA MUSHOLT, CHRISTINA SCHIPPER, JOCHEN SIEBER, THOMAS FORST, ANDREAS PFÜTZNER, *Frankfurt, Germany, Mainz, Germany*

Acuracy of blood glucose readings is dependent from complete strip filling with sufficient sample volume. The devices are supposed to display an error message in case of incomplete filling. This laboratory study was performed to test for the performance of 31 devices in case of incomplete strip filling. Samples with 2 different glucose levels (60-90 and 300-350 mg/dL) were used to generate three different sample volumes: 0.20 µl (below any required volume), 0.32 µl (borderline volume), 1.20 µl (sufficient volume). After a point-of-care reference measurement (StatStrip, NovaBiomedical), the strip was filled (6x) with the respective volume and the response of the meters (2 devices) was documented (=72 determinations/meter type). Correct response was defined as either an error message indicating incomplete filling or a correct reading (±20 % compared to reference reading).Only 5 meters showed always correct responses (AccuChek Compact+ and Mobile (Roche), OneTouch Verio (Lifescan), BG*Star and iBGStar (sanofi-aventis)). The majority of the meters (17) had up to 10 % of wrong reactions (Precision Xceed and Xtra, FreeStyle lite and Freedom lite (all Abbott); GlucoCard+, GlucoMen GM (Menarini); Contour, Contour USB, Breeze2 (Bayer); OneTouch Easy, Ultra2 and UltraSmart (Lifescan); Wellion Dialog and Premium (MedTrust); FineTouch (Terumo), AccuCheck Aviva (Roche); and GlucoTalk (Axis-Shield)). 10-20 % wrong reactions were seen with OneTouch Vita (Lifescan); AccuChek Aviva Nano (Roche);OmniTest+ (BBraun); and AlphaChek (Progen). More than 20 % wrong reactions were obtained with Pura (Ypsomed), GlucoCardX and GlucoMen LX (Menarini), Elite (Bayer), and MediTouch (Medisana).In summary**,** the majority of commercially available blood glucose meters and strips may occasionally display a wrong reading in case of incomplete strip filling. These findings underline the importance of appropriate patient education on this aspect of blood glucose self-monitoring.

Supported by: sanofi-aventis

861-P

Differences Between Perceived Versus Measured Blood Glucose Test Results in People With Type 2 Diabetes

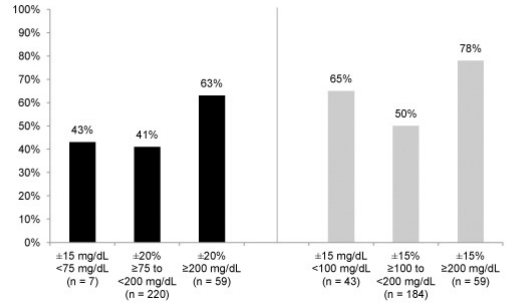
JEREMY PETTUS, JIMM GREER, PATRICIA STENGER, HOLLY SCHACHNER, NANCY DUNNE, JOAN LEE PARKES, SCOTT PARDO, STEVEN V. EDELMAN, *San Diego, CA, Del Mar, CA, Tarrytown, NY*

Research suggests that some people with diabetes believe that they know what their blood glucose (BG) level is and use these perceptions to make decisions about their self care practices. This study assessed the difference between self-reported, estimated BG values and BG values as measured on a BG meter. Subjects aged ≥18 years with type 2 diabetes (N=297) attending 1 of 2 Taking Control of Your Diabetes conferences were asked questions about their testing behaviors and perceived BG level. Study staff then performed a fingerstick to measure the BG value on a BG meter. 77% of subjects reported that their body tells them without testing if their BG is low or high, and 71% made decisions about their diabetes without testing. Nearly half (46%) of subjects estimated BG values that were more than ±15 mg/dL of actual glucose values <75 mg/dL or more than ±20% of actual glucose values ≥75 mg/dL (based on current ISO accuracy criteria); 58% estimated BG values that were not accurate based on more stringent accuracy criteria (within ±15 mg/dL or ±15% at glucose concentrations <100 and ≥100 mg/dL, respectively). The percentage of inaccurate BG estimates evaluated across various glucose ranges is shown (Figure). Time since last BG test, time since last meal, testing frequency, and A1c had no effect on the results. After fingerstick testing, nearly all (99%) felt knowing their BG by checking could help them make different diabetes decisions. These findings suggest the importance of regular BG testing rather than estimation of BG values to help people with diabetes to make better informed decisions for effective diabetes management.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

Figure. Percentage of inaccurate BG estimates based on actual meter results using current ISO 15197:2003 and proposed more stringent standards for accuracy assessment.



Supported by: Bayer HealthCare LLC, Diabetes Care

862-P

Real-Time and Retrospective Detection of Nocturnal CGM Signal Attenuation

FRASER CAMERON, NIHAT BAYSAL, BRUCE BUCKINGHAM, DARRELL WILSON, B. WAYNE BEQUETTE, *Troy, NY, Stanford, CA*

Continuous glucose monitors (CGM) track glucose concentration, but are prone to signal attenuation when pressure is applied to the site. When the attenuations are misinterpreted as valid readings they can prompt inappropriate action or degrade CGM based performance metrics for outpatient trials. We developed a real-time method for detecting invalid readings, and a retrospective method for imputing the glucose trend.Sensor attenuations typically begin with a sudden, steep drop from valid readings and end with a rapid return to valid readings. The real-time method flags invalid readings using a negative steepness threshold on the CGM rate-of-change and a Kalman filter that detects the sudden drop. The end of the sensor attenuation is detected by testing for two successive CGM readings with a negative second derivative.The retrospective analysis assumes a smooth CGM signal and gives less weight to short, sharp troughs in the CGM readings. Mathematically, this method minimizes the rate-of-change between successive glucose estimates while fitting the CGM readings. In successive rounds of optimization CGM readings that fall more than 10 mg/dL below the corresponding filtered estimates are given less weight. The process is repeated until the solution is stable.We tested these methods on 39 nights (250 hours) of inpatient data using Abbott and Medtronic sensors with semi-hourly reference glucose values. 13 periods of attenuations and invalid sensor readings were observed.These algorithms provide a promising method for both real-time and retrospective detection of sensor attenuations.

Results

Method \ Metric	Episodes Detected (# \ %)	False Flags (Readings \ %)
Real-Time	10 \ 76%	28 \ 0.9%
Retrospective	12 \ 92%	7 \ 0.2%

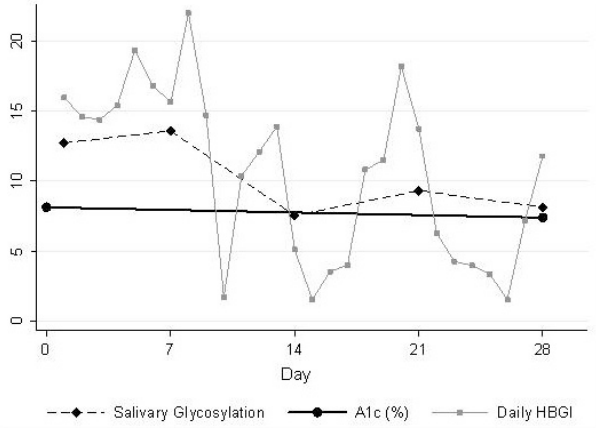
Supported by: JDRF (22-2011-647, 3-2011-80)

863-P

Non-Invasive Salivary Protein Glycosylation as a Short-Term Glycemic Index

SRINIVASA R. NAGALLA, CARYN A. SNYDER, JOHN A. MICHAELS, CHARLES T. ROBERTS, VISHNU PATURI, *Beaverton, OR*

The standard parameter for monitoring of glycemic index is hemoglobin A1c, which reflects average glycemia over the previous 3 months. Fructosamine and glycated albumin can provide potential assessment of more near-term glycemia, but all of these are invasive and require specific laboratory analysis. We evaluated salivary glycoprotein levels as a non-invasive alternative by comparing it to A1c and continuous glucose monitoring (CGM) in 8 type 1 and type 2 diabetics. Saliva was collected at days 1, 7, 14, 21 and 28 and blood collected at baseline and day 28. Salivary glycosylation was measured by lectin-binding immunoassays and was normalized for total protein concentration. To account for asymmetry in the blood glucose measurement scale and suppress normal fluctuation in the target range for glucose control, the High Blood Glucose Index (HBGI) was calculated to quantify glycemia from the CGM data. Daily, weekly, and 28-day HBGIs were computed and matched to the time of each study visit. The Figure shows weekly salivary glycosylation and daily HBGI over 28 days of CGM in a type 2 diabetic with beginning and ending A1c's of 8.1% and 7.4%, respectively. Six participants did not achieve optimal control as defined by baseline HbA1c's <7.0%. During CGM, these participants achieved a 33% reduction in HBGI. A1c only slightly changed over this time period (-0.4 ± 0.5%), and did not reflect the degree of glycemic variation observed. Average salivary glycosylation levels collected weekly over 4 weeks demonstrated a stronger correlation with CGM than A1c (r=0.81 vs. r=0.52) and represent a promising, non-invasive method for glycemia monitoring.



864-P

Continuous Glucose Monitoring Performance during Exercise in Pregnant Women With Type 1 Diabetes

KAVITA KUMARESWARAN, DANIELA ELLERI, JANET ALLEN, KAREN CALDWELL, DAVID SIMMONS, MARIANNA NODALE, MALGORZATA WILINSKA, STEPHANIE AMIEL, HELEN MURPHY, ROMAN HOVORKA, *Cambridge, United Kingdom, London, United Kingdom*

Accuracy of continuous glucose monitoring (CGM) may be reduced during physical activity. As part of a 24-hour closed-loop insulin delivery study in 12 women (age 32.9y, BMI 27.1kg/m^2) with type 1 diabetes (duration 17.6y, HbA1c 6.4%) during pregnancy (gestation 19wks), we evaluated performance of Freestyle Navigator CGM during afternoon (15.00-18.00h) and morning (09.30-12.30h) exercise (55min brisk treadmill walking followed by 2hrs recovery), compared with sedentary conditions (18.00-09.30h). Reference plasma glucose measured by YSI2300 Analyser assessed CGM performance. Median relative absolute difference (MRAD) between paired sensor and reference glucose values (493 data pairs), measuring sensor accuracy, was significantly lower during sedentary conditions compared with during afternoon and morning exercise. These differences remained significant even after correction for plasma glucose relative rate of change (p<0.001). Post-hoc analysis revealed significant difference between exercise and resting conditions (p<0.001), but not for afternoon versus morning exercise (p=0.90). The Clarke Error Grid showed 95.9% of values within clinically acceptable zones (A+B) during resting conditions, compared with 86.9% during afternoon and 86.4% during morning exercise. The MRAD was higher during hypoglycaemia compared with hyper- and normo-glycaemia, for both exercise and sedentary periods. In conclusion, compared with sedentary conditions, CGM performance was lower during exercise. This difference was independent of the higher rate of change of glucose associated with physical activity.

Sensor accuracy measures during sedentary and exercise conditions

	Sedentary Conditions	Afternoon Exercise+ Recovery	Morning Exercise+ Recovery	P value (ANOVA)
Median RAD overall(%)	11.8	19.7	16.7	<0.001
Median RAD hypoglycemia (%)	16.7	28.1	39.4	NS
Median RAD normoglycemia(%)	10.7	19.9	17.6	NS
Median RAD hyperglycemia(%)	12.6	13.3	8.2	NS
Median Bias (mmol/l)	0.16	0.63	0.77	<0.001
ISO Criteria (%)	76.1	59.0	62.6	0.003
Plasma Glucose Relative Rate of Change (% per hour)	12	20	22	<0.001

Supported by: Diabetes UK

865-P

Multiscale Glycemic Fluctuations and Functional Outcomes—A Novel Multimodal Approach

XINGRAN CUI, ANDREW GALICA, BRAD MANOR, CHUNG-KANG PENG, VERA NOVAK, *Boston, MA, Wuhan, Hubei, China, Chungli, Taiwan*

This study applied a novel method based on empirical mode decomposition (EMD) to quantify glycemic variance (GV-EMD) at multiple physiological cycles and to determine their relationship to glycemic control and functional measures. 35 T2DM (19 women, 16 men, mean age 65 ± 9 yrs) and 25 controls (12 women, 13 men, mean age 66 ± 10 yrs) underwent continuous glucose monitoring (CGM) for 3 days and neuropsychological testing. GV-EMD was quantified as the standard deviation (SD) from each cycle. The T2DM group exhibited significantly greater variability during the day as compared to night (cycles 3, 4) and to the control group (cycles 1-5, day & night) (LS models, adjusted for age and sex). In the T2DM group, $GV\text{-}EMD_{cycles\ 1\text{-}5}$ fluctuations were associated with higher HbA1c ($p < 0.01$). Slower GV-EMD cycles (4, 5) were related to increased microalbumin/creatinine ratios ($p = 0.02$) and worse scores on learning and memory tests ($p = 0.02$). Faster GV-EMD cycles (1-3), were associated with less depression ($p = 0.03$). The relationship between GV-EMD and outcomes was independent of number and durations of hypoglycemic episodes. The relationship to A1c and microalbumin/creatinine was also reproduced with the traditional SD measure for raw CGM data. GV-EMD allows the study of glycemic variance at different time scales, enabling a detailed assessment of the physiological mechanisms (autonomic, meal, sleep-awake cycles) underlying glycemic variance. GV-EMD may better identify the relationship between glycemic variance and hyperglycemia, microvascular disease and cognitive outcomes.

Supported by: 1R01AG028076-A2; 1R21- DK084463-01

866-P

Glucose Volume of Distribution (Vd) May Explain Glucose Concentration Curves After Mixed Diets in Type 2 Diabetes Treated With Metformin Alone

JOHN S. MELISH, *Honolulu, HI*

Powers (Am J Clin Nutrition, 2010) reported continuous glucose monitoring (CGM) results obtained from 14 Type 2 patients (A1c 7.8%) each ingesting 2 calorically equivalent mixed diets containing 85.5 g v. 43 g carbohydrates (CHO). The results (mg/dl vs. time) from each diet were similar for each individual and were separately pooled. The area under the curve (AUC) with the 85.5 g diet was not twice as large, high, or long. A pharmacokinetic model [(Melish, Diabetes, 2011), treating first pass post-hepatic glucose appearance (FPPHGA) as zero order rate change and hepatic glucose production suppression and peripheral glucose uptake as first order constant rates] was applied to these data.: The rates of dietary glucose appearance (Ra=mg/dL/min) and disappearance (k_d, fraction/minute) were nearly the same for both diets. Most different was the glucose volume of distribution (Vd) which increased on the 85.5 g as compared with the 43 g diet. First pass post-hepatic glucose appearance (FPPHGA) was calculated as 1-EXP(kd*time to baseline). As these were relatively well controlled diabetics, it is postulated that capillary recruitment in the presence of increased insulin accounted for the increase in the V_d in the 85.5 g CHO diet and thereby a relative lowering of that glucose curve relative to the 43.0 g curve while preserving the other kinetic parameters including Clearance (Cl) = (V_d*k_d). Changes in V_d related to insulin response may be needed to explain glucose concentration curves resulting from differing insulin/glucose ratios on a mixed diet.

Pharmacokinetic Variables for Each Diet

Available	Vd	kd	GRAHFP	GlucoseRa	Cl	AUC
CHO (g)	(dL)	min-1	(mg)	(mg/dL/min	(dL/min)	(mg/dL)*min
43.0	115	0.00816	35.25	3.46	1.54	718.2
85.5	189	0.00615	63.37	2.79	1.62	787.1

867-P

Information Management Significantly Improved the Glycemic Status in Type 2 Diabetes Patients: Results from the Multicenter Observational VISION study

JOERG WEISSMANN, ANGELIKA MUELLER, KRISTINA PRALLE, HEINZ-JUERGEN RUESSMANN, BETTINA GREGERSEN, DIETHELM MESSINGER, ILDIKO AMANN-ZALAN, *Mannheim, Germany, Berlin, Germany, Dinslaken, Germany, Osted, Denmark*

The study aim was to evaluate everyday benefit of Information Management (IM) on HbA1c outcome, therapy adaptations and - with a view to patients - therapy understanding and satisfaction using the Accu-Chek® Smart Pix device reader and analysis tool as an integral part of outpatient diabetes treatment.VISION examined the process quality and medical outcome of using the Accu-Chek Smart Pix reports as basis for therapy decision and patient communication in the context of primary care of 914 adults with type 1 and type 2 diabetes respectively (T1D, N=248 / T2D, N=666) with poor glycemic control (HbA1c ≥7.5%). Data from the T2D collective - thereof 88% insulin treated - were analyzed for change in glycemic status by comparing HbA1c values before (visit 1; baseline) versus about 3 (visit 2) and 6 months (visit 3) after integrating the tool in the office work flow. Also, therapy adjustments and physician's opinion on patient appraisal of therapy were assessed via questionnaire.Within approx. 3 and 6 months of IM usage in T2D care, HbA1c significantly ($p<0.0001$) dropped on average by -0.88% (visit 2) and -0.93% (visit 3) from baseline (8.66%). This clinically relevant effect was accompanied by a distinct and significant ($p<0.01$) improvement in patient therapy understanding and satisfaction. In addition, according to physicians recommended treatment adjustments were predominantly based on information derived from the Accu-Chek Smart Pix reports: e.g. ≥ 80% for various insulin therapy adaptions and lifestyle changes, respectively.In this study, usage of an IM system in usual outpatient T2D care significantly and strongly improved glycemic control and therapy appraisal. Physicians confirmed a therapy process optimization by using the Accu-Chek Smart Pix analyses for therapy decision assistance. These findings fit well in recently reported improvements in quality of diabetes care using information processed in electronic health records.

868-P

A Pilot and Feasibility Study of a Fully Automated, Closed Loop, Text Message Based System to Improve Diabetes Control

SHAMSA ALI, ROBERTA MCDUFFIE, SHUQIAN LIU, NICHOLAS AVITABILE, NICHOLAS AVITABILE, AJAZ BANKA, LIZHENG SHI, VIVIAN FONSECA, *New Orleans, LA*

Frequent follow up and interaction with patients greatly improves diabetes control, but the current healthcare system limits sufficient contact, leading to delays in improvement of control. We have modified a text message based system using cellular telephones developed to send clinical reminders to patients (MedAdherence Inc.). The diabetes remote monitoring system (DRMS) sends patients text messages reminding them to test blood glucose, which the patient can text back. Using a modification of the ADA algorithm, the system automatically advises patients on changes to medications including insulin dose adjustment. In addition, simple messages on healthy living were sent via cellphone at random intervals. There is no human contact other than for emergency glucose values or routine appointments.We carried out a pilot feasibility trial of the system in 18 patients with T2DM who were randomized to DRMS or usual care for six months. The mean (±SD) HbA1c in patients on DRMS fell from 8.2 ± 0.6 to 7.2 ±0.8 ($p=0.013$) and with routine care from 8.3 ± 0.2 to 8.2 ±0.9 ($P=0.600$). Six patients in each group completed the study, and all patients randomized to DRMS expressed satisfaction and ease of use of the system.We conclude that an automated system for diabetes medication adjustment based on standard algorithms using text messaging via cellular phone is feasible and improves diabetes control with low incremental costs. Larger clinical trials are needed to establish this technology in clinical practice.

869-P

Intra-Subject Variability Makes Prediction of Post-Prandial Glucose Response Difficult in Subjects With Type 1 Diabetes

PAOLO ROSSETTI, FRANCISCO JAVIER AMPUDIA-BLASCO, ALEJANDRO LAGUNA, JOSEP VEHÍ, JUAN F. ASCASO, JORGE BONDIA, *Valencia, Spain, Girona, Spain*

Postprandial (PP) glucose excursions are the mayor contributors to plasma glucose (PG) variability (V) of subjects with type 1 diabetes (T1DM). In addition, the poor reproducibility of PP glucose response is one of the most challenging issues in the everyday diabetes care.Aim of this study was to examine which variables best predicted the 5-hour PP (0-5h PP) PG response. Twelve subjects with T1DM, treated with continuous subcutaneous insulin infusion, were studied both in outpatient (O-study) and inpatient conditions (I-study). They all used a bolus calculator and were advised to maintain their usual breakfast and level of physical activity, and to avoid snacks before the study. In the O-study they underwent at least two 3-day periods of continuous glucose monitoring during which they had a standardized lunch daily, containing 40, 60 or 100g of carbohydrates (CHO). In the I-Study, each subject received two 40g CHO and two 100g CHO meals, in random order at lunch. Insulin feed-back was performed to standardize pre-meal PG (PGt0). PG was measured every 5-10 min.We measured the 0-5h PP PG response as the area under the curve of PG ($AUC\text{-}PG_{0\text{-}5h}$), and V as the individual coefficient of variation (CV) of $AUC\text{-}PG_{0\text{-}5h}$. We then investigated the relationship between BMI, diabetes duration, A1c, the insulin to CHO ratio (I:C), the mean

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

amount of CHO, PGt0, the mean prandial insulin dose (ID), and AUC-$PG_{0\text{-}5h}$.A multiple regression analysis revealed a significant model both in the O- and I-Study (adjusted R^2 0.59 and 0.62, respectively): PGt0 was the variable that best predicted AUC-$PG_{0\text{-}5h}$ explaining about 50% of PG response, while ID, I:C and CHO were poor predictors. As expected V was greater in the O-Study (CV 29.6±11,8% vs 14.5±10,5%), but was independent of the studied factors. In conclusion, high intra-subject variability accounts for the greatest part of unpredictability of PP glycemic response. Causes of variability should be identified to improve PP glycemic control.

Supported by: E. Union PIEF-GA-2009-252085. Spanish Min. of Science DPI2010-20764-C02-02

870-P

HbA1C Can Recognize the Unknown Diabetes in Acute Pancreatitis With Hyperglycemia That Have a Poorer Outcome Than the Acute Pancreatitis Without Diabetes

XIAOLONG ZHAO, CHANGMEI HUANGPU, LIMING LI, *Shanghai, China, Zhenjiang, China*

To investigate the prevalence of diabetes in acute pancreatitis (AP), and to compare the clinical features of acute pancreatitis in patients with and without diabetes.We retrospectively collected 318 patients with AP in two clinical centers from January 2009 to October 2010. Patient with a previous history of diabetes or with glycosylated hemoglobin A1c (HbA1c) higher than 6.5% were identified as acute pancreatitis with diabetes (APD), while patients without history of diabetes and in whom the HbA1c was not higher than 6.5% were considered as AP only. In total, 318 patients with AP were enrolled. Among them, 40 were APD and 278 were AP; thus the prevalence of diabetes in AP was 12.6%. Twenty five percent (10/40) of the diabetic cases were indentified using HbA1c. The mortality rate was significantly higher in the APD group (15.0%, 6/40) than that in the AP group (1.1%, 3/278). Survival curves showed there was a significant survival difference between the APD group and AP group via the log-rank test. Multivariate Cox regression analysis showed that sex, age, diastolic blood pressure, body mass index (BMI) were significantly associated with mortality. Compared with AP patients, subjects with APD had significantly longer time from initial symptoms to admission [1.6 (95% CI: 0.5-3.2) vs. 0.9 (95% CI: 0.1-2.2) d], older age of onset (57.2 ± 11.0 vs. 44.3 ± 7.8 yrs), higher levels of glucose (13.9 ± 8.2 vs. 7.3 ± 4.1 mM), higher levels of HbA1c [8.5 (95% CI: 6.6-11.4)% vs. 5.9 (95% CI: 4.9-6.4)%)], and longer duration of hospitalization (18.3 ± 4.6 vs. 13.2 ± 5.1 d). Electrocardiograms showed that APD patients had a significantly higher risk of heart ischaemia than AP patients (22/40 vs. 20/278). HbA1c may be a useful parameter to identify the unknown diabetes. Physicians should be alert to acute pancreatitis with diabetes since the APD group had poorer outcome than the AP group

Supported by: Chinese National Natural Science Foundation

871-P

Performance of a New Meter Designed for Assisted Monitoring of Blood Glucose (AMBG)

SANDRA MACRURY, JANICE MACLEOD, LORETTA JONES, *Inverness, United Kingdom, West Chester, PA, Milpitas, CA*

Assisted Monitoring of Blood Glucose (AMBG) is performed for a patient by a healthcare provider (HCP) or other caregiver. Blood glucose meters used by HCPs for AMBG and/or point-of-care testing require different attributes compared with glucose meters designed for home use. These attributes include safety considerations (i.e., minimized risk of blood borne pathogen transmission), capability for testing multiple blood sample types, and enhanced performance specifications. The OneTouch® Verio™Pro+ glucose meter incorporates all these attributes. The onboard test strip ejector facilitates strip handling and minimizes HCP contact with each blood-dosed strip thereby minimizing the risk of exposure to blood borne pathogens.Glucose meters used in clinical settings for AMBG also require quality control (QC) tests to be performed regularly. The OneTouch Verio Pro+ meter provides onscreen prompts to remind HCPs to perform QC tests and automatically recognizes when control solution is applied. After reading the Operator's Guide, 100% (38/38) of HCPs assessed reported that they knew how to correctly respond to a control solution prompt and 89.5% (34/38) stated that reminders to conduct a QC test will help them to be compliant with their institution's regulatory requirements.The table shows the results of a study conducted to ascertain meter performance at 4 clinical sites with 189 capillary, 177 venous, and 200 arterial blood samples compared with YSI reference values. The OneTouch Verio Pro+ glucose meter shows enhanced performance across the glucose range and incorporates many important clinical attributes required for AMBG.

OneTouch Verio Pro+ performance with arterial, capillary, and venous blood, versus YSI reference.

	Glucose < 100 mg/dL*	**Glucose ≥ 100 mg/dL***	All Results
	Data within ± 12 mg/dL, n/N (%)	**Data within ± 12.5%, n/N (%)**	**Data within ± 12 mg/dL or 12.5%*, n/N (%)**
Arterial	27/27 (100)	164/173 (94.8)	191/200 (95.5)
Capillary	21/23 (91.3)	163/166 (98.2)	184/189 (97.4)
Venous	25/26 (96.2)	149/151 (98.7)	174/177 (98.3)
All blood sample types	73/76 (96.1)	476/490 (97.1)	549/566 (97.0)

*Accuracy limits (± 12 mg/dL for glucose < 100 mg/dL or ± 12.5% for glucose ≥ 100 mg/dL) have been proposed by CLSI POCT12.

872-P

WITHDRAWN

873-P

Impact of Continuous Glucose Monitoring (CGM) Use on Quality of Life (QOL): A Survey of Current Users

WILLIAM H. POLONSKY, DANIELLE HESSLER, FARAH BOWMAN, DAVID PRICE, *Del Mar, CA, San Francisco, CA, San Diego, CA*

Few studies have examined the impact of newer CGM systems on QOL. 2400 insulin-using adults (> 18 y) who were current Dexcom CGM users with ≥ 6 months CGM experience were invited to complete an online questionnaire examining their perception of benefits and losses since CGM initiation, current CGM use, and physician involvement. After 11 days, 877 completed surveys were received and the survey site was closed. Participants: type 1 DM (93%); mean age (42 years); 46% male; 72% used CSII; 65% college graduates; and 90% non-Hispanic White.78% reported CGM use ≥ 22 days/month; 64% checked the receiver screen > twice/hour; and 94% reported at least moderate confidence in using the CGM data. 59% noted their physician downloaded and reviewed their CGM data at most or every visit.79% of respondents reported CGM had helped (moderately or a great deal) improve their QOL. 16 items examined specific benefits and losses. For each, participants indicated whether things were now much worse, slightly worse, no change, slightly better, or much better due to CGM use. Factor analysis detected 3 subscales: perceived control over DM (PCOD, 7 items), hypoglycemia safety (HS, 5 items), and interpersonal support (IS, 3 items). Mean scores pointed to broad positive improvement in PCOD (86% of patients), HS (84%), and, to a lesser degree, in IS (37%); consistent worsening in any of the three subscales was rare (≤ 5%).Multiple regression analysis revealed the most consistent independent predictors of perceived benefits across the 3 subscales were more frequent CGM use (all β's > .12, P < .001) and greater confidence in using CGM data (all β's > .18, P < .001). Pump use, more fre-

quent receiver screen views, and more frequent physician data review were not linked in any consistent manner to greater perceived benefits. These data suggest that current Dexcom CGM users perceive substantial QOL benefits from use of the device; benefits are more apparent in those who use the device more frequently and those who are confident in using the data.

Supported by: Dexcom

874-P

The Abbott Freestyle Navigator Continuous Glucose Monitor Achieves Accuracy in ICU Patients Comparable to Healthy Subjects When Calibrated at 6 Hour Intervals

CATHERINE C. BEAUHARNAIS, HUI ZHENG, DAVID M. NATHAN, STEVEN J. RUSSELL, *Boston, MA*

Studies of intensive insulin therapy (IIT) in the ICU have been confounded by hypoglycemia. Continuous glucose monitoring could allow automated, closed-loop blood glucose control. We tested the accuracy of the Abbott Diabetes Care Freestyle Navigator continuous glucose monitor (CGM) in the ICU setting.Navigator sensors were worn for up to 72 hours by 60 patients receiving insulin (NeuroICU n=27, Medical ICU n=16, Cardiac ICU n=12, Surgical ICU n=6). BG measurements on arterial blood were used to calibrate CGM voltage traces *post hoc*. Calibrations schemes included the stock algorithm (calibrations at 1, 2, 10, and 24 hours) and algorithms retaining the 1 and 2 hour calibrations with additional calibrations at 24, 12, 8, 6, 4, or 2 hour intervals. Reference BGs were paired with the nearest CGM values; BG values used for calibrations were paired with the preceding CGM values. The stock algorithm gave mean absolute relative deviations (MARDs) higher in the ICU population (14.2%) than found in healthy subjects with type 1 diabetes (~12-13%). However, calibrating at 6 hour intervals gave a MARD of 12.7%. Accuracy was not significantly affected by peripheral edema, pressor dependence or ICU.

	Stock	24hrs	12hrs	8hrs	6hrs	4hrs	2 hrs
MARD	N=66514.2%	N=69115.7%	N=68114.6%	N=67113.4%	N=65512.7%	N=66212.3%	N=66411.9%

We conclude the Freestyle Navigator can achieve accuracy in ICU patients comparable to that in healthy subjects with type 1 diabetes. This accuracy is sufficient for effective closed-loop glucose control in subjects with type 1 diabetes, suggesting that the Navigator could also provide the input to a closed-loop blood glucose control device for use in the ICU.

875-P

Accuracy of a New Laser Technology Device for Non Invasive Measurement of Glucose in Man

CHIARA MOLINARI, ANDREA M. BOLLA, FERRUCCIO CERIOTTI, GAETANO A. DI TERLIZZI, FRANCESCA PERTICONE, PIETRO TROMBETTA, MARINA SCAVINI, EMANUELE BOSI, *Milan, Italy, Como, Italy*

A truly non invasive glucose monitoring would represent an outstanding advancement for the management of diabetes. Aim of this study was to test the accuracy of Glycolaser®, a new device for the non invasive glucose measurement based on an innovative laser technology. We studied 171 adults aged 47.2±16.9 yrs, 40.4% females: 31 controls, 136 patients with either type 1 or type 2 diabetes and 4 patients with hypoglycemia. Participants were studied on one occasion, either fasting (n=137) or in post prandial (n=34) conditions. Glycolaser® measurements were compared with plasma glucose assayed with the hexokinase method on a venous blood sample drawn simultaneously. Agreement of glucose measurements with the two methods was analyzed using: a) the bias plot (ISO limits: within ±15 mg/dl for glucose values <75 mg/dl and within ±20% for glucose values ≥75 mg/dl); b) the Clarke Error Grid; and c) the Parkes Error Grid. Forty-nine percent of Glycolaser® measurements were within the ISO limits (7.7% for glucose levels <75 mg/dl and 52.5% for glucose levels ≥75 mg/dl). The distribution of Glycolaser® measurements in the regions of the Clarke Error Grid was: A 47.4%; B 41.5%; C 1.7%; D 8.2%; E 1.2%, with 88.9% of Glycolaser® measurements in clinically acceptable regions (A+B). The distribution of Glycolaser® measurements in the regions of the Parkes Error Grid was: A 56.7%; B 33.3%; C 8.2%; D 1.8%; E 0%, with 90.0% of Glycolaser® measurements in clinically acceptable regions (A+B). Sex, age, fasting or postprandial condition did not influence Glycolaser® measurements. Although the accuracy of the present device is not yet fulfilling the ISO standards, the overall performance of the non invasive Glycolaser® is not far from that of the best invasive blood glucose meters currently on the market. The improvement of the performances of the Glycolaser® prototype is expected to make the accurate non invasive measurement of glucose achievable in the near future.

Supported by: Gulya Srl

876-P

WITHDRAWN

877-P

Sulfonylurea Treatment Without DPP4 Inhibitor is Associated With Higher Glycemic Variability by Continuous Glucose Monitoring System

MI YEON KIM, JI YOUNG JOUNG, SUN-MI PARK, YOON YOUNG CHO, SANG-MAN JIN, SE WON KIM, HYE JEONG KIM, SUNGHWAN SUH, JI CHEOL BAE, SUN WOOK KIM, MYUNG-SHIK LEE, MOON KYU LEE, KWANG-WON KIM, JAE HYEON KIM, *Seoul, Republic of Korea*

DPP4 (dipeptidyl peptidase-4) inhibitor is known to decrease glycemic variability compared to sulfonylurea. However glycemic variability in patient taking both sulfonylurea and DPP4 inhibitor has not been investigated yet. We conducted a retrospective study on 591 patients from Samsung Medical Center, Seoul, Korea who wore continuous glucose monitoring system (CGMS) to assess the association between glycemic variability and types of oral glucose lowering agents. Drugs were on stable dose for 3 months prior to CGMS. For the parameters of glucose variability, mean glucose, standard deviation (SD) of glucose, coefficient variation (CV%) and mean of the daily differences (MODD) were calculated from the CGMS data.Among them, 235 (39.8%) were using oral hypoglycemic agents without insulin (139 on sulfonylurea based therapy, 18 on DPP4 inhibitor based therapy, 46 only metformin and 32 on both sulfonylurea and DPP4 inhibitor). Indices of glycemic variability (SD total, CV%, MODD) were significantly increased in sulfonylurea based treatment group compared to metformin only group (p=0.010, 0.043, 0.018, respectively), when adjusted with sex, age, diabetes duration, C-peptide. However, DPP4 inhibitor based treatment group and sulfonylurea+DPP4 inhibitor group failed to show significant difference compared to metformin only group (Table 1).This result implies that sulfonylurea based treatment without DPP4 inhibitors can produce an increment in glucose variability which predicts the diabetic complications.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

Table 1. Estimated mean ± SE adjusted with sex, age, diabetes duration, C-peptide.

	SU based (n=139)	DPP4i based (n=18)	Metf only (n=46)	SU+DPP4i (n=32)
Mean	164.70 ± 3.42	166.32 ± 9.22	150.43 ± 6.12	162.91 ± 7.13
SD	47.47 ± 1.47*	40.63 ± 3.96	37.65 ± 2.63	44.37 ± 3.06
CV%	28.89 ± 0.73*	34.50 ± 1.98	24.72 ± 1.31	27.15 ± 1.53
MODD	44.96 ± 1.70*	40.23 ± 4.59	34.24 ± 3.04	41.86 ± 3.55

* p-value<0.05 compared to metformin only group.SU based, Sulfonylurea monotherapy or sulfonylurea with any other agent except DPP4 inhibitor; DPP4i based, DPP4 inhibitor monotherapy or DPP4 inhibitor with any other agent except sulfonylurea; SU+DPP4i, Sulfonylurea plus DPP4 inhibitor with or without any other agent.

878-P

Frequency of Inability to use A1C as Marker of Glycemic Control in Two Academic Diabetes Clinics

JANEFRANCES CHUKWU, KAREN WEILAND, KATHLEEN DUNGAN, IRL B. HIRSCH, DACE L. TRENCE, *Seattle, WA, Columbus, OH*

A1C is widely accepted as the standard measurement of glycemic control, despite the lack of this marker accurately representing the glycemic picture in patients with concurrent medical conditions. There are numerous reasons for invalid A1C levels. We report a chart review at two academic diabetes clinics (A, B) each with 300 consecutive patients, specific to reasons that would preclude the use of A1C.For both clinics, over 80% of patients were non-Hispanic white. In clinic A, 42 or 14% were found to have reasons precluding the use of A1C. In clinic B, 12 or 4% were identified. The distribution of reasons for each clinic are noted in Table 1. Additionally in clinic A, in 9 (3%), there was a mismatch between self-monitoring of blood glucose (criteria of minimum of 3 tests per day/ month for 2 months) and A1C based on the ADAG 95% confidence intervals.In conclusion, in academic diabetes clinics, there is considerable limitation in the ability of A1C measurement to be used as a tool that accurately reflects glycemic control among all patients with diabetes. Clinicians need to use caution when interpreting glycemic control for both individuals and their clinic or office population. Groups collecting metric measures as evidence of optimal care, should be aware of A1C limited accuracy.

Table 1

Comorbidities (as %)	Clinic A (n=42)	Clinic B (n=12)
anemia	64	50
hypertriglyceridemia (>500 mg/dl)	12	0
iron supplementation/EPO	10	8
reticulocytosis	7	0
alchohol use	5	17
cirrhosis	2	25

879-P

Correlation between Circadian Rhythm and Glycemic Control in Patients With Type 2 Diabetes

MASATO IWASAKI, FUMIHIKO SATO, TAKAHISA HIROSE, CHIHARU ITO, YUKI SOMEYA, RISAKO YAMAMOTO, JUNKO YOKOTA, RYOKO MINAKATA, YOSHIFUMI TAMURA, RYUZO KAWAMORI, HIROTAKA WATADA, *Tokyo, Japan*

Recently, it has come gradually clear that sleep disturbances have been shown to influence metabolic diseases, including diabetes. However, there is little evidence on the relationship between circadian rhythm and glycemic control in humans.This study investigated the circadian rhythm, quality of sleep, and glycemic control in 330 Japanese outpatients with type 2 diabetes mellitus. Blood samples were taken from the participants, and sleep disturbance was assessed using the Morningness-Eveningness Questionnaire (MEQ) and the Pittsburgh Sleep Quality Index (PSQI). The MEQ is a self-assessment questionnaire developed to evaluate circadian and sleep rhythm in individuals, and was used to classify the patient into either a morning or evening type. The PSQI is a self-administered questionnaire designed to evaluate sleep quality, where the higher the score, the worse the sleep quality. Of the 330 participants, 307 (93.0%) responded to the questionnaires. Of those responding, the mean age was 59.9 years, mean BMI was 24.5, and the mean sleep duration was 6.5 ± 1.12 hours. The MEQ scores classified the participants into five behavioral categories: definitively morning type (n = 11), moderately morning type (n = 98), neither type (n = 172), moderately evening type (n = 17), and definitively evening type (n = 0). The mean of the PSQI scores was 5.20 ± 2.83, with 40.8% of the participants scoring 6 or higher. Although the PSQI was not shown to be correlated with HbA1c values, the MEQ was shown to be significantly correlated with HbA1c values (r = 0.145, P = 0.017).Thefore, these data suggest that the closer to an "evening type" patient with type 2 diabetes is, the higher his or her HbA1c value will tend to be.

880-P

User Performance Evaluation of a New Blood Glucose Monitoring System

TIMOTHY S. BAILEY, ANN TIDEMAN, CARMINE GREENE, MARIA VIGGIANI, JI YU, SCOTT PARDO, JOAN LEE PARKES, *Escondido, CA, Tarrytown, NY*

The performance of a new blood glucose monitoring system (BGMS) that uses a new generation of blood glucose test strips (CONTOUR® NEXT* test strips) containing the flavin adenine dinucleotide-glucose dehydrogenase enzyme and a proprietary electron mediator was evaluated in a clinical trial in the hands of intended users. A total of 116 subjects aged 18 to 79 years with type 1 (n = 45), type 2 (n = 68), or type unknown (n = 3) diabetes participated. Using the labeling materials provided, untrained subjects learned to use the BGMS and performed a fingerstick self-test. Health care professionals (HCPs) also tested fingerstick samples from subjects on the BGMS. All BGMS results were compared to YSI reference results. Subjects completed a questionnaire assessing the ease of use of the BGMS and the user guide instructions. Overall, 100% of subject and HCP results met current ISO 15197:2003 criteria (Table 1); in addition, 99.1% of subject and 100% of HCP results met proposed more stringent guidelines. Regression analysis demonstrated >98% correlation between BGMS and reference results. Parkes Error Grid analysis showed that 100% of subject and HCP results were within Zone A. Questionnaire results showed that most subjects agreed or strongly agreed that the BGMS was easy to use (98.3%), user instructions easy to understand (88.8%), and meter display easy to read (99.1%) and see and understand the test results (100%). In conclusion, the new BGMS using the CONTOUR® NEXT test strips demonstrated a high level of accuracy and was perceived to be easy to use in the hands of its intended users, both people with diabetes and HCPs.*Not cleared in the US at time of submission.

Table 1. Results Within Current ISO 15197:2003 Criteria and Proposed More Stringent Criteria

Glucose concentration	Data comparison[a]	Number (%) of results within the specified error limits			
		±5 mg/dL	±10 mg/dL	±15 mg/dL	±20 mg/dL
<75 mg/dL	Subject vs YSI (n = 7)	6 (85.7%)	7 (100%)	7 (100%)[b]	7 (100%)
	HCP vs YSI (n = 7)	4 (57.1%)	7 (100%)	7 (100%)[b]	7 (100%)
		±5%	±10%	±15%	±20%
≥75 mg/dL	Subject vs YSI (n = 108)	83 (76.9%)	104 (96.3%)	107 (99.1%)	108 (100%)[b]
	HCP vs YSI (n = 108)	76 (70.4%)	104 (96.3%)	108 (100%)	108 (100%)[b]
		±5 mg/dL	±10 mg/dL	±15 mg/dL	±20 mg/dL
<100 mg/dL	Subject vs YSI (n = 33)	31 (93.9%)	33 (100%)	33 (100%)[c]	33 (100%)
	HCP vs YSI (n = 33)	25 (75.8%)	33 (100%)	33 (100%)[c]	33 (100%)
		±5%	±10%	±15%	±20%
≥100 mg/dL	Subject vs YSI (n = 82)	60 (73.2%)	78 (95.1%)	81 (98.8%)[c]	82 (100%)
	HCP vs YSI (n = 82)	56 (68.3%)	78 (95.1%)	82 (100%)[c]	82 (100%)

YSI, Yellow Springs Instruments; HCP, health care professional; ISO, International Organization for Standardization.
[a]Results for 1 subject were not included in the comparisons due to the protocol-defined time limit for blood processing being exceeded.
[b]Current ISO 15197:2003 criteria (ie, ≥95% of results shall fall within ±15 mg/dL or ±20% for samples with glucose concentrations <75 mg/dL and ≥75 mg/dL, respectively).
[c]Proposed more stringent criteria (ie, ≥95% of results shall fall within ±15 mg/dL or ±15% for samples with glucose concentrations <100 mg/dL and ≥100 mg/dL, respectively).

Supported by: Bayer HealthCare LLC, Diabetes Care

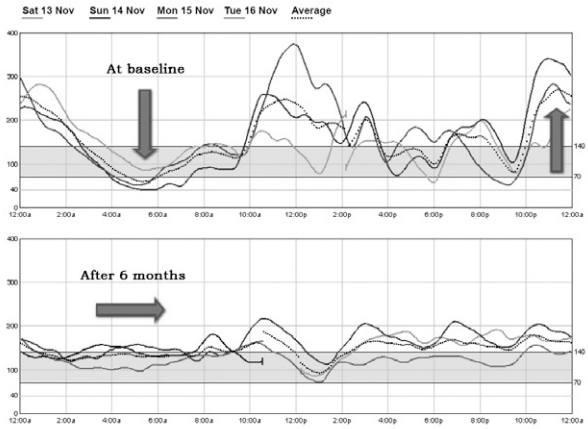
881-P

High Bed Time Glucose and Early Morning Low Sugars in Elderly Subjects With Type 2 Diabetes(T2DM): An Incidental Finding With Clinical Significance

JOTHYDEV KESAVADEV, ARUN SHANKAR, JAYASREE LALLY, GEETHU SANAL, GOPIKAKRISHNAN GOPALAKRISHNAN, SUNITHA JOTHYDEV, *Trivandrum, India*

With prolonged survival insulin becomes indispensible in T2DM.This study evolved out of an incidental finding during telemedicine follow up.In our center, patients are followed up via DTMS® (Diabetes Tele Management System) consisting of multidisciplinary team of doctors, dietitians, nurse educators etc. Patients report fasting, 2 hrs sugars after 3 main meals; modifications in dosages of medications and lifestyles are made over telephone/

internet periodically.An accidental but consistent observation of post dinner high sugars followed by relatively low fasting glucose in a subset of elderly with T2DM duration 13 ± 2.5 yrs, age 60 ± 7.4 yrs on twice daily biphasic insulin prompted us to perform CGM (Continuous Glucose Monitoring) in 10 patients which supported this finding.114 patients with this trend were started on basal bolus insulin regimen and followed up for 6 months. CGM (fig.1) & Quality of life using the Hypoglycaemic Fear Survey-II were analyzed at baseline & 6 months.There was 78.24% increase in fasting sugar compared to baseline. Post-dinner value decreased by 19.61% over a period of 6 months. 92% responded to therapy.Twice daily biphasic insulin being the commonest insulin regimen in T2DM, this finding will have robust clinical relevance, in this subset of elderly subjects where hypoglycemic unawareness is also described. We recommend maintaining safe post dinner values, avoiding early morning dip in glucose values by 'slow' up titration & intelligent choice of therapeutic regimens eg: basal bolus regimen/pump therapy as per comfort and affordability.



CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULIN DELIVERY SYSTEMS

Guided Audio Tour: Insulin Delivery Mechanisms *(Posters 882-P to 889-P), see page 13.*

882-P

Human Hyaluronidase + Rapid Analog Insulin (RAI) Improves Postprandial Glycemic Control in Type 2 Diabetes (T2DM) Compared to Insulin Lispro Alone

RICHARD M. BERGENSTAL, DAVID KLONOFF, TIMOTHY BAILEY, DANIEL E. VAUGHN, DOUGLAS B. MUCHMORE, *Minneapolis, MN, San Mateo, CA, Escondido, CA, San Diego, CA*

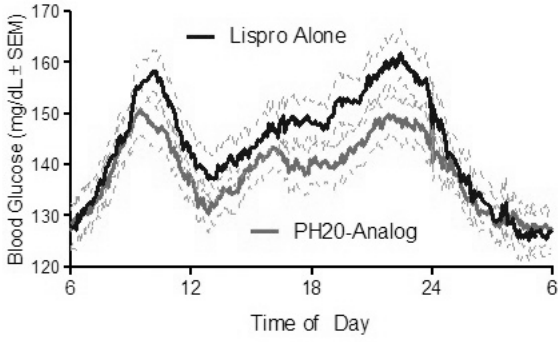
Recombinant human hyaluronidase (rHuPH20) accelerates absorption & action of prandial insulins. We compared control in T2DM using insulin lispro or RAI+rHuPH20 (Analog-PH20). After a 4-6 week run-in using prandial glulisine + bid glargine, 121 subjects (Age 59±9.9 yrs, BMI 35.2±4.4, A1C 7.1±.5) were randomized (double blind crossover) to either lispro+rHuPH20 or aspart+rHuPH20 vs insulin lispro alone for two 12 week intensive management periods; prandial doses were immediately before meals. Primary endpoint of A1C noninferiority (.4% margin) was achieved with no treatment difference (95% CI -.12, +.05). Mean postmeal (90 min) excursions were reduced by 21% (p=.0001) over the 12 week period with more subjects consistently at AACE/IDF goals (2 hr BG <140 mg/dL (Table).

Percent of subjects consistently achieving PPG goal*

	Analog-PH20	Lispro	p-value
Breakfast	56.3	35.7	.0006
All Meals	45.2	28.0	.0007

* at least 2/3 of meals during 3 days of scheduled SMBG profiles at the end of each treatment

Continuous monitoring over 3 days at the end of treatment showed improved excursion profiles with reduced glycemia throughout daytime hours (Figure). Hypoglycemia rates were comparable between treatments as were total daily insulin dose (123±67 for Analog-PH20 vs 127±69 U for lispro, p=.31) and weight gain difference (.47 lb less gain on Analog-PH20, p=.43). Adverse event rates were comparable, and Analog-PH20 was well tolerated.



883-P

Reducing Intramuscular (IM) Insulin Injection Risk: Evidence-Based Recommendations

LAURENCE HIRSCH, MICHAEL GIBNEY, *Franklin Lakes, NJ*

Needle lengths for subcutaneous (SC) insulin therapy are 12.7 to 4 mm. Recent injection technique recommendations advocate using needles 4-6 mm to reduce pain and risk of IM injection, which may alter insulin uptake and cause hypoglycemia. Skin thickness (ST) and subcutaneous fat thickness (SCT) were shown to vary by body site; ST varies minimally by age, race, gender, or BMI. SCT is more variable and is increased with higher BMI, in females, and at the abdomen and buttocks. This analysis describes IM injection risk at insulin injection sites, related to needle length. ST and SCT were measured by high-frequency ultrasound at the arm, thigh, abdomen and buttock in adults with diabetes (N=388; 55% male, 18-85 yrs, BMI 19.6-64.5 kg/m^2). Depth of drug delivery was calculated for different length needles and insertion angles. Risk factors for IM insertion were evaluated by logistic regression. IM injection risk is inversely related to BMI and greater in males (each p<.001). With the most commonly-used 8 mm needle inserted at 90°, IM risk is greatest in the thigh (27.5%) and least in the buttocks (3.6%), p<.001. The thigh - the 2nd most frequently used injection site - has greater risk than other body sites (p<.001). Angled insertion (45°) reduces risk ≥50%, but does not eliminate it. IM risk is much reduced (p<.001) with 4 mm needles vs all other lengths (1.5% thigh, 0% other sites). Needle length, along with insertion method and body site, are important factors affecting IM insulin injection risk. Clinicians, educators and patients should consider these, to reduce variability of insulin delivery and of glycemic control.

Calculated Risk of IM Injection by Body Site, Needle Length, and Injection Angle

Needle Length	Injection Angle	Thigh	Arm	Abdomen	Buttock
4mm	90	1.5%	0%	0%	0%
4mm	45	NA	NA	NA	NA
8mm	90	27.5%	18.6%	8,1%	3.6%
8mm	45	7.7%	4.5%	1.9%	1.6%
12.7mm	90	60.4%	52.7%	37.2%	24.0%
12.7mm	45	35.5%	26.7%	11.7%	6.4%

Supported by: Becton Dickinson

884-P

Glycaemic Control and Variability in Type 1 Diabetic Patients With A1c Below 8% Treated by Insulin Pump is Better When Intra-Peritoneal Infusion is Chosen

MARIE JOSÉE DUPUIS, MARIANNE RIBOTTON, JÉROME PLACE, LOUIS MONNIER, ERIC RENARD, ANNE WOJTUSCISZYN, *Lévis, QC, Canada, Montpellier, France*

The aim of our study was to evaluate the glycaemic variability in type 1 diabetic (T1D) patients treated by continuous insulin infusion (CII) either by intraperitoneal (IP) or sub cutaneous (SC) pump with A1c below 8%.Continuous Glucose Monitoring System (CGMS®) recordings were performed in 30 T1D patients treated by CII IP (n=16) and SC (n=14) who had a stable A1c below 8%. The glucose variability was evaluated by calculating SD, MAGE and MODD for the global, intra-day and inter-day variability, respectively. Time spent in dysglycaemia (>180mg/dL or <70mg/dL) was also noticed on recordings. Hypoglycaemia sensing threshold was noted. t -test was used for statistical analysis.HbA1c was 7,0±0,5,% lower in IP than in SC treated patients (6,7±0,6 vs 7,2± 0,4 %; p=0,02) consistent with time spent in hyperglycaemia (4.30 hrs vs 7hrs per day ;p=0,01). Patients still experimented

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

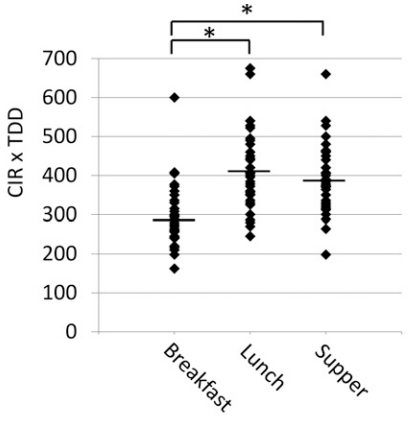
23,0±14,5 hypoglycaemia/month on self monitored blood glucose data. Out of them, 5,8±7,9 hypoglycaemic events were <50mg/dl. Time spent in hypoglycaemia was about 2hrs per day (9,2 ± 7,3% of time) without statistical difference between the two ways of insulin infusion or the level of HbA1c (&lt or &gt to 7%). Hypoglycaemia sensing threshold was globally low: 0,55±0,21: 59±19 (SC) vs. 48±22 mg/dl (IP) (p= 0.19). Glycaemic variability was still high in all patient but lower in IP vs SC treated patients: SD was at 55±12 mg/dL (60±12 SC vs 50±9 IP; p= 0,01), MAGE at 149±40mg/dl (163±46 SC vs. 132±23 IP ;p= 0,03) and MODD was at 58±17 mg/dL (66±16 SC vs 50±13 IP ; p= 0,01). These index were statistically similar in patients with A1c &lt or &gt to 7%.Our data demonstrated that well-controlled T1D patients on A1c criteria are still presenting a high glucose variability with numerous and dangerous hypoglycaemia. IP CII is better than SC CII with a better control of high glucose excursion a better hypoglycaemia sensing, reaching a better HbA1c with lower glucose variability.

885-P

Carbohydrate-to-Insulin Ratio is Calculated to be 300–400 Divided by Total Daily Insulin Dose in Type 1 Diabetic Patients Who Are on Insulin Pump Therapy

AKIO KURODA, TETSUYUKI YASUDA, MITSUYOSHI TAKAHARA, FUMIE SAKAMOTO, RYUUICHI KASAMI, KAZUYUKI MIYASHITA, TAKA-AKI MATSUOKA, SUMIKO YOSHIDA, ERI KONDO, ITSURO ENDO, KEN-ICHI AIHARA, HIDEAKI KANETO, TOSHIO MATSUMOTO, IICHIRO SHIMOMURA, MUNEHIDE MATSUHISA, *Tokushima, Japan, Suita, Japan*

Objectives: To determine bolus insulin dose, carbohydrate-to-insulin ratio (CIR) is widely calculated from the formula, i.e., CIR = 500/Total daily insulin dose (TDD) throughout the day. However, this formula has not been validated yet. Therefore we investigated CIR in type 1 diabetic patients (T1DM) treated with insulin pump after adjustment of proper basal insulin rate.Research Design and Methods: Forty-five T1DM without detectable C-peptide were investigated during several weeks of hospitalization. The patients were served standard diabetic diets (25-30 kcal/kg ideal body weight) in which carbohydrate content was identical in each meal. Target blood glucose levels were set at 5.6 mM before each meal and 8.3 mM at 2 hours after each meal. Basal insulin rate was confirmed during each meal omission. After basal insulin rate was fixed and target blood glucose levels were achieved, TDD and CIR were collected, and CIR x TDD was calculated in each meal. Results: Mean blood glucose before meals and 2 hours after meals were 6.7±2.4 and 8.3±3.4 mM respectively. TDD was 31.5±9.0 (means ± SD) units. CIR x TDD at breakfast was significantly lower than those at lunch and supper (288±73 v.s. 408±92 and 387±83, *:p<0.001).Conclusions: CIR has diurnal variance and is approximately calculated from the formula CIR =300-400/TDD in T1DM on insulin pump.



Supported by: Japan Diabetes Foundation

886-P

Acceleration of Insulin Action by Infusion Site Warming

EDA CENGIZ, STUART WEINZIMER, JENNIFER SHERR, EILEEN TICHY, MELODY MARTIN, LORI CARRIA, WILLIAM TAMBORLANE, *New Haven, CT*

The Yale Ultra-Fast Acting Insulin Project was undertaken to explore ways to accelerate the time action profiles of rapid-acting insulin analogs to improve performance of closed and open-loop insulin delivery. With the euglycemic clamp technique, we previously reported that warming the skin around the insulin infusion site to 38.5ºC with the InsuPatch ($IP_{38.5}$) results in an earlier time to peak insulin action (T_{GIRmax}) as compared to control clamps without IP activation (No IP) for a 0.2 unit/kg bolus of aspart insulin. To examine whether the time action profile of aspart insulin could be accelerated further by increasing IP temperature to 40ºC (IP_{40}), paired clamps (IP_{40} vs. No IP) using the identical protocol have been performed in 5 adolescents with type 1 diabetes (T1D) and results compared to those in 13 adolescents with T1D previously studied with $IP_{38.5}$. There were no significant differences in the maximum glucose infusion rate (GIR_{max}) or the overall area under curve for GIR ($AUC_{GIR\ 0\text{-}300min}$) between IP_{40}, $IP_{38.5}$ and No IP In contrast, skin warming with IP_{40} and $IP_{38.5}$ reduced the time to reach half maximum ($T_{early50\%}$) and maximum GIR (T_{GIRmax}) and increased $AUC_{GIR\ 0\text{-}90min}$; effects that were greater with IP_{40} vs. $IP_{38.5}$. Our preliminary results indicate that skin warming accelerates the early pharmacodynamic action of subcutaneously injected insulin and suggest that the effect is accentuated by increasing the warming temperature within the approved range for skin warming devices.

	IP40ºC	**IP 38.5ºC**	**No IP**
Number of subjects	5	13	18
GIR_{max} (mg/kg/min)	10±3	7.9±1	7.6±1
$T_{early\ 50\%}$ (min)	**34±4***	**40±3§**	**59±3**
T_{GIRmax} (min)	**66±2*δ**	**90±5§**	**119±6**
$AUC_{GIR\ 0\text{-}300min\ (mg/kg)}$	1266±190	1280±117	1128±81
$AUC_{GIR\ 0\text{-}90min\ (mg/kg)}$	520±97	**354±40§**	274±27

* p=0.02-0.006 IP_{40} vs. 5 paired No IP control studies, § p=0.01-0.001 $IP_{38.5}$ vs. 13 paired No IP control studies, δ p=0.02 IP_{40} vs. $IP_{38.5}$. Data are presented in mean±SEM.

887-P

Improved Pancreatic Beta Cell Function in Type 2 Diabetes During Long-Term Continuous Subcutaneous Insulin Infusion Therapy

SOO B. CHOI, HYUN JU AN, KYUNG JIN KIM, YUN H. NOH, *Chungju, Republic of Korea, Seoul, Republic of Korea*

Type 2 diabetes is characterized with impaired beta cell function and reduced beta cell mass which deteriorate over time. To see if beta cell function can be improved in type 2 diabetic patients through long-term continuous subcutaneous insulin infusion (CSII) therapy, we examined changes in serum C-peptide levels during the treatment.We discontinued oral antidiabetic drugs (OADs) and applied CSII therapy to subjects with type 2 diabetes who had failed to control hyperglycaemia with OADs and/or insulin injections (number, 228 with 57% of male; age, 58.2 ± 11.1 years; duration, 9.0 ± 6.5 years; HbA1c 8.8 ± 2.0%). Blood samplings were performed yearly for 5 years at 12 hour-overnight fasting and 30 and 120 minutes after ingestion of a standard mixed meal (500 kcal; carbohydrate 52.9%, lipid 30.4%, protein 16.7%) with at least 9 hours cessation of CSII.During the 5 year-CSII treatment, the mean HbA_{1c} significantly decreased from 8.8 ± 2.0 % to 7.1 ± 1.1% ($p < 0.001$) and the mean serum C-peptide level at 120 minutes after meal ingestion significantly increased from 4.56 ± 2.27 to 5.72 ± 2.20 ng/ml ($p < 0.001$). The C-peptide increment from fasting to 120 minutes after meal also increased by 2.91 ± 2.00 ng/ml after 1 year-CSII therapy, 3.50 ± 1.90 ng/ml after 2 years 3.74± 1.90 ng/ml after 3 years, 4.02 ± 2.02 ng/ml after 4 years, and 4.15 ± 1.91 ng/ml after 5 years respectively.The resolution of glucotoxicity and maintenance of euglycaemia through long-term CSII therapy may contribute to the restoration of beta cell function in terms of serum C-peptide level after meal in type 2 diabetic patients.

Supported by: Novo Nordisk

888-P

Health Outcomes of Switching from Vial to Disposable Pen Among Type 2 Diabetes Patients Treated With Insulin Glargine

LIN XIE, STEVE ZHOU, WENHUI WEI, JASVINDER GILL, CHUNSHEN PAN, ONUR BASER, *Ann Arbor, MI, Bridgewater, NJ, Boca Raton, FL*

Disposable pen may facilitate insulin administration better than vial and syringe methods for patients with type 2 diabetes mellitus (T2DM). This retrospective database study evaluated outcomes associated with switching from insulin glargine vial to pen (i.e. SoloSTAR®) among patients with T2DM. Patients were identified from IMPACT®, a national managed-care database. Endpoints included 1-year follow-up persistence (remaining on treatment without discontinuation) and adherence (adjusted medication possession ratio [aMPR]), daily average consumption (DACON) of insulin, glycemic control (A1C), incidence of hypoglycemia, and health care costs. From 2007 to 2010, "Switchers", who switched to pen use after ≥2 prior vial usages, were compared to "Continuers", who continued using vial only. Cohorts were

matched by 1:1 propensity score matching to compare 1-year outcomes (603 patients in each cohort, mean age 53 years, 43% women). During follow-up, treatment persistence was higher in Switchers than in Continuers (65.3% vs 49.8%; P<0.0001), as was adherence (aMPR: 0.79 vs 0.76; P=0.0173). Between Switchers and Continuers, there were no differences in DACON (42.8 vs 42.3; P=0.7757), change in A1C from baseline (-0.03 vs -0.11; P=0.4577), incidence of hypoglycemia (10.8% vs 11.6%, P=0.6479), or total health care costs ($20,870 vs $20,747; P=0.9434), despite higher diabetes-related drug costs ($3,393 vs $2,889, P<0.0001). Switching to pen use, baseline use of rapid-acting insulin via pen, higher baseline DACON, and higher baseline-adjusted MPR were all associated with higher persistence (all P<0.0001). This real-world study showed that switching from vial to pen for insulin glargine administration increased treatment persistence and adherence with similar clinical outcomes, but at no increase in total health care costs. Further analysis is needed to assess why persistence was better for pen than vials. These results may assist with optimizing T2DM management.

Supported by: sanofi-aventis

889-P

Accelerating Rapid Acting Insulin Analogs Pharmacokinetic Profile by Using CSII With the InsuPatch Device

DAVID C. KLONOFF, IRINA NAYBERG, JOANN DAVID, ZOHAR LANDAU, DMITRY FELDMAN, ALEXANDER SHUSTERMAN, JULIO WAINSTEIN, DAN LENDER, OFRI MOSENZON, ITAMAR RAZ, *San Mateo, CA, Holon, Israel, Jerusalem, Israel*

The pharmacodynamics (PD) and pharmacokinetics (PK) onset profiles of current short acting insulin analogs are slower than what is needed. The InsuPatch device was developed in order to accelerate insulin PK profile by applying controlled mild heat to an insulin infusion site. This heat increases local blood flow which can induce faster insulin absorption from the infusion site. The aim of this study was to test the effect of the InsuPatch device on the PK profile of subcutaneously infused short acting insulin analogs in a series of euglycemic clamp studies.Fifty six subjects with Type 1 diabetes on insulin pump therapy were enrolled to the study (mean age 33.4±13.5years, 23 female, HbA1c 7.75±0.85%), 55 subjects completed the study. Each subject had 3 clamp procedures: 2 with the InsuPatch device on day 1 and day 3 of a 3-day infusion set cycle, and 1 without the device on day 1 of the infusion set cycle. At the beginning of the clamp subjects received an insulin bolus of 0.15 IU/Kg subcutaneously followed by an i.v. glucose infusion to sustain a euglycemic state.Results: Use of the device increased blood insulin levels during the first hour as measured by the amount of insulin under the curve during the first hour, AUC1HR. The AUC1HR was found to increase by 29.7 ± 7 % (median) when the device was used (P<0.012%) when comparing day 1 under control and test conditions. The peak concentration of insulin was significantly higher when the InsuPad device was used (with InsuPatch on day 1: 57.0 ± 28.7 mIU/L; with InsuPatch on day 3: 70.4 ± 40.8 mIU/L; without InsuPatch on day 1: 47.6 ±19.3 mIU/L p<0.008 [day 1 test vs. control]).Summary: Use of the InsuPatch device was found to accelerate the insulin PK profile. The results suggest that the InsuPatch device might improve post meal glycemic control in diabetic subjects using short acting insulin analogs.

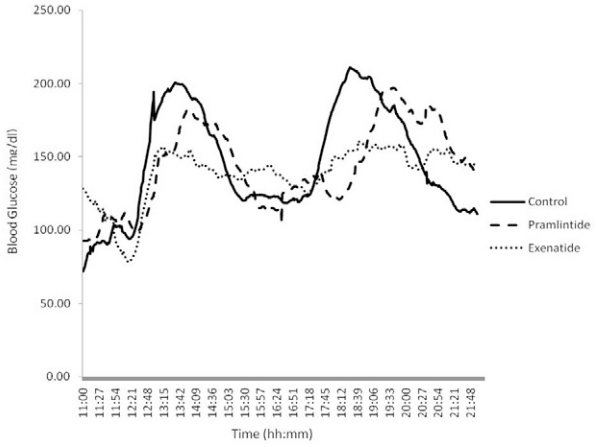
Guided Audio Tour: Closing the Loop *(Posters 890-P to 895-P), see page 13.*

890-P

Closed Loop System in Conjunction With Pramlintide and Exenatide Improves Post-Prandial Hyperglycemia

NEESHA RAMCHANDANI, VENKAT S. RENUKUNTLA, MARTIN CANTWELL, RUBINA A. HEPTULLA, *Bronx, NY, Northridge, CA*

The closed loop (CL) system mimics physiologic insulin delivery. However, it fails to correct post-prandial hyperglycemia with glycemic peaks >200 mg/dl. We hypothesized that adjunctive therapy with glucagon suppressors pramlintide or exenatide would attenuate post-prandial hyperglycemia seen with insulin monotherapy using the Medtronic ePID CL system. Five subjects with T1DM (4F, average age = 27.5 ± 2.7 yrs, diabetes duration 15.7 ± 6.4 yrs, HbA1c = 7.1 ± 1.2%, BMI = 26.1 ± 3.2 kg/m^2) were randomized in a crossover design to receive either 1) CL alone, 2) CL + Pramlintide, or 3) CL + Exenatide. Subjects were admitted overnight, the CL system commenced at 6 am, and adjunctive study medications were given before lunch (12 pm) and dinner (5 pm) and their effects monitored for 5 hours after each meal. Results: Compared to the CL only arm, the 10-hour mealtime glycemic profile (12 pm - 10 pm) was significantly better in the CL + Pramlintide (p<0.02) and CL + Exenatide (p<0.009) arms. There was no significant hypoglycemia after meals with either pramlintide or exenatide. Additionally, the mealtime glycemic profile was better in the CL + Exenatide arm compared to the CL + Pramlintide arm (p=0.008). This was achieved without any increased risk of hypoglycemia. Conclusion: Both pramlintide and exenatide appear to attenuate meal-related hyperglycemia seen with insulin monotherapy in the ePID CL system, with exenatide having a more significant positive effect than pramlintide.



Supported by: NIH

891-P

Effect of a Hybrid Closed-Loop (HCL) on Restoring Metabolic Control at the Onset of Diabetes

BRUCE BUCKINGHAM, ROBERT SLOVER, STUART WEINZIMER, LINDA A. DIMEGLIO, ANDREW BREMER, MARTIN CANTWELL, DONGYUAN XING, KATRINA RUEDY, DIABETES RESEARCH IN CHILDREN NETWORK (DIRECNET), TRIALNET STUDY GROUP, *Stanford, CA, Denver, CO, New Haven, CT, Indianapolis, IN, Nashville, TN, Northridge, CA, Tampa, FL*

The purpose was to determine if hybrid closed-loop (HCL) control within one week of diagnosis of type 1 diabetes would stabilize glucose levels, and if this effect could be maintained on discharge to home using sensor-augmented insulin pump (SAP) therapy. Subjects between the ages of 6 to 45 were recruited at 5 centers to be randomized in a two-to-one ratio to either intensive diabetes management or standard care within 1 week of diagnosis. The intensive group was admitted for at least 3 days of HCL control using the Medtronic MiniMed ePID algorithm with one-on-one nursing and physician supervision. The algorithm uses q min glucose sensor readings to determine q minute pump insulin doses based on the present glucose, glucose rate of change, and pending insulin action. Reference blood glucose (RBG) (YSI, HemoCue or GlucoScout) was measured q 30 minutes. Subjects were given 75-80% of an estimated meal bolus 0 to 20 minutes before eating. There were no dietary restrictions. Subjects were discharged on a Revel™ SAP system. Fifty subjects aged 7 to 37 years were randomized to HCL. On initiation of HCL therapy the mean RBG/SG was 239/237 mg/dl. The mean RBG/SG level improved by day 3 of HCL Rx to 140/139 mg/dl (p <0.001 for both). During HCL therapy, the median percentages of RBG/SG values ≤50 mg/dl =0.0%/0.0%, ≤70 mg/dl = 0.7/1.6%, 71-180 mg/dl = 82/80%, >200 mg/dl = 10/10% and > 250 mg/dl = 2.1/2.0%. There were no episodes of seizures, loss of consciousness or DKA. During the first week at home the mean SG level was 131 mg/dl. The mean total daily insulin dose was 1.2 units/kg on day 1 of HCL therapy, 1.2 units/kg on day 3 of HCL therapy, and 0.8 units/kg 2 weeks after discharge. In summary, HCL therapy can be safely implemented at multiple centers, with rapidly improved glucose levels observed within three days of HCL. In addition, near-normal glycemic control was maintained in the home setting using SAP therapy in the week following discontinuation of HCL therapy.

892-P

Safety of Nighttime 2-Hour Suspensions of Basal Insulin in Pump-Treated Type 1 Diabetes (T1D) Even in Absence of Low Glucose

JENNIFER L. SHERR, MILADYS M. PALAU COLLAZO, LORI R. CARRIA, AMY T. STEFFEN, MELINDA ZGORSKI, KATE WEYMAN, EILEEN M. TICHY, EDA CENGIZ, WILLIAM V. TAMBORLANE, STUART A. WEINZIMER, *New Haven, CT*

The low glucose suspend feature of the Medtronic Veo sensor-augmented pump system automatically interrupts the basal insulin infusion for up to 2 hours (hrs) if patients fail to respond to low glucose alarms; a feature aimed at preventing prolonged hypoglycemia, especially at night. Concerns that failing sensors with falsely low glucose levels could lead to ketosis due to

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

inappropriate suspension of basal insulin when actual glucose levels are elevated has delayed approval of this system in the U.S.. We enrolled 8 subjects with T1D (age 22±2 yr, T1D duration 10±5y, A1c 7.2±0.5) in a study examining the safety of nighttime 2 hr basal suspension over a range of starting blood glucose (BG) levels. During the study period, subjects measured blood beta hydroxybutrate (BHB) and BG levels each night at 9PM and the next morning at 8 AM before breakfast. On half of the nights, the basal insulin infusion was not suspended. On other nights the basal insulin infusion was programmed to include a zero basal rate for 2 hrs at random times after 11:30PM (e.g., 1:30-3:30AM or 2-4AM). To date, during 56 suspend and 66 non-suspend nights (Table) BG levels were similar at 9 PM on suspend versus non-suspend nights but increased by ~50mg/dL the next morning on suspend nights. There was no difference in 9PM BHB levels. Furthermore, there were no statistically significant or clinically important differences in BHB levels at 8AM. These preliminary data suggest that systems that suspend basal insulin infusions for 2 hrs are safe and should not lead to clinically significant ketonemia even if BG is elevated at the time of the suspension.

	Suspend Nights (n=56)	Non-Suspend Nights (N=66)	p-value
Blood glucose (mg/dL) Mean±SD			
9PM	148±67	175±103	0.31
8AM	201±73	154±85	0.0005
Beta Hydroxybutrate (mmol/L) Mean±SD			
9PM	0.06±0.07	0.07±0.10	0.91
8AM	0.14±0.14	0.08±0.10	0.07

Supported by: JDRF (22-2009-799), NIH (R01 DK085618, UL1 RR024139, P 30 DK045735)

893-P

The Use of the MD-Logic Remote Safety System During Outpatient Closed-Loop Study at a Diabetes Camp

MOSHE PHILLIP, THOMAS DANNE, TADEJ BATTELINO, THE DIABETES WIRELESS AP CONSORTIUM (DREAM), *Petah Tikva, Israel, Hannover, Germany, Ljubljana, Slovenia*

Artificial pancreas (AP) system is currently studied in clinical research centers when only few patients are connected simultaneously to the system. AP needs to be evaluated in outpatient conditions on a large group of patients during several months before it can be available for clinical use. In order to assure patients' safety and to monitor the AP effectiveness, we developed the MD-Logic Safety & Remote system (MDSR) which offers an additional safety layer to the AP. The MDRS provides an opportunity to remotely supervise multiple patients and their real-time glycemic control using a safe internet connection. In addition, it alarms on technical and safety problems from the AP, insulin pump and sensor. The MDRS has been used during transitional cross-over outpatient study comparing the MD-Logic AP (MDLAP) to sensor augmented pump therapy at a diabetes camp during a multi-center and multinational study in Germany, Slovenia and Israel (the DREAM project). Eighteen children and adolescents were connected in a diabetes camp in Slovenia to the MDRS for two consecutive nights. Results show that overnight time below 3.5mmol/l significantly decreased (P<0.04) and time within 3.5-7.8mmol/l significantly increased (P<0.04) during closed-loop compared to control nights. Performance analysis of the MDRS system shows that 99.9% of data sent from the patients' PC to the MDRS, was received within 10 seconds. There were 1.1±1.6 safety alarms per patient per night. Seventy five percent out of 20 safety alarms were related to sensor accuracy issues which were resolved by manual calibration of the sensors. The average number of technical alarms was 3±2.5 per patient per night; one third of them were related to communication problem between the patients' PC and the insulin pump which were remotely resolved by the study team. The MDRS system was proven to be safe and efficient in supporting outpatient studies with artificial pancreas system.

Supported by: sanofi-aventis

894-P

The Use of Automated, Ambulatory Glucose Control System for Overnight Glucose Control in Adolescents With Type 1 Diabetes

MICHAEL J. O'GRADY, ADAM RETTERATH, D. BARRY KEENAN, NATALIE KURTZ, MARTIN CANTWELL, GLENN SPITAL, MICHAEL N. KREMLIOVSKY, ANIRBAN ROY, ELIZABETH A. DAVIS, TIMOTHY W. JONES, TRANG T. LY, *Perth, Australia, Northridge, CA*

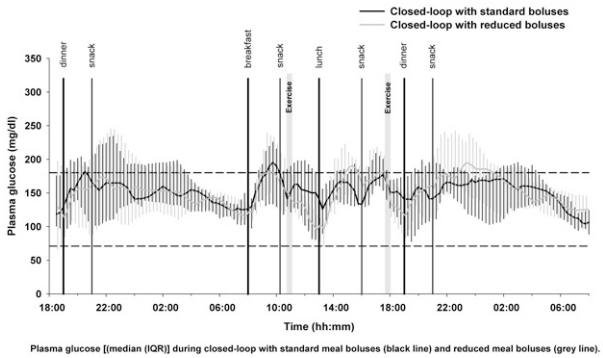
The Medtronic Portable Glucose Control System (PGCS) is an ambulatory system consisting of two subcutaneous glucose sensors (Enlite), the Proportional-Integrative-Derivative (PID) control algorithm operating on a BlackBerry® platform, ISM to Bluetooth radiofrequency (RF) translator and an off the shelf Veo insulin pump. Interstitial fluid sensor glucose is measured once per minute. The BlackBerry smartphone receives sensor data via the RF translator, calculates insulin recommendation based on PID algorithm and sends delivery commands to the pump via the translator. The system is calibrated using fingerstick blood glucose every 12h or on demand. Remote monitoring can be enabled by data transmission over cellular network.The aim of this study was to determine the efficacy and safety of a fully automated, ambulatory overnight glucose control system. Adolescents with type 1 diabetes were admitted over 2 consecutive nights for overnight glucose control. PGCS closed-loop mode was commenced 3h after the evening meal following fingerstick blood glucose calibration. Subjects were monitored with venous glucose samples obtained every 30min and analysed by glucose oxidase technique. Investigator intervention occurred if plasma glucose levels were <50mg/dL or >270mg/dL.To date, 8 subjects (age 16.0±3.9y, HbA1C 7.2 ±1.1%, diabetes duration 9.2±6.4y, pump duration 4.9±2.7y) have completed 16 nights. The system maintained mean YSI plasma glucose values of 114±30mg/dL and plasma glucose values between 70-180mg/dL were achieved 89.6% of the time in closed-loop mode. The proportion of time sensor glucose values were within 70-180 mg/dL was greater for closed loop than open loop (92.8% vs 62.8%; p <0.0001) and time spent <60mg/dL was also less (0.9% vs 3%; p<0.0001). Preliminary results suggest that PGCS is safe and effective in achieving overnight glucose control in adolescents with type 1 diabetes.

895-P

Closed-Loop (CL) Insulin Delivery With Reduced Meal Insulin Bolus to Minimize Risk of Postmeal Hypoglycemia in Adolescents With Type 1 Diabetes (T1D)

DANIELA ELLERI, JANET M. ALLEN, MARTINA BIAGIONI, KAVITA KUMARESWARAN, LALANTHA LEELARATHNA, KAREN CALDWELL, MARIANNA NODALE, MALGORZATA E. WILINSKA, PETER CALHOUN, CRAIG KOLLMAN, CARLO L. ACERINI, DAVID B. DUNGER, ROMAN HOVORKA, *Cambridge, United Kingdom, Tampa, FL*

Hybrid CL, coupling automated basal insulin delivery with manual premeal boluses, may lead to postmeal hypoglycemia. We evaluated hybrid CL with reduced meal boluses in 8 adolescents with T1D [M 3; age 15.9±1.5yrs; A1C 8.9±1.6%; mean±SD; total daily dose 0.9(0.7, 1.1)U/kg/d; median (IQR)] studied at a research centre for 36h on two occasions in a cross-over design. Subjects were randomised to CL with either standard insulin boluses calculated using subjects' pump bolus calculator or CL with boluses reduced by 25%. Boluses were given before main meals (50-80gCHO) but not with snacks (15-30gCHO). Between-meal insulin pump delivery was manually adjusted every 15min as per advice of a model-predictive-control algorithm informed by a real-time continuous glucose monitor. Subjects undertook moderate-intensity exercise on a stationary bicycle at 140bpm heart-rate for 20min (morning and afternoon). Total insulin delivery was lower with reduced boluses [61.9 (55.2, 75.0) vs 72.5 (63.6, 80.3) U/36h, p=0.01]. Plasma glucose was identical 151±16mg/dl on the two occasions. Time spent in target glucose 71-180mg/dl was 80(65, 96)% with standard vs 74(66, 84)% with reduced bolus (p=0.87). Time above 180mg/dl was 18(4.1, 34.2)% vs 21.8(16.3, 33.5)% (p=0.87) and time below 70mg/dl was 0(0, 1.8)% vs 0(0, 1.5)% (p=0.88). Hypoglycemia occurred once within 1.5h postmeal during CL with standard bolus. In conclusion, CL with 25% reduction of meal boluses was not statistically different from CL with standard boluses apart from reduced overall insulin delivery in adolescents with T1D.



Plasma glucose [(median (IQR)] during closed-loop with standard meal boluses (black line) and reduced meal boluses (grey line).

Supported by: NIH (1R01DK085621-01)

896-P

LY2605541: Leveraging Hydrodynamic Size to Develop a Novel Basal Insulin

RYAN J. HANSEN, GORDON B. CUTLER, JR., ANDREW VICK, ANJA KOESTER, SHUN LI, ANGELA M. SIESKY, JOHN M. BEALS, *Indianapolis, IN, Chesterfield, MO*

Improvements in basal insulins have focused primarily on slowing subcutaneous (SC) release; however, exogenously administered insulin is prone to glomerular filtration and therefore to significant renal clearance.To develop a novel basal insulin analog with the goal of both slowing SC absorption and reducing renal clearance, insulin lispro was site-specifically and covalently modified with a 20-kDa polyethylene glycol (PEG) moiety at lysine B28, via a covalent urethane bond, increasing the hydrodynamic size. Dynamic light scattering analysis indicated that PEGylated insulin lispro (LY2605541 [LY]) had a hydrodynamic diameter of 7.8 ± 0.4 nm, a diameter 4x larger than insulin lispro and analogous to the size of a ~75kDa globular protein.In rats treated with streptozotocin to induce diabetes, LY's increased hydrodynamic size resulted in a robust dose response profile with slowed absorption from the SC site, exemplified by a shift in T_{max} (~25x), and reduced clearance (~10x) with concomitant glucose-lowering properties. The 5/6th nephrectomized rat model was used to assess the impact of PEGylation on renal clearance of the molecule. Comparing 5/6th nephrectomized rats with sham controls, no renal clearance differences were observed with LY whereas insulin lispro clearance was reduced. Based upon these preclinical PK/PD data, human plasma profiles were modeled for once-daily dosing of LY. The model predicted gradual attainment of steady-state plasma LY levels with a peak-to-trough ratio of <1.5.In conclusion, LY2605541 was designed to have a large hydrodynamic size which slows insulin absorption and reduces renal clearance. LY demonstrated prolonged duration of action in preclinical studies. These effects formed the basis for further pursuit of LY as a novel basal insulin, wherein subsequent development confirmed the prolonged PK/PD profile in Phase I-II studies.

Supported by: Eli Lilly and Company

897-P

Intervention Needed to Optimize Insulin Pump Use

KIMBERLY A. DRISCOLL, SUZANNE B. JOHNSON, JORDAN CUEVAS, ELIZABETH GILL, NANCY WRIGHT, LARRY C. DEEB, *Tallahassee, FL*

Insulin pumps are unique because they permit objective measurement of several behavioral indicators of insulin adherence. Insulin pump adherence is comprised of four fundamental blood glucose monitoring-insulin bolus behaviors (BGM-BOLUS): 1) blood glucose monitoring (BGM), 2) insulin bolusing, and the sophisticated relationship between BGM and insulin bolusing (hereafter referred to as BGM-BOLUS LINK behaviors): 3) BGM before insulin bolusing; and 4) insulin bolusing following a high (150-249 mg/dL) or very high (>250 mg/dL) BGM reading. Data were downloaded from the MiniMed Paradigm insulin pumps of 49 children and adolescents (Mage = 13.35 years + 2.92; range = 7.79-19.12) with type 1 diabetes. In addition, we surveyed diabetes providers including nurses, certified diabetes educators, and endocrinologists about adherence targets regarding the four BGM-BOLUS adherence behaviors. Based on their responses, we determined the following target rates of adherence: BGM of >4 times per day >90% of the time; insulin bolusing of >3 times per day >90% of the time; BGM occurs prior to insulin bolusing >70% of the time; insulin bolusing following a high (150-249 mg/dL) or very high (>250 mg/dL) BG reading >70% of the time. Results revealed that about two-thirds of the participants were adherent in terms of administering an insulin bolus after a very high BG result. However, very few participants met the target criteria for BGM prior to insulin bolusing and very few bolused after a high BG reading, suggesting that intervention is especially needed to improve BGM-BOLUS LINK behaviors.

Proportion of Patients Performing BGM-BOLUS Tasks	
BGM >=4 times/day >90% of the time	38.8%
Bolus >=3 times/day >90% of the time	57.1%
BGM prior to a bolus >=70% of the time	14.3%
Bolus after a very high (>250 mg/dL) BG >=70% of the time	67.3%
Bolus after a high (151-249 mg/dL) BG >=70% of the time	26.6%

Supported by: LifeScan, Inc.

898-P

Vascular Health in Type 1 Diabetes: CSII vs. MDI

ANDRZEJ S. JANUSZEWSKI, CONNIE KARSCHIMKUS, SYBIL MCAULEY, DAVID N. O'NEAL, ALICIA J. JENKINS, *Melbourne, Australia, Footscray, Australia*

Insulin pumps (CSII) can improve glycemia vs. multiple injections (MDI), but little is known about effects on vascular status. We determined if vascular health and risk factors differ in Type 1 diabetic (T1D) patients on MDI vs.CSII and non-diabetic control subjects. A cross-sectional study of 360 controls, 206 TID-MDI and 55 TDI-CSII subjects was performed. Groups were age (mean 39 yrs) and sex (40% M) matched. Biomarkers: glycemia (HbA1c, 1,5 anhydroglucitol (1,5-AG)), lipids, inflammation (CRP, sVCAM-1, sICAM-1, sE-selectin) and oxidative stress (myloperoxidase (MPO), oxidized (Ox)LDL). As shown in the table CSII (vs. MDI) users had better glycemia, lipids, vascular health (including large and small artery elasticity) and inflammation.T1D-CSII users have better vascular function and risk factors than MDI users. A longitudinal study is merited.

Mean SD or geometric mean (LQ-UQ); ‡ - ANOVA or Kruskal-Wallis p<0.05

	Control	T1D-MDI	T1D-CSII	pCSIIvsMDI	pCSIIvsCON
Yrs T1DBMI (kg/m2)‡	-25.1±4.2	17±112 6.9±5.2	20±122 6.4±4.3	—	-0.02
BP (mmHg)‡	121/6 9±14/101	129/7 1±16/111	124/6 8±17/71	<0.03	—
LAE (ml/mmHgx10)‡	7.2±4.9	6.5±5.6	9.9±7.2	<0.001	<0.001
SAE (ml/mmHgx100)‡	7.6±3.3	6.6±3.4	7.7±3.3	0.03	—
UrineACR (mg/mmol)‡	0.5 (0.3-0.8)	1.5 (0.4-2.7)	0.9 (0.4-1.3)	—	0.01
HbA1c (%)‡	5.1±0.42	8.2±1.5	7.5±1.1	<0.001	<0.001
1,5-AG (µg/ml)‡	0.3±7.1	5.2±3.8	4.9±3.3	—	<0.001
TC (mmol/L)‡	5.1 (4.5-5.9)	4.8 (4.2-5.7)	4.4 (3.9-5.0)	<0.001	<0.001
TG (mmol/L)	1.0 (0.7-1.4)	1.0 (0.7-1.4)	0.9 (0.7-1.0)	—	—
HDL-C (mmol/L)	1.5±0.4	1.5±0.5	1.6±0.4	—	—
LDL-C (mmol/L)‡	3.1 (2.6-3.8)	2.7 (2.1-3.5)	2.3 (1.9-2.8)	<0.001	<0.001
CRP (mg/L)‡	1.1 (0.4-2.7)	1.6 (0.6-4.2)	1.5 (0.7-3.8)	—	—
sVCAM-1 (ng/ml)‡	478 (401-574)	580 (470-706)	490 (396-523)	0.006	—
sICAM-1 (ng/ml)‡	231 (198-273)	269 (227-334)	191 (159-225)	<0.001	<0.001
sE-selectin (ng/ml)‡	40 (28-59)	50 (34-74)	31 (23-45)	<0.001	<0.001
MPO (µg/L)‡	70 (46-100)	93 (59-140)	90 (63-126)	—	<0.001
oxLDL /LDL-C	18.3±6.8	18.9±6.4	18.9±4.2	—	—

899-P

Glucose-Lowering Effect of Insulin Degludec is Independent of Subcutaneous Injection Region

LESZEK NOSEK, HANS-VEIT COESTER, HENRIK F. THOMSEN, CARSTEN ROEPSTORFF, HANNE L. HAAHR, TIM HEISE, *Neuss, Germany, Aalborg, Denmark, Søborg, Denmark*

This randomized, open-label, cross-over trial evaluated the pharmacokinetic and pharmacodynamic properties of insulin degludec (IDeg), a new ultra-long-acting basal insulin, as a function of administration region. Twenty healthy subjects (17 males/3 females; mean age: 37 yrs, BMI: 24.1 kg/m^2) received single s.c. doses of IDeg (0.4 U/kg) in the thigh, the deltoid and the abdomen. Blood samples for pharmacokinetic assessment were taken up to 120 hours after injection, and the pharmacodynamic response was evaluated during a 24-hour euglycemic glucose clamp (Biostator; target blood glucose: 81 mg/dl).As observed with other insulin preparations, total exposure of IDeg ($AUC_{IDeg,0\text{-}120h,SD}$) was slightly greater (by 6-7%) after s.c. injection in the deltoid or the abdomen compared to the thigh. There was no difference between the deltoid and abdomen (Table 1). The glucose infusion rate (GIR) profiles were similar for the three s.c. injection regions: mean $AUC_{GIR,0\text{-}24h,SD}$ (coefficient of variation %) was 2572 (38), 2960 (43), and 2833 (42) mg/kg for thigh, deltoid and abdomen, respectively; mean $GIR_{max,SD}$ was 2.7 (32), 3.0 (42), and 3.0 (37) mg/kg/min, respectively. The glucose-lowering effect extended beyond 24 hours in all subjects for all three s.c. injection regions. In conclusion, IDeg can be administered s.c. in the thigh, the deltoid or the abdomen with similar glucose-lowering effect.

Table 1: Pair-wise comparison of IDeg total exposure between s.c. injection regions

	$AUC_{IDeg,0\text{-}120h,SD}$ (pmol·h/L)
Injection Region	**Mean ratio [95% CI]**
Abdomen vs. thigh	1.07 [1.03; 1.11]
Deltoid vs. thigh	1.06 [1.01; 1.10]
Abdomen vs. deltoid	1.01 [0.96; 1.06]

CI: confidence interval

Supported by: Novo Nordisk A/S

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

900-P

Overnight Normoglycemic Level may be Strongly Associated With Superior Next-Day Glucose Control

ANIRBAN ROY, FRANCINE R. KAUFMAN, BENYAMIN GROSMAN, GAYANE VOSKANYAN, BARRY KEENAN, *Northridge, CA*

To explore the benefits of nocturnal glucose regulation, we compared overnight glucose control to glucose variation the following day by analyzing continuous glucose monitoring (CGM) data from the Medtronic CareLink database.A total of 730 patients with estimated A1C values <7.5% representing 23,809 complete diurnal cycles were identified from the database. The diurnal cycle was divided into two periods - (1) Overnight period - from 0000-0555 hours, and (2) Daytime period - from 0600-2355 hours. To analyze a complete diurnal cycle for both the overnight and daytime periods, at least 80% of the 24 hours CGM sample points were needed for analysis. Overnight glycemic control was divided into 4 groups depending on the duration of in-target sensor glucose readings (Group 1 - 96%, Group 2 - 84%, Group 3 - 48%, and Group 4 - 9% mean in-target CGM durations). The Table shows the next-day glucose control analyzed for each overnight group. Next-day mean CGM values and the percentage of time in the euglycemic and hyperglycemic regions showed a strong positive correlation with overnight glucose control (p<0.0079) with decreasing quality in the next-day glucose control as overnight control ranged from Group 1 to Group 4.

Table 1:

	Overnight Control			
Next-Day control	**Group 1**	**Group 2**	**Group 3**	**Group 4**
CGM readings (n)	7216	6676	4911	5006
CGM (mg/dL), mean (SD)	125.0 (27.6)	144.7 (29.8)	154.7 (35.8)	175.2 (36.2)
%Time 70<CGM<180 mg/dL, mean (SD)	85.4 (15.9)	78.0 (19.5)	68.6 (21.5)	56.7 (23.0)
%Time 180>CGM mg/dL, mean (SD)	10.4 (15.5)	20.0 (20.0)	28.4 (22.8)	41.9 (23.9)

These data suggest that strategies to improve overnight glucose control might have a positive influence on glycemia the next-day. Automating insulin delivery with closed-loop overnight algorithms might be one such viable strategy to improve glycemic control beyond the night time period.

901-P

Feasibility of Adjacent Insulin Infusion and Glucose Sensing via the Medtronic Combo-Set

DAVID N. O'NEAL, SUMONA ADHYA, ALICIA JENKINS, GAYANE VOSKANYAN, GLENN WARD, JOHN B. WELSH, *Fitzroy, Australia, Northridge, CA*

Subcutaneous insulin infusion and nearby glucose-sensing electrodes may interfere with each other. A new combination device, Combo-set (Medtronic MiniMed, Inc.), incorporates an insulin infusion catheter and a CGM sensor separated by a short distance. We evaluated insulin delivery and glucose sensing functions of this device. Ten adult subjects with type 1 diabetes participated in the 3-day study. Each subject had a Combo-set inserted in the abdomen, a contralateral Sof-sensor glucose sensor attached to an iPro recorder as a control, and a contralateral infusion set for routine insulin delivery. The Combo-set delivered insulin diluent except during meal tests on days 1 and 3, when boluses of insulin Lispro were delivered via the Combo-set. Post-bolus venous Lispro levels were determined at 0, 30, 60, 120, and 180 min. The Combo-set was well tolerated without any local skin reactions. The Combo-set sensor and control Sof-sensor had similar performance characteristics. The mean absolute relative difference (MARD) versus capillary blood glucose readings of the Combo-set sensor was similar to that of the Sof-sensor (p=0.63, NS). Clarke Error Grid analysis showed that 96.82% of Combo-set values and 93.14% of Sof-sensor values were in the A+B regions (p=0.20, NS). Combo-set and Sof-sensor readings were comparably accurate during meal tests. Insulin via the Combo-set showed the expected post-bolus peak time (66.6±9.16 min, mean ± SE). Postprandial glycemia with test meals was comparable to profiles obtained on Day 2, when subjects were on their usual diet and received insulin via the control infusion set. One "No Delivery" alarm occurred during the 21 patient-days of use, similar to the historical control rate of other infusion sets (1 per 24 patient-days in the CareLink database of 99,857 patients in 2010). This study shows the feasibility of simultaneous adjacent placement of an insulin infusion catheter and a CGM sensor.

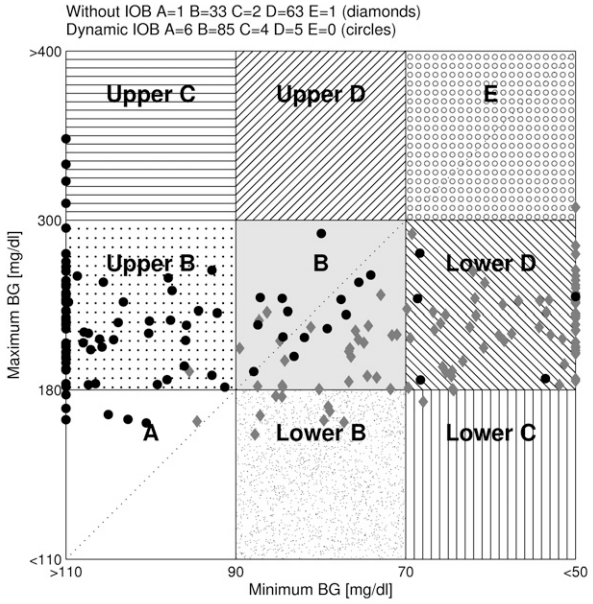
Supported by: Medtronic, Inc.

902-P

Dynamic Insulin On Board: An Approach Based on the Circadian Rhythm of Insulin Sensitivity

CHIARA TOFFANIN, HOWARD ZISSER, FRANCIS J. DOYLE III, EYAL DASSAU, *Pavia, Italy, Santa Barbara, CA*

The duration of insulin action is affected by several factors such as glucose concentration, circadian rhythm and physical activity. A key factor to optimize insulin therapy for people with type 1 diabetes mellitus is an accurate insulin on board (IOB) calculation. Modern insulin pumps utilize a static IOB calculation as part of their bolus wizard without taking into account diurnal insulin sensitivity.A dynamic IOB is proposed that takes this into account as well as subcutaneous absorption delays. This updated IOB function is used to evaluate the effect of correction boluses with changes in insulin sensitivity. A basal-bolus approach with and without the dynamic IOB was evaluated in silico using the UVA/Padova Metabolic Simulator. Two protocols with 3 meals of 1 g-carbohydrate / kg of body weight were evaluated, a nominal one in which insulin sensitivity follows the estimated trend, and one in which it is 15% greater than the estimated trend.When insulin sensitivity decreases (dawn phenomena) the IOB constraints are relaxed in order to allow a larger correction, while when it increases (early morning) these constraints are more restrictive to avoid nocturnal hypoglycemia. In both scenarios the introduction of dynamic IOB constraints reduces hypoglycemia by 17% and 52%, respectively. The CVGA figure shows the results obtained with the robustness scenario: only 5 subjects had a minimum glucose < 70 mg/dl with the dynamic IOB compared to 66 without it.The proposed dynamic approach considerably decreased the number of hypoglycemia events obtained via basal-bolus therapy with a moderate increase of the mean glucose concentration.



Supported by: DP3DK094331-01 and R01DK085628

903-P

Improvement in Glycemic Parameters With Use of the Low Glucose Suspend Feature of the Veo Insulin Pump

PRATIK AGRAWAL, BRIAN KANNARD, JOHN SHIN, SUIYING HUANG, JOHN B. WELSH, FRANCINE R. KAUFMAN, *Northridge, CA*

The low glucose suspend (LGS) feature of the Veo insulin pump system was designed to reduce the severity and duration of hypoglycemia. Patients may use the pump with or without continuous glucose monitoring (CGM) sensors, and CGM-augmented Veo pump users may turn the LGS feature on or off. We examined whether use of the LGS feature influenced glycemic parameters on days CGM sensors were worn. Data from a group of 7810 subjects outside the US using the Veo system were uploaded to the CareLink database from Jan 2010 to Nov 2011. Subjects were categorized according to the frequency of CGM and LGS use. CGM data were used to compare glycemic parameters on LGS-On vs LGS-Off days. Overall, this group of Veo pump patients used CGM sensors for 398902 days. When CGM sensors were worn, the LGS feature was on for 73.6% and off for 26.4% of the time. Mean CGM readings were higher during LGS-On vs LGS-Off days (156.3 vs 153.1 mg/dL, p<0.001). Calculated gly-

cemic parameters in favor of LGS-On vs LGS-Off days included lower AUC <70 mg/dL (0.62 vs 1.00 mg/dL, p<0.001), less time spent <70 mg/dL (5.3% vs 7.4%, p < 0.001), and shorter mean duration of excursions to <70 mg/dL (37.9 vs 46.5 min, p<0.001). There were statistically significant differences in the percentage of time >240 mg/dL (11.23% vs 11.30%, p=0.001) and >300 mg/dL (3.43% vs 3.59%, p<0.001) for LGS-On and LGS-Off days, respectively. AUC values for hyperglycemia >240 mg/dL (5.69 mg.min/dL vs 5.9 mg.min/dL, p<0.001) and >300 mg/dL (1.75 mg.min/dL vs 1.88 mg.min/dL, p<0.001) during LGS-On and LGS-Off days, respectively, also tended to favor LGS-On days. Analysis of real-life data from the CareLink data set shows that use of the LGS feature may reduce hypoglycemia without increasing hyperglycemia. Automation of insulin delivery to reduce hypoglycemia and not deteriorate overall glycemic control appears to be a viable strategy for people with type 1 diabetes.

Supported by: Medtronic, Inc.

904-P

Social Media and Diabetes: Can We Improve Glucose Control in Adolescents on Pump Therapy? One Year Experience

GORAN PETROVSKI, TATJANA MILENKOVIC, ILIJANA PETROVSKA, BILJANA JOVANOVSKA, ISKRA BITOVSKA, IRFAN AHMETI, KATERINA ADAMOVA, *Skopje, The Former Yugoslav Republic of Macedonia*

Background and aims: To evaluate results from social media (Skype and Facebook) and Carelink as tools to improve diabetes control in diabetic adolescents on Medtronic PRT (insulin pump with glucose sensor).Materials and methods: A total of 78 adolescents with type 1 diabetes, ages 14-23, were randomized in two groups: Regular visits (Group 1)- 40 type 1 diabetes patients were treated using standard medical protocol with regular visits at clinic, where data was downloaded at the clinic and intervention (pump settings-basal bolus insulin, education) were given to the patient and Internet visits (Group 2)- 38 type 1 diabetes patients were treated using Carelink personal program (Medtronic Diabetes), where the data was downloaded by the patient at home and interventions (same as group 1) were given via Skype (sound and video) and Facebook (written reports and chats). A1C was obtained before and every three months during the study in one year period..Results: Regular visits were 2.4±1.3 per patient/month in group 1 and Internet visits were 2.6±1.6 per patient/month retrospectively. There was significantly improvement in both groups (group 1 and 2 retrospectively, 7.45 ±0.9% and 7.68 ±1.1% on beginning with 6.22 ±0.8 % and 6.09 ±1.0%, p< 0.05) at the end of the study. The significant improvement was performed in the first six months and continued to maintain in the following months. Internet visits were more preferable by the patients.Conclusion: This brief trial suggests that type 1 diabetes adolescents prefer to communicate with their health care providers using social networks, where new technologies can improve diabetes control same as regular clinic visits.

905-P

Human Hyaluronidase (rHuPH20) Provides Consistent Ultrafast Insulin Absorption and Action Over 3 Days of Continuous Subcutaneous Infusion

DANIEL E. VAUGHN, LINDA MORROW, MARCUS HOMPESCH, DOUGLAS B. MUCHMORE, *San Diego, CA, Chula Vista, CA*

Rapid acting insulin analogs (RAI) demonstrate systematic variation in insulin absorption and action as infusion sites age. We performed euglycemic clamps after bolus infusion of insulin aspart (100 U/mL, 0.15 U/kg) in 2 cohorts of generally healthy adult type 1 pump patients to test the effect of rHuPH20 (given either as a coformulation or administered as a bolus once upon infusion set insertion) on the variability of insulin aspart absorption and action as a function of infusion site age. Consistent with previous reports, absorption kinetics and insulin action of RAI alone varied considerably with infusion site age; the fraction of insulin exposure occurring within 1 hr following bolus infusion was as little as 15% for a new infusion site and doubled to ~30% after 3 days of use. Similarly, both the onset and duration of insulin action varied by up to 30 minutes as the infusion site aged.

Cohort*	Infusion Site Age	Insulin Aspart Alone			With rHuPH20		
		Early Exposure (% total)	Onset of Action (min)	Duration of Action (min)	Early Exposure (% total)	Onset of Action (min)	Duration of Action (min)
Coform	½ days	21	47	164	35	35	147
Coform	2½ days	33	35	147	51	40	133
Pre-Rx	< 2hr	15	60	180	31	34	139
Pre-Rx	1 day	22	34	164	37	32	134
Pre-Rx	3 days	27	30	156	32	31	146

*Coform = Aspart (100 U/mL)+ rHuPH20 (600U/mL);Pre-Rx = rHuPh20 pre-treatment (150 U bolus)

Coformulation of insulin aspart with rHuPH20 accelerated insulin absorption and action across infusion site use relative to insulin aspart alone, although the early exposure did change from ½ day to 2½ days of continuous infusion of the coformulation. Preadministration of rHuPH20 provided a consistent ultrafast profile over 3 days of infusion site use, eliminating the variability in insulin absorption and action associated with infusion site aging.

906-P

Local Tolerability of Insulin Degludec is Comparable to Insulin Glargine: A Meta-Analysis of T1DM and T2DM

LUIGI F. MENEGHINI, PETRA-MARIA SCHUMM-DRAEGER, STEWART HARRIS, MARI-ANNE GALL, NATHAN LASSOTA, JENS S. CHRISTIANSEN, *Miami, FL, Munich, Germany, London, ON, Canada, Søborg, Denmark, Aarhus, Denmark*

Injection site reactions may occur following s.c. insulin administration. Insulin degludec (IDeg) is a new basal insulin that forms a soluble depot of multi-hexamers after s.c. injection. Utilizing patient level data, we examined via meta-analysis whether the number of injection site reactions with IDeg was different from insulin glargine (IGlar) in patients with type 1 diabetes (T1DM) or type 2 diabetes (T2DM). The analysis comprised 6 randomized, open-label, controlled, treat-to-target, phase 3a trials of 26 or 52 weeks duration with once-daily dosing of IDeg (n=3060) and IGlar (n=1198) in T1DM (2 trials) and T2DM (4 trials). The number of injection site reactions was analyzed with a negative binomial regression model. While lower observed rates of injection site reactions were seen in IDeg groups compared to IGlar groups in both T1DM and T2DM (basal only therapy) no statistical significance was seen (Table). A similar proportion of patients (T1DM+T2DM) reported injection site reactions with IDeg (3.6%) and IGlar (3.5%). For both IDeg and IGlar, injection site reactions were most commonly reported as injection site hematoma, injection site reaction (unspecific) and injection site pain. Two injection site reactions for IGlar were classified as severe adverse events. Few patients (0.1%) with IDeg and IGlar withdrew from the trials due to injection site reactions (IDeg: injection site hematoma, injection site pain; IGlar: injection site reaction [unspecified]). In conclusion, this meta-analysis demonstrates good local tolerability of IDeg compared to IGlar following s.c. injection.

Table 1: Injection site reaction analysis outcomes

	Number of patients (n)		Observed rate per 100 exposure years		Estimated rate ratioIDeg/ IGlar	
	IDeg	IGlar	IDeg	IGlar	Rate ratio	95% CI
T1DM + T2DM (pooled)	3060	1198	6.8	7.0	0.86	[0.57; 1.30]
T1DM[a]	801	315	5.3	6.7	N/A	N/A
T2DM	2259	883	7.4	7.1	0.91	[0.56; 1.48]
T2DM - BOT[b]	1506	632	8.7	9.4	0.72	[0.41; 1.27]

[a] Too few events to fit the statistical model; [b] Basal-only therapy

Supported by: Novo Nordisk A/S

907-P

Successful Treatment of Type 1 Diabetes With Intraperitoneal Insulin Infusion when Subcutaneous Insulin Application is not Possible: Two Case Reports

ANDREAS LIEBL, BERHARD GEHR, FRANZISKA BACHER, CLAUS KIEHLING, THOMAS FREI, *Bad Heilbrunn, Germany, Bad Toelz, Germany, Burgdorf, Switzerland*

This is a report on the worldwide first cases treated with the novel DiaPort® system (Roche Diabetes Care) for continuous intraperitoneal insulin infusion CIPII, which could be used before approval with special permission by the German Ministry of Health due to life-threatening situations. Two female patients with type 1 diabetes (age 21 and 32 years, diabetes duration 13 and 4 years, HbA1c 9,3% in both, BMI 22 and 30 kg/m², no late complications) presented with long-term intravenous insulin infusions since 18 months and 9 weeks respectively. The intravenous infusions had resulted in severe complications, e g septic infections of central venous catheters, and lack of peripheral venous access. In both patients over 500 IU insulin subcutaneously had been unsuccessful, and common reasons for insulin resistance including hormon disorders, antibodies and non-compliance had been ruled out. A new DiaPort® with major improvements over the older version (see figure: polyester felt for better ingrowth, softer catheter with better biocompatibility, improved implantation tools) was implanted into the abdominal wall of both patients to start CIPII with regular external insulin pumps.CIPII resulted in immediate near-normoglycemia with daily basal rates of 28 IU and 43 IU of insulin Lispro, and average daily bolus doses of

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

20 IU and 30 IU respectively. Apart from one reversible episode of catheter obstruction, the DiaPort treatment has been safe, successful, and with high patient satisfaction for the first 7 weeks. Further experience will come from the ongoing approval study.

908-P

Pre-Clinical Studies of an Automated Closed-Loop Blood-Glucose Control System for the Hospital Setting Using Interstitial Continuous Glucose Monitoring and Intravenous Insulin and Dextrose

JOHN X. JIANG, FIRAS H. EL-KHATIB, STEVEN J. RUSSELL, EDWARD R. DAMIANO, *Boston, MA*

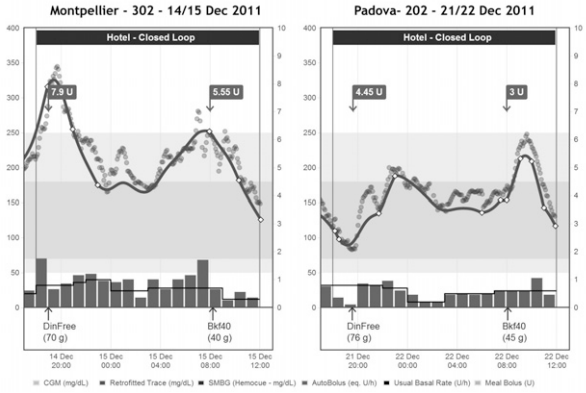
We conducted pre-clinical studies using a fully automated, closed-loop control system designed to regulate blood glucose (BG) in both stress hyperglycemia and diabetes in the hospital setting using interstitial-fluid continuous glucose monitoring (CGM) and intravenous (IV) infusions of insulin and dextrose. Streptozoticin-treated pigs were studied in the immediate post-treatment period while they were both insulin deficient and highly insulin resistant. The sole input to the control system was body weight and CGM glucose (Abbott Freestyle Navigator). Dosing of insulin and dextrose were commanded every 5 minutes by model predictive control and proportional derivative control algorithms, respectively, and delivered by a Hospira Symbiq infusion pump. After the control system regulated BG to ≤ 120 mg/dl, a carbohydrate-rich meal (4 g carbohydrate/kg body weight) was given. Blood glucose was reduced from an untreated mean of 429 ± 33 mg/dl to ≤ 120 mg/dl within 139 ± 57 minutes after the start of closed-loop control (n = 14 experiments). The pigs were initially insulin resistant, requiring 0.25 - 1.0 u/kg insulin to achieve normoglycemia. Once normoglycemia was achieved, BG was maintained at 118 ± 30 mg/dl (this variability in BG is comparable to pigs without diabetes) with much smaller amounts of insulin despite the consumption of a high-carbohydrate meal. Glycemic control was similar in experiments using BG measurements instead of CGM glucose as the input to the control system. The control system effectively regulated BG to near-normal range despite large changes in insulin sensitivity and carbohydrate-rich meals. These experiment pave the way for an upcoming first-in-human study.

909-P

Feasibility of Automated Ambulatory Blood Glucose Control in Type 1 Diabetes Using a Wearable Artificial Pancreas

ERIC RENARD, CLAUDIO COBELLI, BORIS P. KOVATCHEV, PATRICK KEITH-HYNES, NAJIB BEN BRAHIM, JEROME PLACE, DEL FAVERO SIMONE, MARC BRETON, ANNE FARRET, DANIELA BRUTTOMESSO, STEPHEN D. PATEK, ANGELO AVOGARO, *Montpellier, France, Padova, Italy, Charlottesville, VA*

For patients with type 1 diabetes, the availability of automated blood glucose control in everyday life is the final goal of artificial pancreas (AP) research.Here we present outpatient pilot-feasibility studies of wearable AP enrolling two patients with type 1 diabetes at the Univ. of Montpellier and the Univ. of Padova. The wearable AP system, developed at the Univ. of Virginia, linked wirelessly an experimental insulin delivery/glucose sensing device from Insulet Corp, Bedford, MA to a smart-phone used as a hub running a closed-loop control algorithm. The system had the capability for real-time remote patient monitoring via 3G connection. Each study continued for 40 hours, including overnight stay in a hotel on open loop, 12-hour hospital admission to initiate closed-loop control, and 18-hour outpatient closed-loop session. During this ambulatory AP phase, the patients had dinner, night sleep in hotel, breakfast and a morning walk in town. They interacted with the wearable AP via the touch screen of the smart phone. As presented in Figure 1, during the outpatient AP session the closed-loop control algorithm kept blood glucose levels in a safe range (70-250 mg/dl): 100% of the time in one trial (Patient 202), 78% of the time in the other with 22% of the time slightly above after dinner (Patient 302). The remote monitoring worked reliably with no interruptions in both cases. No intervention by physicians was needed.These experiments demonstrate the feasibility and the safety of wearable AP used in ambulatory conditions. Further extensive studies are therefore justified.



Supported by: JDRF

910-P

Proinsulin-Transferrin Fusion Protein as a Potential Hepatospecific Anti-Diabetic Prodrug

JENNICA L. ZARO, YAN WANG, WEI-CHIANG SHEN, *Los Angeles, CA*

Previous in vitro studies have demonstrated a transferrin (Tf)-mediated conversion and activation of a proinsulin (ProINS)-Tf fusion protein in hepatoma cells. In this study, the fusion protein was evaluated for in vivo hypoglycemic efficacy and specific reduction of gluconeogenic enzymes in the liver. His-tagged ProINS-Tf was expressed and purified from HEK293 cells. For in vivo studies, streptozotocin (STZ)-induced diabetic male C57BL/6J mice were fasted 2 h prior to s.c. injection of equimolar insulin (INS), ProINS, or ProINS-Tf, and blood glucose levels were measured at various post-injection timepoints up to 12 h under fasting conditions. The results showed that ProINS-Tf exerted a gradual decrease in blood glucose levels, reaching a maximum effect (84% reduction in blood glucose levels compared to non-treated controls) at 8 h post injection, which was sustained until 12 h. The effect of ProINS-Tf at 12 h was similar to INS at 4 h. Under fasting conditions, blood glucose levels in ProINS-Tf treated mice remained low, while levels in control, INS, and ProINS treated mice returned to baseline.mRNA levels of two key gluconeogenic enzymes, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase were also determined in liver homogenates of ProINS-Tf treated STZ-mice. The data showed that the expression of both enzymes was decreased following treatment with ProINS-Tf, indicating that the gluconeogenic pathway was inhibited.In conclusion, the ProINS-Tf showed a slow, but sustained, in vivo hypoglycemic efficacy and inhibition of gluconeogenic enzyme expression in the liver. The data suggest that the fusion protein inhibits hepatic glucose production (HGP), as indicated by the prolonged suppression of blood glucose levels under fasting conditions, and by the inhibition of hepatic gluconeogenic enzyme expression. Thus, ProINS-Tf fusion protein can potentially be administered as a prodrug with sustained Tf-mediated activation and selectivity in inhibiting HGP.

911-P

Pharmacokinetics of Insulin Aspart in Pump-Treated Type 1 Diabetes (T1D): Reproducibility and Effect of Age, Weight, and Duration of Diabetes

AHMAD HAIDAR, DANIELA ELLERI, JANET ALLEN, KAVITA KUMARESWARAN, JULIE HARRIS, LALANTHA LEELARATHNA, MARIANNA NODALE, KAREN CALDWELL, HELEN MURPHY, MALGORZATA WILINSKA, CARLO ACERINI, MARK EVANS, DAVID DUNGER, ROMAN HOVORKA, *Cambridge, United Kingdom, Montreal, QC, Canada*

We elucidated factors affecting pharmacokinetics of subcutaneous insulin aspart in 70 subjects with T1D treated by insulin pump (39 females, 10 children, 36 adolescents, 24 adults, BMI 22.7±4.2kg/m^2, A1c 8.1±1.3%, total daily insulin 0.8±0.3U/kg/day) who were studied at a clinical research facility on two occasions one to six weeks apart. On each occasion lasting 15 to 37 hours, subjects consumed standard meals accompanied by prandial

insulin. Basal insulin delivery was applied between meals. A pharmacokinetic model was able to fit data well and estimated time-to-peak plasma insulin concentration [T_{max}; 66 (22) min; mean (SD)], metabolic clearance rate of insulin [MCR; 1.68 (0.74) 10^{-2}x L kg^{-1} min^{-1}], and the background plasma insulin concentration [C_b; 4.6 (1.6-9.7) mU L^{-1}; median (IQR)]. Gender differences in insulin kinetics were not observed. T_{max} increased with BMI and weight, MCR increased with duration of diabetes, and C_b decreased with age and duration of diabetes. Little inter-subject variability in insulin kinetics was explained by gender, BMI, total daily dose, A1c and duration of diabetes (T_{max} 13%; MCR 14%; C_b 18%). Reproducibility was highest for MCR (inter-occasion CV 15%), followed by T_{max} (SD 15min) and C_b (SD 4.7mU L^{-1}). We conclude that pharmacokinetics of insulin aspart is not determined by common demographic factors and is on average moderately reproducible when assessed over 15 to 37 hour period in subjects with T1D.

Correlation between T_{max}, MCR and C_b, and clinical and demographic factors

	T_{max}	MCR	C_b
Weight	0.32†	0.05	-0.20
BMI	0.30*	0.00	-0.21
Total daily insulin dose per kilogram body weight	-0.07	-0.06	0.26*
Age	0.10	0.14	-0.33†
A1c	-0.09	0.13	0.10
Duration of diabetes	0.05	0.31†	-0.38†

* P < 0.05 † P < 0.01

Supported by: JDRF, NIDDK, Diabetes UK

912-P

Accuracy and Preference Assessment of FlexTouch vs. Vial & Syringe With Diabetes Patients and Health Care Professionals

ANDREAS PFÜTZNER, TIMOTHY BAILEY, CARLOS CAMPOS, DOUGLAS KAHN, ELLEN AMBERS, MARCUS NIEMEYER, GERMAN GUERRERO, DAVID KLONOFF, *Mainz, Germany, San Jose, CA, Escondido, CA, New Braunfels, TX, Copenhagen, Denmark, Princeton, NJ, San Mateo, CA*

The goal of this study was to evaluate the dosing accuracy of the new prefilled FlexTouch insulin pen (FT) in comparison to vial and syringe (V&S) when used by patients (Pts), caregivers (CG, parents or relatives) and healthcare professionals (HCPs).A total of 120 subjects participated in the trial (40 Pts, 20 CG, 20 physicians, and 40 nurses/certified diabetes educators). The participants were introduced to the devices in randomized order and performed injections of 5, 25, 43 and 79 IU doses into lab tubes. Dosing accuracy was analyzed by weighing the tubes and calculating the mean absolute deviation (MAD) from the intended doses. After completing a device assessment questionnaire (DAQ, questions regarding device design and performance), the procedure was repeated for the other device. Finally, the subjects completed a device preference questionnaire (DPQ).Dosing accuracy was significantly better for FT for the entire cohort at all doses. (MAD±SD for FT/V&S) 5U: 0.4±0.4/0.6±0.6 U; 25U: 0.3±0.4/0.7±0.9 U; 43U: 0.4±0.4/0.9±1.2 U; 79U: 0.5±0.5/1.7±1.6 U, p<0.005 for all doses). Dosing accuracy with FT for all three subgroups was comparable (patients: 0.35-0.59 U; HCP&CG: 0.29-0.54 U). Differences in dosing accuracy were seen with V&S: HCP and CG delivered the doses with significantly higher accuracy thasn Pts (range of mean MAD; Pts: 0.81-2.54 U; HCP&CG: 0.51-1.30 U, p<0.005 at all doses). FT was ranked superior to V&S for all aspects of the DAQ. In the DPQ, 93% of the Pts voted for FT (neutral: 5%, V&S: 2%), (CG: 100%/0%/0%), HCPs: 85%/2%/13%).FlexTouch, compared to V&S, was significantly more accurate at all tested doses and was used with similar accuracy by patients, HCPs, and CGs. Participants rated FT higher than V&S in every component of the DAQ and the vast majority of them preferred FT. These findings show a potential for higher dosing accuracy and improved adherence when using the new prefilled FlexTouch compared to V&S for insulin delivery in diabetes patients.

Supported by: Novo Nordisk A/S

913-P

Long Term Follow-Up in Type 1 Diabetes Patients Using Continuous Subcutaneous Insulin Infusion Systems

JOANA SARAIVA, FRANCISCO CARRILHO, LUÍSA BARROS, CARLA BATISTA, MIGUEL MELO, LEONOR GOMES, ALEXANDRA VIEIRA, MÁRCIA ALVES, SOFIA GOUVEIA, CAROLINA MORENO, MANUELA CARVALHEIRO, *Coimbra, Portugal*

Continuous subcutaneous insulin infusion (CSII) using an external pump is an alternative intensive diabetes therapy recognized to improve metabolic control and glycemic instability in selected type 1 diabetic (T1DM) subjects. The aim of this study was to examine clinical effectiveness and safety of CSII systems over a 5-year follow-up period in T1DM. We performed a retrospective observational study of T1DM patients previously treated with multiple daily insulin therapy who initiated CSII until December 2010. We analyzed A1C, weight and total daily insulin dose (TDD) at the start of therapy, 6 months after and then annually for 5 years. We examined the occurrence of hypoglycemic and diabetic ketoacidosis (DKA) episodes and local problems at infusion site.We followed 92 patients during 4.08±3.01years, 62% female, mean age 28.73±11.7years-old, diabetes duration 15.63±8.97 years. The main reasons for starting CSII were: poor glycemic control in 47.7%, glycemic instability 31.1%, frequent and unnoticed hypoglycemia 12.1% and dawn phenomenon in 4.5%. Baseline A1C was 8.79±1.62% and decreased to a minimum of 7.58±1.0% at 6 months (p<0.05). Compared to baseline, A1C remained lower in all follow-up period (p<0.05). Patients followed during 5 years maintained lower A1C (8.95±1.6% vs 7.60±0.94%, p<0.05), although we verified a slight increase between 1 and 4 years (7.35±1.08% vs 7.75±0.91%, p<0.05). Insulin requirements reduced from 57.7UI/day to 41.3UI/day (p<0.05) at 6 months and we found no statistically weight difference (59.5kg vs 58.3kg). We registed 18 severe hypoglycemia (incidence 0.057/patient/year), 12 DKA (0.038/patient/year) and 11 recurrent infections at the infusion site. Eight (8.7%) patients quit pump therapy mainly because of maladaptation. In conclusion, in this study CSII improved glycemic control during long term follow-up and reduced total daily insulin requirements. The rate of major complications was low and similar to those reported in other studies.

914-P

Remote Monitoring of Nocturnal Continuous Glucose Monitoring Data in Children: Data Analysis from mySentry

KEVIN KAISERMAN, GNANAGURUDASAN PRAKASAM, FRED GUNVILLE, ROBERT H. SLOVER, BRUCE A. BUCKINGHAM, FRANCINE R. KAUFMAN, JOHN B. WELSH, SCOTT W. LEE, *Torrance, CA, Sacramento, CA, Billings, MT, Aurora, CO, Stanford, CA, Northridge, CA*

Continuous glucose monitoring (CGM) sensors are typically connected to low-power radio frequency transmitters. The mySentry system (Medtronic MiniMed, Inc.) consists of an outpost device placed near the patient which amplifies and relays pump and CGM data to a remote monitor so that parents or caregivers elsewhere in the home can be alerted to abnormal glucose values or trends. This may help to reduce the number and severity of nocturnal glycemic excursions. Families of 35 children with type 1 diabetes participated in a 4-week user evaluation of mySentry. Children used the Paradigm Revel sensor-augmented pump system with Sof-sensor CGM sensors without mySentry for 1 week, then with mySentry for 3 weeks. Threshold values for alerts were set individually. Pump and sensor data were uploaded to CareLink Clinical and analyzed retrospectively. Events from 10:00 PM to 8:00 AM were classified as nocturnal. Use of mySentry was associated with favorable trends in the number, duration, and area under the curve (AUC) for sensor glucose values (SGV) ≤ 50 mg/dL among the 8 subjects who had at least 1 hypoglycemic event in both periods, and for SGV ≥300 mg/dL among the 20 subjects who had at least 1 hyperglycemic episode in both periods (Table). In families where a child with type 1 diabetes uses a sensor-augmented pump system, nocturnal glycemic control may be improved by alerting parents and/or caregivers to abnormal sensor glucose values in real time so that appropriate interventions can occur.

Nocturnal hypoglycemia and hyperglycemia (per week) without and with mySentry, mean ± SD

Hypoglycemia (N=8 subjects)	Without	With
Number of excursions to ≤ 50 mg/dL	3.87 ± 2.69	2.35 ± 1.11
Duration ≤ 50 mg/dL (min)	232.73 ± 397.6	154.5 ± 129.01
AUC ≤50 mg/dL (mg/dL × week)	0.13 ± 0.28	0.09 ± 0.11
Hyperglycemia (N=20 subjects)	**Without**	**With**
Number of excursions to ≥ 300 mg/dL	5.76 ± 6.17	4.46 ± 3.25
Duration ≥ 300 mg/dL (min)	619.81 ± 715.1	455.73 ± 510.77
AUC ≥300 mg/dL (mg/dL × week)	2.93 ± 4.09	2.06 ± 2.84

Supported by: Medtronic, Inc.

915-P

The Number of Basal Rates to Achieve Near Normal Glycemia in Intensively Titrated Pump-Treated Type 2 Diabetes

DAWN CLARK, ALLEN B. KING, GARY S. WOLFE, *Salinas, CA*

There is minimal information available to support a single basal rate in pump-treated T2DM for providing near normal basal glucose control30 T2DM subjects with 10 each on non-insulin, basal insulin and basal-bolus

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

insulin treatment ± non-insulin treatment were recruited. All previous basal insulin and non-insulin treatments were discontinued upon starting pump insulin except for metformin (n = 12) and thiazolidinedione (n = 8). The diet was isocaloric (50% carbohydrate) with serially single daily alternating meal omissions for evaluating the basal glucose. The basal rate and the insulin to carbohydrate ratio (ICR) were daily titrated from downloads from continuous glucose monitoring, CGM. The basal glucose goal was 70-130 mg/dl during omitted meal periods and overnight with <10% of 24 h reading <70 mg/dl. The ICR goal was a 2-4 h post meal glucose ± 20% of pre meal glucose. All subjects were started on a singe basal rate.The mean (± SE) age was 56 ± 2 years; DM duration, 12 ± 1 years, A1c, 8.0 ± 0.2 %; BMI, 34.6 (1.0) kg/m^2; and random C peptide, 2.5 ± 0.2 ng/ml. After titration (~ 7 d) the mean ± SE basal CGM glucose was 99.8 ± 4.2 mg/dl and the post-meal glucose was returned to within < 10.0% of the pre-meal glucose within 4 h. 6 subjects (20%) required two basal rates during a 24 hour period while all others, one. The time period of rate increase averaged 2400 to 0700 h with a mean increase of 42% U/hr.This study supports one basal rate as adequate for near normal basal glucose control in the majority T2DM subjects. In these carefully titrated subjects, the resulting proportionality between dosing factors is markedly different from that previously reported when titration was done with periodic self-monitored plasma glucose but nearly identical to our previously intensely CGM titrated study of pump-treated type 1 diabetes.

Supported by: Animas Corporation

916-P

Enhanced Pharmacodynamic Properties of Insulin Aspart due to a Modified Injection Strategy in Subjects With Type 1 Diabetes

JULIA K. MADER, THOMAS BIRNGRUBER, SIGRID DELLER, STEFAN KORSATKO, SUSANNE BOYSEN, SELMA MAUTNER, THOMAS AUGUSTIN, THOMAS R. PIEBER, *Graz, Austria, Maaloev, Denmark*

Splitting a single insulin bolus into multiple, small boluses increases the surface to volume ratio and could lead to faster insulin absorption and improved postprandial glucose control. In this open-labeled, 2-period crossover study we investigated the impact of a modified injection strategy of insulin aspart on pharmacodynamic and pharmacokinetic properties.First, the increased surface to volume ratio of 9 boluses of 2 IU vs. 1 bolus of 18 IU was confirmed by microfocus computed tomography in an ex-vivo trial (3.92 vs. 2.20 mm^2/mm^3). In an 8-hour euglycemic clamp trial (target 5.5 mmol/l) twelve C-peptide negative type 1 diabetic patients were investigated (age 32 ± 9 years, 6 female, BMI 23.9 ± 2.5 kg/m2, HbA1c 7.3 ± 0.6%, diabetes duration 19 ± 10 years). Patients received an insulin dose of 18 IU insulin aspart either as 1 bolus of 18 IU or 9 boluses of 2 IU administered via FlexPen® with an 8 mm needle.The maximum glucose infusion rate was similar in both approaches (10 ± 4 for 9x2 IU vs. 9 ± 4 for 1x18 IU, n.s.). Time to reach maximal GIR was significantly decreased for 9x2 IU: 68 ± 33 min vs. 127 ± 93 min ($p<0.01$). Time to peak insulin concentration was not significantly different (56 ± 14 min vs. 66 ± 38 min, n.s.), however time to half-maximal GIR (25 ± 8 min vs. 35 ± 8 min, $p<0.01$) and time to 10% of peak insulin concentration (9 ± 4 min vs. 14 ± 6 min, $p<0.05$) were significantly decreased. Area under the glucose curve (AUC) was greater for 9 x 2 IU during the first 60 min (219 ± 89 vs. 137 ± 75, $p<0.01$). AUC until maximal glucose infusion rate was significantly smaller for 9x2 IU (242 ± 183 vs. 501 ± 396, $p<0.01$) but there was no difference in total AUC over the whole study period (1361 ± 469 vs. 1565 ± 527, n.s.).Nine injection sites of insulin aspart showed significantly improved pharmacodynamic and pharmacokinetic properties in type 1 diabetes patients. Clinical implications on long term metabolic control have to be investigated in a further clinical trial.

917-P

Feasibility Study Assessing Hypoglycemia-Hyperglycemia Minimizer (HHM) System in Patients With Type 1 Diabetes (T1DM) in a Clinical Research Center (CRC)

LINDA MACKOWIAK, DANIEL A. FINAN, THOMAS W. MCCANN, JR., RAMAKRISHNA VENUGOPALAN, HOWARD ZISSER, HENRY ANHALT, *West Chester, PA, Santa Barbara, CA*

With the goal of developing an automated insulin delivery system to improve glucose control in T1DM, a feasibility study was carried out in a CRC setting assessing the performance of an HHM System, which includes a continuous subcutaneous insulin infusion pump, continuous glucose monitor (CGM), and model predictive control algorithm with a safety module, run on a laptop platform.The study design was a non-randomized, uncontrolled feasibility trial, at 1 US site. The investigational system was studied for approximately 24 hours for each participant during periods of open- and closed-loop control. Insulin and food variables were manipulated to challenge and assess the system.The primary objective was to evaluate the ability of the algorithm to predict a rise or fall in glucose above or below set thresholds, and to command the pump to increase, decrease, suspend and/or resume insulin infusion accordingly. The secondary objectives were to understand the HHM System's ability to safely keep glucose levels within a target range, and to provide guidance in future development.The study population included 13 participants; age 24-57 years; female 11; BMI mean (SD) 24.7 kg/m2 (5.1); duration T1DM mean (SD) 27.2 years (13.3); A1C mean (SD) 7.4% (0.8).The HHM System was able to predict a rise and fall in CGM glucose and correspondingly increase and decrease (stop/resume) insulin delivery in an attempt to minimize glucose excursions. The system provided warnings in advance of significant decreases in CGM glucose. During closed loop, based on the CGM glucose, the time spent <70 mg/dl overnight (12am-7am) was 0.1%; overall 0.5%; post-breakfast (7am-1pm) 1.5%; post-lunch (1pm-8pm) 0%. There were no safety concerns, including no DKA or severe hypoglycemia.In conclusion, the primary and secondary study objectives were met and planning for further studies is underway.

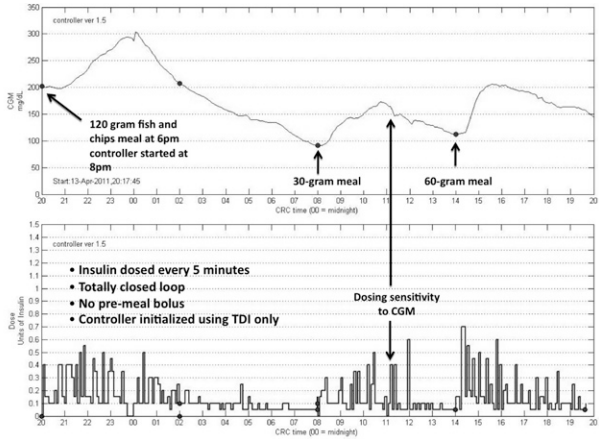
918-P

Phase 1 Study of a Fuzzy Logic Controller in a Closed-Loop Artificial Pancreas System

JENNIFER BOLLYKY, CARLA GREENBAUM, SRINATH SANDA, ROBERT KIRCHER, DON MATHESON, RICHARD MAUSETH, *Seattle, WA, Woodinville, WA*

Artificial Pancreas Systems (APS) connect glucose sensing and insulin pumps with algorithms to improve glycemic control and decrease effort for patients with type 1 diabetes. Here we evaluate a fully-automated APS using a Fuzzy Logic Controller (FLC), an OmniPod pump and Dexcom Seven Plus sensor in a CRC setting.Ten patients using insulin pumps between 18-45 with type 1 diabetes for > 1 year, HbA1c<9% were enrolled in a 24-hour study protocol. The FLC, initialized only with the patient's Total Daily Insulin (TDI) dose, was used to direct insulin doses delivered to patients every 15 minutes without meal announcement, priming boluses or study personnel intervention.Three of the ten patients did not complete the protocol. Two of the patients developed blood glucose (BG) < 60mg/dL due to overestimation of TDI for initialization. The third patient experienced sensor failure necessitating study termination. Seven subjects completed the protocol with results in table below. The figure below shows BG tracing and insulin doses for a sample subject during study period.These preliminary data indicate that a FLC may be able to regulate BG with decreased patient effort in a clinical setting and warrants further study.

	Time	BG average (mg/dL)	% time BG 70-200mg/dL
Hyperglycemia correction	8p-2a	169	74.8%
Diurnal glucose variation	2a-8a	128	98.6%
Small meal (30g CHO)	8a-2p	178	70.0%
Moderate meal (60g CHO)	2p-8p	202	50.4%
Average 24-hour study period	**8p-8p**	**169**	**73.5%**



Supported by: JDRF, Artificial Pancreas Consortium

Clinical Diabetes/ Therapeutics POSTERS

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

919-P

Pharmacokinetics and Pharmacodynamics of Ultra-Long Acting Insulin (LAPS-Insulin) in Animal Models

YOUNG JIN PARK, CHANG KI LIM, KYUNG JOON LIM, DAE JIN KIM, SANG HYUN LEE, GYU HYAN LEE, YOUNG IL KIM, YOUNG HOON KIM, HYUN HEE OH, CHEOL SOO CHOI, SE CHANG KWON, *Hwaseong-si, Republic of Korea, Seoul, Republic of Korea, Incheon, Republic of Korea*

In normal physiological conditions, pancreatic β-cell secrets sustained basal levels of insulin (basal insulin) to control fasting plasma glucose and releases large bursts of insulin after meals. An ideal basal insulin candidate should have characteristics of peak-less and prolonged action to mimic the flat inter-prandial insulin secretion of non-diabetic condition. LAPS-insulin is being developed as ultra-long acting basal insulin by conjugating the recombinant human insulin and constant region of human immunoglobulin fragment via non-peptidyl linker. The objective of this study was to investigate the pharmacokinetics and pharmacodynamics of LAPS-insulin in normal and diabetic animal models to evaluate once-weekly administration potential as ideal basal insulin. In pharmacokinetic study, subcutaneously injected LAPS-insulin showed significantly extended elimination half-life of 15 and 32 hours in normal rats and dogs, respectively. Time-action profiles of LAPS-insulin were monitored in normal rats under euglycemic glucose clamps conditions, and the glucose infusion rate (GIR) value for LAPS-insulin showed prolonged duration for 64 hours with peak-less pattern while insulin glargine lasted only for 5 hours. In addition, LAPS-insulin showed the extended glucose lowering action for 6 days in STZ induced diabetic mice while insulin glargine lowering blood glucose for 4 hours. The prolonged glucose lowering efficacy was also evaluated in db/db mice, and LAPS-Insulin lowered blood glucose for 8 days without hypoglycemia while insulin detemir lowering glucose only for 4 hours. In conclusion, LAPS-insulin shows a sufficiently extended efficacy compared to other long-acting basal insulins in maintenance of glucose level, and shows the potentials suitable for once-weekly ultra long-acting insulin.

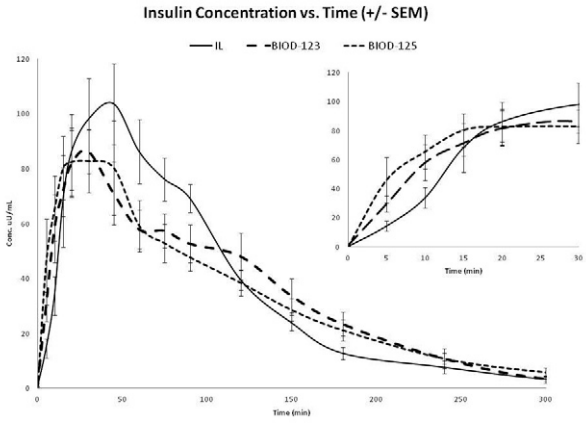
Supported by: Hanmi Pharm. Co., Ltd.

920-P

Pharmacokinetic and Pharmacodynamic Comparison of New Ultra-Rapid-Acting Insulin Formulations in Diabetic Miniature Swine

RODERIKE POHL, ROBERT HAUSER, BRYAN R. WILSON, MING LI, RICHARD SEIBERT, PRAGATI REDDY, MARY GUINNESS, MARILYN JACKSON, ERROL DE SOUZA, *Danbury, CT*

Recombinant human insulin formulations containing citrate and NaEDTA (Linjeta) are more rapidly absorbed but are associated with increased subcutaneous (sc) injection site discomfort compared to insulin lispro (IL) in man. The cause of this sensation is hypothesized to be the transient chelation of interstitial calcium creating altered neuronal firing in the injection vicinity. In the present study, we evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) properties of new formulations of Linjeta modified with calcium to lessen EDTA-Ca binding post injection (BIOD-125) or with the addition of magnesium (BIOD-123) to improve toleration through modulation of neuronal firing. Ten male miniature diabetic swine were given sc doses 0.25 U/kg IL, BIOD-123, BIOD-125 or IL. Following dosing, the swine were fed a standardized meal. Blood glucose and plasma insulin were sampled at multiple timepoints from -30 to 480 min. post dose. Plasma insulin was measured by ELISA and plasma glucose was determined using a YSI device. Insulin PK curves are shown below. The early absorption, as measured by $t_{1/2}$-early (LS mean ± SE; min.) of BIOD-123 (9.3 ± 1.9) and BIOD-125 (7.0 ± 1.9) was significantly faster ($p<0.05$) when compared to IL (17.6 ± 1.9). Changes in glucose concentrations were consistent with the PK profiles. These significant PK improvements in the timing of early absorption suggest that the new modified Linjeta formulations (anticipated to have improved toleration) maintain ultra-rapid speed of absorption relative to IL in the diabetic swine model.



921-P

WITHDRAWN

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

922-P

Performance Metrics of the Hypoglycemia-Hyperglycemia Minimizer (HHM) System in a Closed-Loop Feasibility Study

RAMAKRISHNA VENUGOPALAN, DANIEL A. FINAN, THOMAS W. MCCANN, JR., LINDA MACKOWIAK, EYAL DASSAU, STEPHEN D. PATEK, HENRY ANHALT, *West Chester, PA, Santa Barbara, CA, Charlottesville, VA*

A feasibility study conducted in 13 participants with type 1 diabetes investigating the characteristics of an automatic control algorithm showed encouraging performance metrics and demonstrated potential for developing an artificial pancreas device. This abstract highlights the relationship between the continuous glucose monitor (CGM) trends and the algorithm's insulin delivery characteristics.The study was conducted in a clinical research center (CRC) setting in which each of the participants was under closed-loop control for approximately 20 hrs. Prior to the CRC visit, each participant's basal rate profile was fine-tuned by the investigator as part of the clinical protocol. During the visit, the HHM System--comprising an insulin pump, CGM, and model predictive control (MPC) algorithm with a safety module--dosed insulin automatically.The table provides a simple quantification of how much insulin the algorithm delivered to the participant at "low" and "high" CGM readings, compared to the corresponding basal rates. For CGM values below 90 mg/dL, the algorithm dosed the participants an average of 85.7% less than their corresponding basal rates; for CGM readings above 140 mg/dL, the algorithm dosed 42.2% more. There were no safety concerns, including no DKA or severe hypoglycemia.The HHM System manipulated insulin delivery substantially compared to the corresponding basal rates, depending on CGM readings. These results indicate feasibility for developing such an artificial pancreas device, and planning is underway for further studies.

	Average insulin delivery rate (U/h) when CGM < 90 mg/dL			Average insulin delivery rate (U/h) when CGM > 140 mg/dL		
	Pre-programmed basal	Algorithm	Algorithm difference relative to basal	Pre-programmed basal	Algorithm	Algorithm difference relative to basal
Mean (N = 13)	0.90	0.13	-85.7%	0.86	1.21	+42.2%

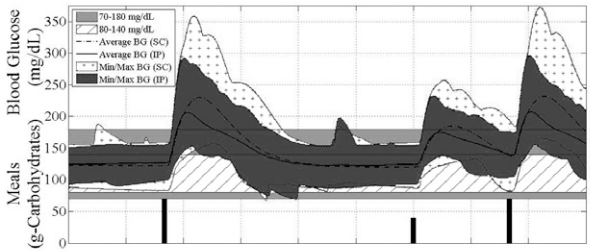
923-P

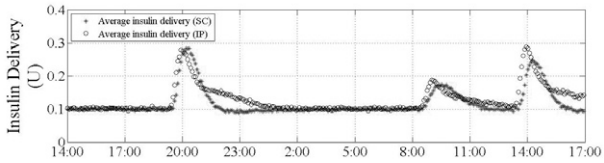
Evaluation of Zone-MPC for Intraperitoneal Insulin Delivery

JUSTIN LEE, EYAL DASSAU, HOWARD ZISSER, LOIS JOVANOVIC, FRANCIS DOYLE III, *Santa Barbara, CA*

Postprandial blood glucose (BG) regulation is one of the main challenges for an artificial pancreas (AP) utilizing a subcutaneous (SC) route, due to its slow pharmacokinetic characteristics. Thus, an AP based on an intraperitoneal (IP) route with rapid absorption (maximum concentration = 10-15 min) and fast clearance (2-3 h) may result in superior postprandial BG regulation (e.g. low postprandial BG peak without hypoglycemia risk). The AP design presented in this study utilizes a SC continuous glucose monitor and zone-MPC algorithm to regulate BG within a range, 80 - 140 mg/dL, by delivering IP insulin via the Roche Spirit Combo pump that is connected to the Diaport® system. The evaluation of the system on 100 in silico subjects from the UVA/Padova FDA-accepted metabolic simulator is presented, in preparation for an upcoming clinical trial. The protocol consists of three unannounced meals of 70, 40 and 70 g-Carbohydrates, dinner, lunch and breakfast, respectively. The results (fig. 1) show that the average postprandial BG peak of the subjects were 31 (dinner), 16 (breakfast), and 28 mg/dL (lunch) lower in the IP case than the SC case. Also, the subjects spent 16 % more time in a clinically acceptable region (70-180 mg/dL) in the IP case with 36 % and 51 % lower HBGI and LBGI, respectively. No hypoglycemic (< 60 mg/dL) events were observed.

Figure 1. Top: average BG of the subjects and a min/max envelope. Bottom: average insulin delivery. These results suggest that the IP route can provide superior BG regulation, which would decrease the likelihood of complications related to type 1 diabetes mellitus, compared to the SC delivery route.





Supported by: JDRF (17-2011-515)

924-P

Model-Based Insulin Therapy: Canine Study

BENYAMIN GROSMAN, ANIRBAN ROY, GAYANE VOSKANYAN, MIKHAIL LOUTSEIKO, NATALIE KURTZ, NEHA PARIKH, FRANCINE R. KAUFMAN, BARRY KEENAN, *Northridge, CA*

A novel algorithm was developed to optimize basal and bolus pump settings. The algorithm is designed to calculate basal rates and carbohydrate ratios for individual patients. Utilizing insulin doses, carbohydrate intake and glucose sensor information, the algorithm determines an insulin regimen to improve glycemia. Performance of the novel algorithm was assessed in diabetic dogs (n=6). Glycemic levels were monitored over three 24-hour periods. During the first period, pump settings previously established for each animal were used; during the second and third phases, insulin infusion rates were adjusted sequentially by ± 0.1 U/h. The data collected in three phases were then used to identify the mathematical model parameters to estimate basal therapy and the carbohydrate ratios. Additionally, the algorithm was assessed in 10 adult virtual subjects *in silico* using the UVA/Padova T1DM metabolic simulator. Comparison was made between the glycemic results with the novel algorithm and the UVA/Padova optimal treatment protocol. In the diabetic dogs, preliminary results showed there was no hyperglycemia as defined as glucose values >180 mg/dL using the novel algorithm. This compared to ~10% of the time spent with glucose levels >180 mg/dL during the control period. In the *in silico* studies, glucose values were in the target range of 70-180 mg/dL for ~95% of the time. The overall glucose range achieved was 67-233 mg/dL. Compared to the UVA/Padova optimal treatment which led to hypoglycemia in one virtual subject, there was an improvement in glycemia with the novel algorithm and no hypoglycemia. In the future, novel algorithms might serve as methodologies to improve the glycemic outcomes of insulin pump therapy in patients with type 1 diabetes.

Supported by: Medtronic, Inc.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—PHARMACOLOGIC TREATMENT OF DIABETES OR ITS COMPLICATIONS

Guided Audio Tour: Off Target Effects of Diabetes Therapies *(Posters 925-P to 932-P), see page 15.*

925-P

HIF-1α as a Novel Molecular Target in Anticancer Effects of Metformin

YUMI TAKIYAMA, JUN HONJO, YUKIHIRO FUJITA, TSUYOSHI YANAGIMACHI, HIROYA KITSUNAI, HIDEMITSU SAKAGAMI, YUICHI MAKINO, MASAKAZU HANEDA, *Asahikawa, Japan*

Clinical studies have shown that metformin exerts anticancer effects. The unique cancer metabolism is aerobic glcolysis defined as the Warburg effect. In progression of carcinoma, aggressive cancer cells should adapt to low oxygen supply by the Pasteur effect. Beyond glycolysis, recentstudies have demonstrated that some epithelial cancer cells increase oxidative mitochondrial metabolism, and that the TCA cycle operates even under hypoxia. These evidences led us to question whether metformin might regulate the mitochondrial metabolism in cancer cells.Here we investigated the effects of metformin using the human anaplasitc thyroid cancer ARO cells. Hypoxia induced a cell-cycle arrest in G0/G1 phases. Interestingly, metformin promoted cell-cycle arrest, following increased apoptosis especially under hypoxic conditions. Hypoxia also induced a significant increase in HIF-1α protein levels. Either metformin or the AMPK activator AICAR inhibited the expression of HIF-1α protein without inhibition of HIF-1α mRNA under hypoxic condition. Metformin also inhibited the expressions of HIF-1 target gene, *e.g.* VEGF and Glut-1. Moreover, metformin and AICAR

enhanced the phosphorylation of AMPK, ACC, and decreased the phosphorylation of mTOR. The mTOR inhibitor rapamycin suppressed expression of HIF-1α protrein. Likewise, the inhibitor of mitochondrial electron transfer chain subunit I (rotenone), not the NADPH oxidase inhibitor DPI, mimicked the effects of metformin on the expressions of HIF-1α and phopsholyrated AMPK. The proteasomal inhibitor MG-132 eradicated the inhibitory effects of metformin on hypoxia-induced HIF-1α protein expression. Furthermore, metformin decreased average oxygen consumption rates and increases intracellular oxygen tension stained with hypoxia-sensitive dye, pimonidazole. Taken together, these data reveal that HIF-1α as well as mitochondrial oxygen metabolism is a novel molecular target in anticancer effects in response to metformin treatment.

926-P

Effect of Pioglitazone on Body Fat and Bone Mineral Content in the ACT NOW Trial

GEROGE A. BRAY, STEVEN R. SMITH, MARYANN BANERJI, DEVJIT TRIPATHY, THOMAS BUCHANAN, ABBAS E. KITABCHI, ROBERT HENRY, FRANKIE B. STENTZ, NICOLAS MUSI, DAWN C. SCHWENKE, PETER REAVEN, RALPH A. DEFRONZO, *Baton Rouge, LA, Winter Park, FL, Brooklyn, NY, San Antonio, TX, Los Angeles, CA, Memphis, TN, San Diego, CA, Phoenix, AZ*

Thiazolidinediones (TZDs) increase body weight (BW) and body fat (BF) and increased risk of fracture in type 2 diabetics, but there are few data in patients with impaired glucose tolerance (IGT). The ACT NOW trial provided a population of IGT patients in whom body composition, including bone mineral content, was followed over 2.4 years. We hypothesized that pioglitazone would differentially affect body fat stores in various regions of the body and might alter bone mineral content. 234 men and women (age = 49.3 ± years and BMI = 34.5±5.9 kg/m2) at 5 of 8 sites in ACT NOW had measurements of body composition by dual energy x-ray absorptiometry (DEXA) optimized for adipose tissue assessment at baseline and at conversion to diabetes or at study end. Body weight and body fat increased significantly more in participants treated with pioglitazone versus placebo (BW = 4.6±0.6kg vs 0.90±0.59 kg; BF=2.9±0.kg 3 vs 0.9±0.3 kg). The percent increase in BF was higher in legs and arms than in the trunk. More fat was gained by women than men in all regions. The change in body fat was inversely related to the change in fasting plasma glucose (r = 0.34, p=0.002) and change in the Matsuda Index of insulin sensitivity (r = - 0.34 p = 0.0004). Of IGT patients who had a DEXA, there were 3 fractures (wrist) in the treated group and none in the placebo group. In the entire IGT population there were an equal number of fractures in the pioglitazone and placebo groups, and all were related to trauma. Using DEXA scans we found that women had significantly lower levels of bone mineral content and density in almost all regions than men. Those treated with pioglitazone had significant decreases in bone mineral density in the pelvis (p<0.001) and thoracic spine (p=0.04), but not in the arms, legs or lumbar spine. We conclude that pioglitazone had detrimental effects on bone mineral density in several bone regions and increased peripheral fat more than truncal fat. Fat weight gain and redistribution were associated with improved insulin sensitivity and decrease in FPG.

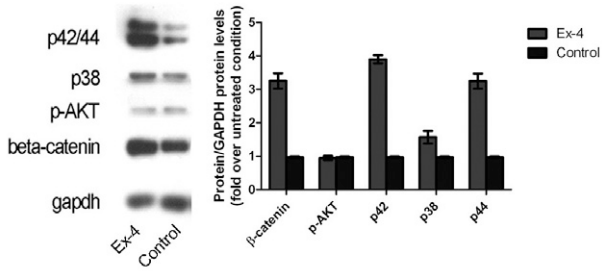
927-P

Glucagon-Like Peptide-1 Receptor Agonists Suppress Adipogenesis and Enhance Osteogenesis of Rat Mesenchymal Stromal Cells and Improve Bone Defects in Spontaneous Type 2 Diabetic GK Rats

HAN-XIAO SUN, JIAN-MIN LIU, NAN LU, DONG-MEI LIU, XIU LUO, LIN ZHAO, XIAO-YING LI, WEI-QING WANG, GUANG NING, *Shanghai, China*

Glucagon-like peptide-1 (GLP-1) receptor agonists, such as exendin 1-39 amide (Ex-4) and liraglutide, are a new class of anti-diabetic therapy. The presence of GLP-1 receptor (GLP-1R) on bone marrow stromal cells (MSC) and osteoblasts renders bone as a potential target for this kind of drugs. We aimed to investigate the regulatory actions of Ex-4 on osteogenesis and adipogenesis in rat MSCs; and to assess the changes in bone mineral density(BMD) and bone micro-architectures in spontaneous type 2 diabetic GK rats following daily intra-peritoneal injection of liraglutide (0.4ug/kg). The rat MSCs were isolated from the bone marrow of tibiae and femora. When 0.1nM Ex-4 was added to adipogenic or osteogenic medium of MSCs, it suppressed lipid droplets formation and mRNA levels of PPARγ and C/EBPα, while increased Runx2, ALP, collagen 1 expression, respectively. Western blot analysis revealed the enhanced expression of p42/44, p38 and β-catenin after 6 days of treatment (Fig 1). In-vivo study showed that the decreased BMDs at femur and lumbar-spine, the lower BV/TV, Tb.Th and higher Tb.Sp values in GK rats could be rescued by 28 days of liraglutide treatment. Our results indicated that GLP-1R agonist can promote osteogenesis while inhibit adipogenesis of rat MSCs, and can also prevent the bone loss and ameliorate the bone quality defects in type 2 diabetic GK rats. GLP-1R agonist may be useful in treating diabetes-related bone damage.

Fig.1 Effects of Ex-4 on Wnt and MAPK pathway activation



Supported by: Chinese National Natural Science Foundation: 30725037, 81070693

928-P

Pioglitazone and Bladder Malignancy During Observational Follow-Up of PROactive: 6-Year Update

ERLAND ERDMANN, ERIC SONG, ROBERT SPANHEIMER, ANNE-RUTH VAN TROOSTENBURG DE BRUYN, ALFONSO PEREZ, *Cologne, Germany, Deerfied, IL*

PROactive was a double-blind, placebo-controlled outcomes study investigating pioglitazone for secondary prevention of macrovascular events in type 2 diabetes. Although there was no difference in the cumulative incidence of overall malignancies between treatment groups (3.7% for pioglitazone *vs* 3.8% for placebo), an imbalance in the number of diagnosed bladder malignancies was reported (n=14 for pioglitazone *vs* 5 for placebo). Of the 5238 randomized patients, 3599 (74%) then entered a 10-yr non-interventional observational study with no allocation to study medication, which included reporting of any new malignancies. An interim 6-yr analysis compared overall and bladder malignancies based on original randomization to pioglitazone or placebo. During the observational period alone (mean 5.8 yr), diagnoses of any malignancy were similar between the two groups (Table), and there were fewer cases of bladder malignancy in the pioglitazone group. For the combined PROactive double-blind and observational periods (up to 9.5 yr in total; mean 8.7 yr), a similar % of patients had a diagnosis of any malignancy or specifically bladder malignancy in the pioglitazone and placebo groups (Table). When pioglitazone usage during the observational period was considered, there was no significant difference in bladder malignancies between those with any and those with no pioglitazone use for both periods combined (Hazard ratio=0.98, 95% CI [0.55, 1.77], p=0.96). The imbalance in bladder cancer incidence during the double-blind period of PROactive did not persist in this interim analysis of the observational follow-up study.

Number (%) of patients with a diagnosis of any malignancy or specifically bladder malignancy during PROactive double-blind period and observational follow-up according to original double-blind therapy and regardless of subsequent treatment

Treatment Period and Endpoint	Original treatment during double-blind period		Relative risk	95% CI
	Pioglitazone	Placebo		
Observational period only	(n=1820)	(n=1779)		
Any malignancy	164 (9.0%)	156 (8.8%)	1.03	[0.83, 1.27]
Bladder malignancy	10 (0.5%)	17 (1.0%)	0.57	[0.26, 1.25]
Double-blind period + observational period	(n=2605)	(n=2633)		
Any malignancy	257 (9.9%)	247 (9.4%)	1.05	[0.89, 1.24]
Bladder malignancy	23 (0.9%)	22 (0.8%)	1.06	[0.59, 1.89]

Supported by: Takeda Pharmaceuticals

929-P

Impact of Anti-diabetic Drug Selection on Weight Change and HbA1c Outcomes in Treatment Naïve Patients With Type 2 Diabetes

BRANDON K. BELLOWS, XIANGYANG YE, SUDHIR UNNI, JAYANTI MUKHERJEE, UCHENNA H. ILOEJE, CARRIE MCADAM-MARX, *Salt Lake City, UT, Wallingford, CT*

Previous work found that treatment naïve patients with type 2 diabetes (T2DM) prescribed an anti-diabetic with weight gain properties were less likely to be at HbA1c goal (OR 0.71) and experience weight loss (OR 0.46; both p<.001) at 12 months than those prescribed a drug with weight loss or weight neutral properties. The current study examined the association of anti-diabetics grouped by weight-effect properties on weight and glycemic control in a subset of patients with uncontrolled (HbA1c ≥7%) T2DM. Adults

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

(≥18 years) with uncontrolled T2DM initiating therapy (index date) associated with weight gain [sulfonylurea (SU), thiazolidinedione (TZD)] or weight loss/neutrality [metformin (MET), DPP-4 inhibitor (DPP-4), GLP-1 agonist (GLP-1)] were identified in a national electronic medical record database between 1/1/00 and 6/30/10. Study outcomes were weight gain (increase ≥3%) vs. no weight gain and glycemic control (HbA1c <7% vs. ≥7%) after 12 months of follow up. Multivariable logistic regressions were used to determine the likelihood of weight gain and glycemic control by drug group controlling for baseline characteristics such as age, weight, and race.The study included 15,684 patients. Mean (SD) age was 60.4 (11.7) years; 51.6% were female. Baseline HbA1c was 8.3% and weight was 96.4 (22.6) kg. Patients on SU/TZD were significantly more likely to gain weight at 12 months compared to MET/DPP-4/GLP-1 [OR 3.15 (95%CI 2.88, 3.45)]. Patients on SU/TZD had a lower proportion with glycemic control (50.2% vs. 56.6%) and were significantly less likely to achieve glycemic control at 12 months compared to patients on MET/DPP-4/GLP-1 [OR 0.73 (0.68, 0.78)].Patients with uncontrolled T2DM prescribed SU or TZD were more likely to gain weight and less likely to attain glycemic control than those receiving MET, DPP-4, or GLP-1. These results suggest the weight-effect properties of a drug should be considered when selecting drug treatment for patients with uncontrolled T2DM.

Supported by: Bristol-Myers Squibb

930-P

Event Rate Assessment of Bladder Cancer and Nine Other Cancers for Pioglitazone Relative to Insulin

CARLOS VALLARINO, ALFONSO PEREZ, GREGORY FUSCO, HUIFANG LIANG, MORGAN BRON GREEN, SUDHAKAR MANNE, VENKATESH HARIKRISHNAN, GUIANDRE JOSEPH, SHAWN YU, *Deerfield, IL*

This retrospective cohort study used i3 InVision Data Mart to assess event rates of bladder cancer and a composite of nine other cancers (prostate, female breast, lung, pancreatic, endometrial, non-Hodgkin's lymphoma, colorectal, kidney and malignant melanoma) in new users of pioglitazone (PIO) and insulin mainly as third-line therapies. Kaplan-Meier curves were generated for the occurrence of these outcomes based on adjustment with inverse probability weights derived from propensity scores. Hazard ratios (HR) for PIO versus insulin and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models.A total of 56,536 type 2 diabetes patients (PIO group: 38,588; insulin group: 17,948) aged ≥45 years were selected from May 1, 2000 to June 30, 2010 (mean follow-up: 2.2 years for PIO and 1.9 years for insulin). For bladder cancer, the incidence rate showed no significant difference between the two groups; the HR for PIO versus insulin was 0.92 (95% CI [0.63, 1.33], p=0.64). The results were similar for bladder cancer with and without confirmation based on cancer-related procedures. There was no evidence of increasing risk of bladder cancer over time periods with PIO. Incidence rate analysis for the composite of nine other cancers favored the PIO group; the HR for PIO versus insulin was 0.78 (95% CI [0.71, 0.85], p<0.0001). The total incidence rates (per 100,000 person years) of nine other cancers for PIO (1798) and insulin (2456) were more than 10 times higher than the rate of bladder cancer alone (PIO: 113; insulin: 152).The results suggest there is no increased risk of bladder cancer and lower risk of nine other selected cancers with pioglitazone compared with insulin.

931-P

Linagliptin Reduces Ischemic Brain Damage Following Stroke in a High-Fat Diet Mouse Model: a Comparison to Glimepiride

VLADIMER DARSALIA, ANNA OLVERLING, HENRIK ORTSÄTER, THOMAS KLEIN, ÅKE SJÖHOLM, CESARE PATRONE, *Stockholm, Sweden, Biberach, Germany*

Type 2 diabetes (T2D) is a major risk factor for premature and severe stroke. Linagliptin is a dipeptidyl peptidase (DPP)-4 inhibitor with unique pharmacological properties approved for the treatment of T2D. The aim of this study was to determine the efficacy of linagliptin in protecting against stroke-induced ischemic brain damage in a diabetic animal model. C57BL/6J male mice fed a high-fat diet for 36 weeks were treated with oral linagliptin (10 mg/kg/d; n=7), the sulfonylurea glimepiride (2.5 mg/kg/d; n=7), or vehicle (n=7) during Weeks 30-36. Blood glucose levels, body weight, and food intake were measured at regular intervals during the study. At Week 33, animals were subjected to 30 min of transient middle cerebral artery occlusion to induce a stroke. Drug treatment was continued until Week 36 when the animals were sacrificed. The severity of ischemic damage was measured by evaluation of stroke volume and by stereological counting of neurons in the striatum and cortex. Glimepiride caused a marked reduction in non-fasted glucose (-48%; p<0.001), but did not show any neuroprotective benefit compared with vehicle. In contrast, linagliptin, which demonstrated weaker effects on the glycemic status (-23%; p<0.01), produced a pronounced and statistically significant reduction in ischemic stroke damage compared with vehicle, as measured by the quantification of surviving neurons in the stroke-damaged brain (p<0.01). These results indicate that the mechanism of linagliptin-induced neuroprotection is complex and cannot be explained solely by the reduction in hyperglycemia. In conclusion, this study is the first to show that DPP-4 inhibition in a diabetic animal model leads to neuroprotection following stroke, independent of glycemic changes. The results presented here demand further investigation of the neuroprotective actions of DPP-4 inhibitors in the treatment of diabetes as well as their possible use as anti-stroke medication in non-diabetic conditions.

Supported by: Boehringer Ingelheim

932-P

Dipeptidyl Peptidase IV Inhibition Does Not Adversely Affect Immune and Virologic Status of HIV+ Men and Women

SCOTT R. GOODWIN, DOMINIC N. REEDS, MICHAEL ROYAL, HEIDI STRUTHERS, ERIN LACINY, KEVIN E. YARASHESKI, *St. Louis, MO*

HIV+ people are at higher risk for developing insulin resistance, diabetes, and cardiovascular disease than the general population. Dipeptidyl peptidase IV (DPPIV) inhibitors (sitagliptin; Januvia) are a new class of glucose-lowering medications with pleiotropic actions that may benefit HIV+ people. However, the immune and virologic safety of DPPIV-inhibition in HIV is unknown. DPPIV is identical to CD26; a cell surface glycoprotein involved in T-cell activation and chemokine (Stromal-Derived Factor 1α (SDF1α) and Regulated upon Activation Normal T-Cell Expressed and Secreted (RANTES)) processing. We hypothesized that DPPIV inhibition will not adversely affect immune (CD4+ T-cells) or virologic (plasma HIV RNA) status, increase immune activation (sTNFRII), or inactivate immune cell CD26 activity (promote HIV entry) in HIV+. Randomized, placebo controlled, double blind trial of non-diabetic HIV+ men (n=17) and women (n=3) (38±12yrs, 10±6 yrs HIV+) taking anti-HIV therapy, with stable immune (625±134 CD4+ T-cells/μL) and virologic (<48 copies HIV RNA/mL) status received sitagliptin (100mg/d) or matching placebo for up to 24 wk. CD4+ T-cells and HIV RNA were measured every 4 wk; fasting serum RANTES, SDF1α, sTNFRII, and oral glucose tolerance (oGTT) were quantified at baseline, wk 8 and end of study. ANOVA was used for between group comparisons; p<0.05 was considered significant. Compared to placebo, sitagliptin did not reduce CD4+ number; HIV RNA remained <48 copies/mL, RANTES and sTNFRII concentrations did not increase. Sitagliptin reduced total serum SDF1α concentration (p<0.0002) at wk 8 and study end. oGTT glucose levels improved more in the sitagliptin vs placebo group. Despite lowering SDF1α levels, sitagliptin appears safe in healthy, non-diabetic HIV+ men and women; no adverse affect on immune or virologic status, no increase in an immune activation biomarker, and improved glycemia, so cardiovascular efficacy outcome studies are planned.

Supported by: The Campbell Fdn, NIH

Guided Audio Tour: Cardiovascular Effects of Diabetes Therapy *(Posters 933-P to 940-P), see page 15.*

933-P

Pioglitazone Improves Myocardial Glucose Uptake and Myocardial Blood Flow in Type 2 Diabetic Subjects

MARJORIE MOLINA-WILKINS, GEOFFREY D. CLARKE, FENG DONG, SANDRA MARTINEZ, JOHN R. KINCADE, JESUS GARDUNO-GARCIA, SAMIA B. GEEVARGHESE, VERNA MENDEZ, ADRIANA MONROY, RUCHA J. MEHTA, AURORA MEROVCI, CAROLINA SOLIS-HERRERA, STEVEN BAILEY, ROBERT J. CHILTON, PATRICIA IOZZO, MUHAMMAD ABDUL-GHANI, RALPH A. DEFRONZO, MUSTAFA KANAT, *San Antonio, TX, Pomona, CA, Pisa, Italy*

Insulin resistance in skeletal muscle, liver and adipocytes is a cardinal feature of type 2 diabetes. Recent studies have demonstrated decreased insulin-mediated glucose uptake in the myocardium in T2DM. Increased central fat has been associated with decreased whole body insulin sensitivity. Pioglitazone is a thiazolidinedione which has been shown to increase whole body insulin sensitivity and mobilize fat from the central to the subcutaneous depot. In this study, we examined the effect of pioglitazone on pericardial fat content, whole body insulin sensitivity, myocardial glucose uptake, and myocardial blood flow in 7 type 2 diabetic individuals with Coronary Artery Disease (age = 53±9 years, BMI = 31.1±3.9 kg/m^2, and HbA1c = 6.6±1.4%). A 20-week treatment with pioglitazone (45 mg per day) caused a significant increase in whole body glucose uptake, measured with the euglycemic insulin clamp (3.4±1.2 to 5.8±1.9 mg/kg/min, P=0.002), and myocardial glucose uptake, measured with FDG and PET scan (0.28±0.13 to 0.51±0.12,

mmol/min/mL tissue P <0.001). Myocardial blood flow, measured with ^{15}O-water and PET scan was significantly increased following pioglitazone treatment (0.83±0.13 to 1.04±0.18 ml/min/gr tissue, P<0.01). Pioglitazone decreased both pericardial fat and mediastinal fat content measured with MRI (15.2±3.7 to 14.1±3.8 cm^2, P=0.03 and 34.2±12.8 to 30.9±13.6 cm^2, P=0.05). These results suggest that pioglitazone has beneficial effects on myocardial metabolism and blood flow in diabetic individuals.

Supported by: Takeda Pharmaceuticals

934-P

Effect of Anti-Diabetic Drugs on Cardiovascular Outcomes in Patients With Type 2 Diabetes and Coronary Artery Disease

GUANG NING, JIE HONG, YIFEI ZHANG, THE SPREAD-DIMCAD STUDY GROUP, *Shanghai, China*

Background: The two major classes of hypoglycemic agents sulfonylurea and biguanide may differentially affect macrovascular complications and mortality in diabetic patients. However, the clinic evidence is sparse. We compared the long-term effects of glipizide and metformin on the major cardiovascular events in type 2 diabetes(T2DM) patients who had a history of coronary artery disease(CAD) in a randomized, double-blind, placebo-controlled clinical trial.Methods: In the SPREAD-DIMCAD randomized trial, patients with T2DM and CAD were randomly assigned to receive either glipizide plus metformin placebo or metformin plus glipizide placebo for 3 years. The primary end points were time to the composite of recurrent cardiovascular events, including death from a cardiovascular cause, death from any cause, nonfatal myocardial infarction, nonfatal stroke or arterial revascularization). The trial was registered at ClinicalTrials.gov, number. NCT00513630. Findings: 304 participants were randomly assigned to glipizide or metformin. At the end of study drug administration, both groups achieved a significant decrease in glycated hemoglobin level (7·1% in glipizide group and 7·0% in metformin group). At a mean follow-up of 5·0 years, 91 participants had developed 103 primary end points. Intent-to-treat analysis showed an adjusted hazard ratio (HR) of 0·54 (95% CI 0·30-0·90, p=0·026) for the composites of cardiovascular events among the patients received metformin, compared with glipizide. The secondary end points and adverse events were not significantly different between the two groups.Interpretation: Treatment with metformin for 3 years substantially reduced major cardiovascular events in a mean follow-up of 5·0 years in high risk patients compared with glipizide. Our results provide a basis for recommendation of metformin as a cardiovascular disease prevention strategy in diabetic patients.

935-P

Pioglitazone and Macrovascular Outcomes During Observational Follow-up of PROactive: 6-Year Update

ERLAND ERDMANN, ERIC SONG, ROBERT SPANHEIMER, ANNE-RUTH VAN TROOSTENBURG DE BRUYN, ALFONSO PEREZ, *Cologne, Germany, Deerfield, IL*

In PROactive, a double-blind, placebo-controlled outcomes study in type 2 diabetes mellitus (T2DM) patients with known macrovascular disease, pioglitazone provided a non-statistically significant 10% relative risk reduction for the primary composite endpoint (all-cause death, myocardial infarction [MI], acute coronary syndrome [ACS], cardiac intervention, stroke, major leg amputation, leg revascularization) and a statistically significant 16% reduction for the main secondary endpoint (death, MI, stroke) after a mean 34.5 months. Of 5238 randomized patients, 3599 (74%) subsequently entered a 10-yr non-interventional observational study with no exclusion criteria or allocation to study medication; patients are treated per standard medical practice. An interim 6-yr analysis used a Cox proportional hazard model to compare non-adjudicated macrovascular events (using the same endpoints excluding ACS) between pioglitazone and placebo based on patients' original randomization in PROactive. For the observational period alone (mean 5.8 yr, during which fewer than 15% of patients received pioglitazone at any time) or the combined PROactive double-blind and 6-yr observational period (up to 9.5 yr in total; mean 8.7 yr), there were no statistically significant differences in the primary or secondary endpoints for pioglitazone *versus* placebo (Table). These results suggest that the improved cardiovascular outcome seen with pioglitazone during the double-blind period of PROactive did not persist during the observational period in the absence of continued pioglitazone treatment.

Number (%) of patients with macrovascular events during PROactive observational follow-up according to original double-blind therapy and regardless of subsequent treatment

Treatment Period	Endpoint	Original treatment during double-blind period		Hazard ratio	95% CI	p-value
		Pioglitazone	Placebo			
Double-blind (PROactive, mean 34.5 mo)		(n=2605)	(n=2633)			
	Primary	514 (19.7%)	572 (21.7%)	0.90	[0.80, 1.02]	0.095
	Main secondary	301 (11.6%)	358 (13.6%)	0.84	[0.72, 0.98]	0.027
	All-cause death	177 (6.8%)	186 (7.1%)	0.96	[0.78, 1.18]	0.678
Observational only (mean 5.8 yr)		(n=1820)	(n=1779)			
	Primary	767 (42.1%)	766 (43.1%)	0.98	[0.89, 1.08]	0.687
	Main secondary	567 (31.2%)	553 (31.1%)	1.01	[0.90, 1.14]	0.869
	All-cause death	368 (20.2%)	363 (20.4%)	1.00	[0.86, 1.15]	0.976
Double-blind + observational (max 9.5 yr; mean 8.7 yr)		(n=2605)	(n=2633)			
	Primary	1118 (42.9%)	1147 (43.6%)	0.95	[0.87, 1.03]	0.216
	Main secondary	829 (31.8%)	855 (32.5%)	0.95	[0.86, 1.05]	0.293
	All-cause death	545 (20.9%)	549 (20.9%)	0.98	[0.87, 1.11]	0.797

Primary endpoint = composite of all-cause death, MI, cardiac intervention, stroke, major leg amputation, leg revascularization; in PROactive, also included acute coronary syndrome.
Main secondary endpoint = composite of all-cause death, MI, stroke.

Supported by: Takeda Pharmaceuticals

936-P

An Observational Study of Effect of Incretin Therapies on Cardiovascular Risk and Insulin Dose

CHRISTOPHER J. SMITH, RUSSELL DRUMMOND, *Glasgow, United Kingdom*

Incretin based therapies are not simply glucocentric but also confer weight benefits and possible blood pressure reduction.We sought to ascertain the relative cardiovascular risk benefit of these agents in an observational analysis of routine care in a university hospital.We analysed the effect on HbA1c, weight, systolic BP and lipid profile over 12 months. T test determined statistical significance. We calculated cardiovascular risk with the UKPDS calculator. We corrected for sex, age, diabetes duration, heart rhythm and smoking status.We also wanted to observe the effect of incretin therapies, when used with insulin, on insulin dose.Exenatide (n=102) lowered mean HbA1c from 9.41% to 9.08% (p=0.04), weight from 110.35kg to 105.82kg (p<0.001) but not systolic BP (134.76mmHg to 134.11mmHg (p=0.29)). UKPDS risk for CHD lowered from 18.5% to 16.3%.30 patients used combination of insulin and exenatide. Mean daily insulin dose fell from 83.1units to 77.5units (p=0.363).Liraglutide (n=97) lowered mean HbA1c from 9.94% to 9.42% (p=0.003), weight 107.97kg to 104.07kg (p<0.001)) and systolic BP 138.36mmHg to 134.84mmHg (p=0.04). UKPDS risk for CHD fell from 22.4% to 20.2%.42 patients used insulin and liraglutide combination. Mean daily insulin dose reduced from 101.0units to 94.7units (p=0.04).Finally Sitagliptin (n=102) lowered HbA1c from 9.22% to 8.95% at 12 months (p=0.07) and had no effect on weight (93.30kg to 92.72kg p=0.44) or systolic BP (137.03mmHg to 139.81 mmHg p=0.29). UKPDS risk fell from 18.5% to 17.3%.12 patients used combination of insulin and sitagliptin. Daily insulin dose significantly rose, from 62.8units to 76.0units (p=0.009).We have demonstrated, similar to previous data, that while all 3 agents lower HbA1c, GLP1 treatment is associated with weight loss, and liraglutide reduced blood pressure. All 3 agents were associated with a reduction in CV risk scores.Liraglutide decreased insulin requirements, whereas exenatide had no effect, and dose rose on sitagliptin.

937-P

Heat Treatment With Mild Electrical Stimulation Reduces Visceral Adiposity and Improves Insulin Resistance and Inflammatory Markers in Male Subjects With Type 2 Diabetes

TATSUYA KONDO, RINA MATSUYAMA, KATSUTOSHI MIYAGAWA, RIEKO GOTO, JUNJI KAWASHIMA, HIROYUKI MOTOSHIMA, HIROFUMI KAI, EIICHI ARAKI, *Kumamoto, Japan*

Induction of heat shock protein (HSP) 72 improves glucose homeostasis and reduces visceral adiposity in diabetic mice. The present study investigated whether HSP72 induction could exert similar effects on T2DM patients.Forty subjects with T2DM were randomly assigned into 2 groups. One group was treated with MET (Mild Electrical stimulation with hyperThermia: 12V, 55 pps, 60 min at 42°C, 4 times a week. MET induces more HSP72 than simple thermo-therapy) for 12 weeks and the other was not for the same period. Then, crossover treatment was performed.Visceral adipose volume measured by CT scan was significantly decreased by 10.9 ± 0.7% (p=7.0*10^{-5}) and Wc was also reduced by 2.8 ± 0.2% (p=0.0003) upon MET treatment, whereas BW and subcutaneous adipose volume were not. Both systolic and diastolic blood pressure were significantly reduced by 4.35 ± 0.20% (p=0.006) and 6.56 ± 0.76% (p=0.0004), respectively. With respect to glucose homeostasis, fasting plasma glucose and insulin levels were both decreased by 10.4 ± 3.7% (from 148.6 to 133.1 mg/dL, p=5.7*10^{-7}) and 25.9 ± 2.26% (from 15.0 to 11.1 μU/mL, p=0.001), respectively. HOMA-IR was significantly improved by -34.3 ± 6.7% (p=9.7*10^{-8}). HbA1c showed a

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

significant reduction from 7.76% to 7.35% (delta HbA1c=0.42%, p=9.6*10^{-8}). CRP, adiponectin, and TNF-α were all improved by -14.2 ± 1.7% (p=0.033), +12.6 ± 3.7% (p=0.037), and -21.6 ± 4.2% (p=0.036), respectively. In addition, LDL-C was decreased by 5.3 ± 0.9% (p=0.038) and HDL-C was increased by 5.6 ± 1.1% (p=0.008).Taking these results, we could confirm that MET treatment improved glucose homeostasis and insulin resistance in males with T2DM. Visceral adiposity and inflammatory cytokines also showed favorable changes. These beneficial alterations are quite similar to those observed in metabolic syndrome subjects. Therefore, MET could be a therapeutic alternative to treat metabolic disorders including T2DM.

Supported by: Ministry of Education, Science, Sports, and Culture of Japan

938-P

Glycemic Management in Heart Transplantation: Glycemic Outcomes

AMISHA WALLIA, CRISTINA GARCIA, SURUCHI GUPTA, KATHLEEN SCHMIDT, DIANA JOHNSON, MARK E. MOLITCH, *Chicago, IL*

We assessed management of hyperglycemia by an inpatient Glucose Management Service (GMS) following Heart Transplant (HT) in patients (pts) with (DM) and without (nonDM) a prior diagnosis of diabetes. HT pts receive postop steroids (500 mg solumedrol tapered to 20 mg prednisone over 3-5 d). Charts of 92 HT pts from 6/1/05 - 7/31/09 were analyzed for up to 1 year post-HT. Values are given as mean ± SD and glucose (GLU) levels are in mg/dL. Two-sample t-tests and Fischer's exact test were used.Insulin regimens were examined in detail in 72 (53 nonDM, 19DM) of the 92 HT pts (20 excluded: 1 death, 4 no GMS consult < 5 days post-HT, 4 missing data, 11 outliers [on insulin drip >5 d]). There were no significant differences between the DM and nonDM pts for mean GLU levels prior to starting IV insulin (DM 254±99, nonDM 263±69), on Day 1 of drip (DM 156±40, nonDM 166±34), in the hours on IV prior to conversion (CON) to SQ insulin (DM131±26, nonDM 130±31) or on post-CON fasting GLU (DM 137±51, nonDM 121±26). There were no significant differences between DM and nonDM pts for total glargine dose (units) on day of CON (DM 32.9±20, nonDM 32.2±18), on Day 1 post-CON (DM 32.4±20, nonDM 27.3±16) and subsequent days 2 & 3. Only on Day 2 post-CON (of 6) was there a significant difference in mean GLU levels in DM vs NonDM (146±29 vs. 127±29 p= 0.02).Of the total 92 pts, 26 (28%) had a diagnosis of DM prior to HT and 4 had an A1c $\geq$ 6.5 (undiagnosed DM) found peri-HT. Of the 66 without a prior diagnosis of DM, 12 (18%) were treated for hyperglycemia at discharge & 13 (20%) at 1 mo. One pt had fasting GLU $\geq$ 126 at 1 mo, untreated. At 1 year 19/66 (29%) had DM [by A1c, fasting GLU, or meds] but 4/19 (21%) were untreated. Of the 19, 9 (47%) had been normal at 1 mo post-HT & 5 pts with DM at 1 mo had insufficient data for classification at 1 yr.Inpatient insulin protocols implemented by a GMS are successful in obtaining glycemic control in pts with and without DM even with high dose steroid use. Outpatient protocols are needed to accurately assess DM status before and after HTto adequately guide treatment for all pts.

939-P

Association of Adherence to Colesevelam HCl and Major Cardiovascular Events

XIN YE, CHUNLIN QIAN, TRACY LI, *Parsippany, NJ*

Objective: To examine the relationship between adherence to colesevelam and risk of major cardiovascular (CV) events, ie, acute myocardial infarction (AMI) and stroke among type 2 diabetes mellitus (T2DM) patients newly treated with colesevelam.Methods: The study sample consisted of T2DM patients in a large, national claims database in 2007-2010 who newly initiated colesevelam with at least 6 and 12 months continuous enrollment prior- and post- drug initiation date, respectively. Adherence to colesevelam was measured as Medication Possession Ratio (MPR), calculated as total days of supply during a one-year period after drug initiation date (adherence cohort assignment period [ACAP]) divided by 365. Patients were assigned to one of three adherence cohorts (High: MPR>=0.8, medium: 0.5<=MPR<0.8, low: MPR<0.5.). The outcome was the time to the first hospitalization with a primary diagnosis for AMI or stroke during the follow up period from the end of ACAP to the end of enrollment period in the database. Association of colesevelam adherence with the outcome was examined by multivariate Cox regression, adjusting for patient demographics, baseline comorbidities, concomitant medications, and AMI or stroke during ACAP.Results: A total of 12,180 patients were included in the analysis, of which 2,405 (19.8%), 1,930 (15.9%), 7,845 (64.4%) were high, medium and low adherence, respectively. Compared to patients with low adherence, high adherence patients were 46% less likely to be hospitalized for AMI or stroke during the follow up period (Hazard Ratio: 0.54; 95% CI: 0.33 - 0.91; P=0.019). Other significant factors included female sex, younger age, absence of concomitant use of beta blockers, insulin and antiplatelets and absence of AMI or stroke during the ACAP.Conclusions: High adherence to colesevelam was associated with significantly lower risk of major CV events (AMI and stroke) among T2DM patients. This finding suggests that adhering to colesevelam therapy may provide long-term cardiovascular benefits.

Supported by: Daiichi Sankyo

940-P

Effects of Acute Hyperglycemia on Coronary Flow Reserve in Type 2 Diabetes and Modulation by Glucagon-Like Peptide-1 (GLP-1): A Study Using Bedside Contrast Echocardiography

SAHAR S. ABDELMONEIM, MARY E. HAGAN, EDWARD MENDRICK, BRENDA KIRBY, BARBARA NORBY, RITA BASU, ANANDA BASU, SHARON L. MULVAGH, *Rochester, MN*

We have shown that acute hyperglycemia reduces Coronary Flow Reserve (CFR) in nondiabetics. To evaluate the effects of acute hyperglycemia on CFR in type 2 diabetes (T2D) and its modulation by Glucagon-like peptide-1 (GLP-1) we enrolled 6 subjects with no CAD [4 male, age 54± 7yrs, BMI 31± 4 kg/m^2, fasting blood glucose (BG) 7.6± 1.3 mM, HbA1C 7± 0.7%] who underwent 2 visits in random order (GLP-1 visit: GLP-1 infusion at 1.2 pmol/kg/min and normal saline (NS) visit: NS infusion). During each visit a two step pancreatic clamp with somatostatin and replacement glucagon infusion was conducted. Insulin was infused at 0.75 mU/Kg TBW/min to mimic postprandial plasma insulin concentrations and glucose was infused for 4 hrs to maintain euglycemia for first 2 hrs (BG 5.1 ± 0.3 vs 5.3 ± 0.3 mM; GLP-1 vs NS P=0.378) followed by hyperglycemia for 2 hrs (BG 13.1 ± 0.3 vs. 13.5 ± 0.4 mM; GLP-1 vs NS P= 0.128). Myocardial contrast echocardiography (MCE) was performed at bedside during the final 30 min of each glycemic step using diluted Definity continuous infusion (200 ml/hr) at rest and during regadenoson vasodilator stress [400 ug IV bolus] to quantify myocardial blood flow (MBF) and determine CFR [stress MBF/rest MBF] at each glycemic step. Mean CFR during hyperglycemia were significantly reduced vs euglycemia in NS (P=0.049) and GLP-1 (P=0.031), table. Stress MBF and CFR during GLP-1 showed a trend for improvement at hyperglycemia, table.

Conclusions: CFR, as determined noninvasively by MCE, was significantly decreased in T2D and showed a trend for improvement after GLP-1

MCE parameters in T2D (NS and GLP-1 visits)

	Euglycemia		P value	Hyperglycemia		P value
	NS	GLP-1		NS	GLP-1	
Rest MBF (db/sec)	1.7±0.55	2.24±1.19	0.224	1.86± 0.58	2.85±1.51	0.267
Stress MBF(db/sec)	2.5±0.75	4.05±2.2	0.192	1.49±0.51	4.03±2.3	0.045
CFR	1.66±0.62	2.31±0.83	0.225	1.02±0.22	1.56±0.66	0.077

Supported by: Mayo Foundation (S.L.M.)

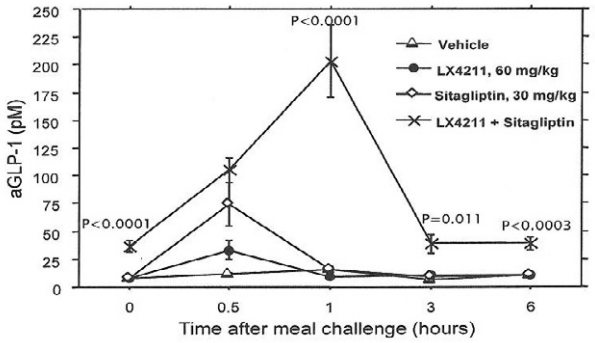
Guided Audio Tour: Incretin Therapies in Diabetes *(Posters 941-P to 948-P), see page 17.*

941-P

The Combination of LX4211 and DPP4 Inhibition Synergistically Increases Serum Levels of Active GLP-1 After Oral Glucose Challenge in Mice

DAVID R. POWELL, MELINDA SMITH, SHARON ZHAO, JENNIFER GREER, ANGELA HARRIS, ARTHUR SANDS, BRIAN ZAMBROWICZ, ZHI-MING DING, *The Woodlands, TX*

LX4211, a dual SGLT1/SGLT2 inhibitor, increases serum levels of total GLP-1 and active GLP-1 (aGLP-1) after an oral glucose (G) challenge. These increases result from inhibition of intestinal SGLT1 by LX4211, which delays small intestinal G absorption and triggers increased release of GLP-1 by the gastrointestinal tract. Sitagliptin (Sita) is a DPP4 inhibitor that increases aGLP-1 levels by inhibiting DPP4-mediated aGLP-1 inactivation. We asked whether the combination of LX4211 and Sita would increase aGLP-1 levels more than either compound alone after oral G challenge. Male C57BL6J mice, 27 weeks of age and fed 45% lard diet from weaning, received either vehicle, LX4211 (60 mg/kg), Sita (30 mg/kg), or both LX4211 and Sita by oral gavage for 14 days. 30 minutes after their last dose, these mice received a G-containing meal (9.2 g G/kg, 2.5 g protein/kg, 0.6 g fat/kg) by oral gavage. Serum aGLP-1 levels were measured using the Millipore aGLP-1 ELISA kit on samples obtained at baseline and at 0.5-, 1-, 3- and 6-hours after G gavage. Data were analyzed by 2-way ANOVA.



As shown in the above figure, a significant interaction of LX4211 and Sita was demonstrated at baseline and at 1-, 3- and 6-hours post G challenge, indicating a synergistic increase in aGLP-1 with the combination of LX4211 and Sita compared to effects seen with each compound alone. Two additional studies confirmed these findings. These data suggest that LX4211 and DPP-4 inhibitors have complementary mechanisms of action leading to a synergistic increase in aGLP-1 levels that may be advantageous to patients with T2DM.

942-P

WITHDRAWN

943-P

A Novel Therapeutic Use of Glucagon-Like Peptide1 Receptor Agonist for the Treatment of Overt Diabetic Nephropathy in Patients With Type 2 Diabetes

AIZAN HIRAI, SHIGEKI IMAMURA, KEIJI HIRAI, *Togane, Japan*

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease worldwide. Proteinuria should be considered a risk marker for progressive loss of renal function in type 2 diabetes with nephropathy, as well as a target for therapy. The predictive power of proteinuria (>0.5g/day) for progressive renal insufficiency has been previously demonstrated in patients with DN. Several therapeutic options are available to reduce proteinuria. Interruption of the renin-angiotensin system with either angiotensin-converting enzyme inhibitor (ACEI)s or angiotensin II receptor blocker (ARB)s is frequently used. By a preclinical animal study, glucagon-like peptide-1 receptor (GLP-1R) agonists directly prevent progress of DN in early stage with GLP-1R in kidney tissue. Although beneficial effects of GLP-1R agonist on lowering blood glucose and reduction of body weight have been established, the effect of GLP-1R agonists on proteinuria in type 2 diabetic patients has not been reported. Therefore we studied if GLP-1R agonist could decrease proteinuria in 21 type 2 diabetic patients (male: 12 and female: 9) with overt DN who were already treated with combining dietary sodium restriction (6g/day) and blockade of renin-angiotensin system. Liraglutide 0.3mg s.c a day was started as an initial dose and followed with weekly increment of 0.3mg, up to 0.9mg by the end of the third week. After 5 months study period, HbA1c and BMI were significantly decreased from 7.0% to 6.4% ($p<0.01$), and 27.6 kg/m^2 to 26.4 kg/m^2 ($p<0.01$), respectively, while there were no significant changes in systolic blood pressure and estimated glomerular filtration rate. Urinary protein to creatinine ratio was significantly decreased from 2.30 g/g to 1.27 g/g ($p<0.001$). To our knowledge, the present study suggests for first time that the use of liraglutide to overt DN in type 2 diabetic patients is associated with a reduction of proteinuria.

944-P

Serum Level of Soluble CD26/DPP-4 Predicts the Response to Sitagliptin, a Dipeptidyl Peptidase-4 (DPP-4) Inhibitor, in Patients With Type 2 Diabetes Inadequately Controlled by Metformin and/or Sulfonylurea

YOSHIMASA ASO, TOSHIHIKO INUKAI, KIKUO KASAI, *Mibu, Japan, Koshigaya, Japan*

Dipeptidyl peptidase 4 (DPP-4) inhibitors is a new class of anti-hyperglycemic agents that is now available for the treatment of type 2 diabetes. We investigated the relationship between the baseline serum level of soluble CD 26/DPP-4 and the response to treatment with sitagliptin, a DPP-4 inhibitor, over 24 weeks in patients who had type 2 diabetes inadequately controlled by metformin and/or sulfonylurea therapy. We studied 52 consecutive patients with type 2 diabetes who had poor glycemic control despite treatment with metformin and/or sulfonylurea. All patients were given 50 mg/day of sitagliptin and were followed at monthly intervals for 24 weeks. Treatment with sitagliptin decreased significantly hemoglobin (Hb) A1c from 7.91±1.08% at baseline to 6.96±1.18% at 8 weeks, 7.04±0.77% at 16 weeks, and 7.08±0.80% at 24 weeks. The baseline serum level of sCD26 was positively correlated with HbA1c at both 16 weeks and 24 weeks. Furthermore, Serum sCD26 level at baseline was also positively correlated with the changes from baseline of HbA1c at 16 and 24 weeks ($r=0.318$, $P=0.0296$; and $r=0.516$, $P= 0.0003$, respectively). In a multivariate logistic regression model that explained 56.1% ($R^2=0.561$) of the variation of the changes from baseline of HbA1c at 24 weeks, the baseline HbA1c ($\beta=-0.638$, $P<0.001$) and serum sCD26 ($\beta=0.357$, $P=0.041$) were independent determinants of the change of HbA1c at 24 weeks. In conclusions, a higher serum level of sCD26 is associated with a worse response to sitagliptin in patients with type 2 diabetes inadequately controlled by metformin and/or sulfonylurea therapy.

945-P

Efficacy and Safety of Once-Weekly (QW) Albiglutide vs. Once-Daily (QD) Liraglutide in Type 2 Diabetes (T2D) Inadequately Controlled on Oral Agents: Harmony 7 Trial

RICHARD E. PRATLEY, ANTHONY BARNETT, MARC M. FEINGLOS, ILANA HARMAN-BOEHM, MICHAEL NAUCK, FERNANDO OVALLE, SUSAN JOHNSON, MURRAY STEWART, JUNE YE, JULIO ROSENSTOCK, *Orlando, FL, Brimingham, United Kingdom, Durham, NC, Beer Sheva, Israel, Harz, Germany, Birmingham, AL, King of Prussia, PA, Research Triangle Park, NC, Dallas, TX*

Adherence to GLP-1 receptor agonists may be related, in part, to gastrointestinal adverse events (AEs) or injection frequency. This 32-week, open-label, parallel-group, Phase III study evaluated the efficacy and safety of a QW GLP-1 receptor agonist, albiglutide (ALBI), compared with QD liraglutide (LIRA) in patients with T2D inadequately controlled (A1C 7%-10%) on metformin, thiazolidinedione, sulfonylurea, or any combination of these.Patients were randomized to ALBI 30 mg QW titrated to 50 mg at week 6 (n = 404) or LIRA 0.6 mg QD titrated to 1.2 mg at week 2 and 1.8 mg at week 3 (n = 408). The primary endpoint was the change from baseline in A1C for ALBI vs LIRA. Non-inferiority would be established if the upper bound of the 95% confidence interval (CI) for treatment difference was < 0.3%.Demographics were well matched: A1C, 8.16 ± 0.9%; age 55.6 ± 10.1 years; BMI 32.8 ± 5.9 kg/m^2; diabetes duration 8.4 ± 5.8 years. Change from baseline in A1C was –0.78% ± 0.99 with ALBI and –0.99% ± 1.02 with LIRA (treatment difference: 0.21%). ALBI significantly reduced A1C from baseline ($P< .001$), but did not meet non-inferiority (95% CI: 0.08-0.34%). Both arms had a significant change from baseline in weight; LIRA (–2.19 kg) greater than ALBI (–0.64 kg).

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

Fasting plasma glucose change from baseline was –22.1 mg/dL for ALBI and –30.4 mg/dL for LIRA, $P = .050$.The most common AEs were gastrointestinal (ALBI 35.9%, LIRA 49.0%). Fewer patients had nausea/vomiting on ALBI (9.9%/5.0%) than LIRA (29.2%/9.3%). Other AEs of special interest on ALBI/LIRA included hypoglycemia (16.3%/20.8%), and injection site reactions (12.9%/5.4%).In conclusion, both ALBI and LIRA effectively reduced A1C and weight, although ALBI did not meet the pre-specified criterion of non-inferiority to LIRA. ALBI had a more favorable tolerability profile and dosing regimen, which may improve patient adherence in clinical practice.

946-P

Weekly Subcutaneous Doses of Glymera (PB1023) a Novel GLP-1 Analogue Reduce Glucose Exposure Dose-Dependently

MARK CHRISTIANSEN, MARK MATSON, RON BRAZG, LYNNE GEORGOPOULOS, SUE ARNOLD, WILLIAM KRAMER, LEON SHI, POUL STRANGE, *Walnut Creek, CA, St. Paul, MN, Renton, WA, Malvern, PA, North Potomac, MD, Princeton Junction, NJ*

Glymera is a 636 amino acid polypeptide comprised of GLP-1 genetically fused to a physiologically inert repeating polymeric elastin-like peptide expressed in E.coli. Glymera retains potency similar to native peptide and is formulated as a liquid for sc administration. This study assessed multiple dose safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in adults with T2DM.Subjects treated with 1 or 2 oral anti-diabetic drugs (OAD) discontinued their OADs during a 2 week run-in period. 54 subjects were randomized to weekly double blind injections of either placebo or Glymera for 4 weeks. Subjects were dosed after a liquid mixed meal tolerance test (MMTT). Safety, PK and PD were reviewed before escalation to the next dose of 0.3, 0.6, 0.9, and 1.35 mg/kg, respectively.PK exhibited slow absorption with sustained duration of exposure and minimal accumulation. Dose-response was evident for FPG, MMTT AUCglucose and average glucose (AG) assessed by continuous glucose monitoring (CGM). At the 1.35 mg/kg dose, placebo-adjusted AG change from baseline was -50 mg/dl (≈ -1.8% A1C) ($p<0.0001$). AG showed minimal loss of efficacy 7 days after the prior dose. CL/F indicated no correlation of clearance to body weight supporting transition to fixed instead of weight-based dosing. The dose and AG data fit an Emax model with Emax of -48 mg/dl compared to placebo, and 80% of that effect (ED80) at a dose of 63 mg.Glymera was well tolerated. The only dose related trend in adverse events (AE) was nausea at the highest doses. 3 subjects experienced mild or moderate injection site erythema that resolved spontaneously. 1 of these received subsequent doses that did not result in exacerbation or recurrent erythema. This subject and 1 other developed low titer non-neutralizing antibodies. There was no indication of adverse effects on any other safety parameters and no serious AEs reported.Conclusion: Glymera has properties that support development of a once weekly dose.

Supported by: PhaseBio Pharmaceuticals

947-P

WITHDRAWN

948-P

Effect of Sitagliptin on Post-Prandial Glucagon and GLP-1 Levels in Patients With Type 1 Diabetes: Investigator-Initiated, Double-Blind, Randomized, Placebo-Controlled Trial

EMILY G. MOSER, SATISH K. GARG, BRUCE BODE, LESLIE KLAFF, CHRISTIE BEATSON, WILLIAM R. HIATT, JANET K. SNELL-BERGEON, *Aurora, CO, Atlanta, GA, Renton, WA*

This study evaluated the effects of sitagliptin, (DPP-IV inhibitor, approved for patients with type 2 diabetes), in adult patients with type 1 diabetes to improve glycemic control through decreasing postprandial glucagon. This investigator-initiated, double-blind, randomized-parallel 20-week study enrolled 141 subjects. Subjects received sitagliptin 100 mg/day or matching placebo for 16-weeks, and a subset of 85 patients wore blinded continuous glucose monitors (CGM) for 5 separate 7-day periods. The primary outcome was post-meal (Boost™) reduction in 4-hour glucagon area under the curve (AUC), and secondary endpoints included changes in A1c, CGM data, insulin dose, GLP-1, GIP, and C-peptide levels.There were no differences at screening between groups; however, after 4-week run-in phase, A1c was significantly lower in the sitagliptin group than the placebo group. Post-meal GLP-1 levels were significantly higher and glucagon was suppressed at 30 minutes in the sitagliptin group after 16-weeks. Change in A1c, insulin dose, weight, and C-peptide did not differ by group after 16-weeks of treatment. However, C-peptide positive patients randomized to sitagliplin had a non-significant trend toward decrease in A1c, mean glucose and time spent in hyperglycemia.Sitagliptin use in type 1 diabetes did not change glucose control, insulin dose or weight despite post-meal rise in GLP-1 levels. C-peptide positive subjects treated with sitagliptin had a non-significant trend in decreasing hyperglycemia which needs further evaluation.

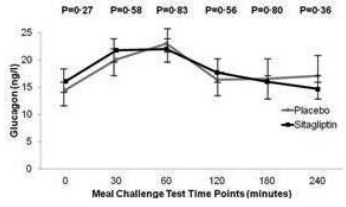


Figure 1A Glucagon at baseline

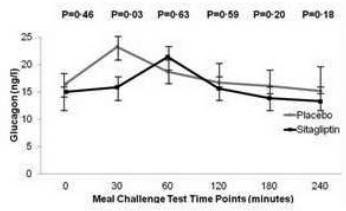


Figure 1B Glucagon after 16 weeks of treatment

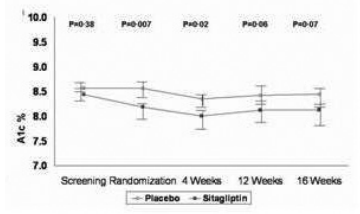


Figure 1C HbA1c over study period

Supported by: Merck and Co.

Guided Audio Tour: Managing the Complications of Diabetes *(Posters 949-P to 956-P), see page 17.*

949-P

Randomized, Prospective, Open-Label, Comparative Study to Evaluate the Efficacy of Itopride Hydrochloride in the Management of Delayed Gastric Emptying in Type 1 Diabetic Patients

IRINA V. GLINKINA, IRINA Y. BUDENNAIA, ALEKSEY V. ZILOV, VALERY M. MAKHOV, GALINA A. MELNICHENKO, *Moscow, Russian Federation*

To evaluate the efficacy of itopride in the management of delayed gastric emptying in type 1 diabetic patients. 27 type 1 diabetic patients with delayed gastric emptying (11 males, 16 females; mean of age 35 +/- 11.8 years; mean of type 1 diabetes' duration 20.2 +/- 11.5 years) were enrolled in a randomised, prospective, open-label, comparative study for a period of 6 weeks. The 1st group (15 of 27) was treated with itopride 50 mg three times daily before meals, the 2nd group (12 of 27) was a control group. HbA1c level, age, duration of type 1 diabetes, prevalence of complications did not differ between groups. To assess prevalence of gastrointestinal (GI) sensations we used a validated questionnaire. To evaluate gastric emptying we used a meal test with 91 mg ^{13}C-octanoic acid added to 1 egg. Breath samples were obtained before meal and every 15 minutes during next 4 hours. The $^{13}CO2$ breath content was measured by isotope ratio mass spectroscopy ("Heli - View", MediChem Ltd, South Korea). Itopride accelerated gastric emptying (T ½ > 75 min) compared to before administration: median T ½ 85,4 [82,0; 101,0] min vs. 48,9 [41,2; 54,3] min ($p < 0,001$). The 1st group had more patients with normal gastric emptying (11 of 15) than the 2nd group (4 of 12) ($p = 0,038$). Itopride improved heartburn (9 vs. 3, $p = 0,035$) and diarrhea/obstipation (12 vs. 6, $p = 0,039$) compared to before administration. In the 2nd group prevalence of GI sensations didn't change.Itopride, in a dose of 150 mg daily for 6 weeks, tends to accelerate gastric emptying in type 1 diabetic patients with delayed gastric emptying. Itopride improves heartburn and diarrhea/obstipation.

950-P

Venous Serum Bicarbonate Level Predicts Arterial pH in Adults With Diabetic Ketoacidosis

EBENEZER A. NYENWE, JIM Y. WAN, ABBAS E. KITABCHI, *Memphis, TN*

Diabetic ketoacidosis (DKA) is a severe metabolic complication of uncontrolled diabetes, the incidence of which continues to rise. Also, the economic burden of DKA remains substantial; therefore measures aimed at reducing the cost of treating this potentially fatal condition are desirable. DKA is defined by the triad of hyperglycemia, ketonemia and metabolic acidosis which is usually assessed by measuring pH of arterial blood. However, blood gas analysis requires expensive equipment which may not be available in all facilities especially in developing countries where DKA mortality remains high. Basic metabolic panel, which is cheap and readily available in most facilities, measures the critically important electrolytes in patients with DKA including bicarbonate. Therefore we investigated the utility of serum bicarbonate in estimating arterial pH in adults with DKA. We obtained demographic and admitting biochemical parameters in adults with DKA. DKA was diagnosed and treated based on current ADA guidelines. The data were summarized and analyzed using regression analysis. Our sample included 396 patients aged 36 ± 13 years, 59% of whom were males. Admitting biochemical profile was as follows, glucose- 644 ± 258 mg/dL, bicarbonate- 10.9 ± 5 mEq/dL, anion gap- 25 ± 7, osmolality- 307 ± 23 mOsmol/L, potassium- 5.2 ± 1.1 mEq/dL, creatinine- 2.0 ± 1.2 mg/dL, pH- 7.15 ± 0.13. Serum bicarbonate correlated significantly with arterial pH (Pearson correlation coefficient- 0.6, $P< 0.0001$). Multivariate regression model showed that bicarbonate was the best predictor of arterial pH ($P < 0.0001$), using this model, we determined that arterial pH equals 6.97 + (0.0163 × bicarbonate). Serum bicarbonate level of 20.6 predicted arterial pH of ≤ 7.3 with over 95% sensitivity and 92% accuracy. We conclude that venous serum bicarbonate is a convenient, accessible, affordable and reliable way estimating arterial pH in adults with DKA, especially in facilities where blood gas analysis is not readily available.

951-P

TZP-102 Ghrelin Receptor Agonist Improves Symptoms of Diabetic Gastroparesis in Both Type 1 and Type 2 Diabetes

NIELS EJSKJAER, RAYAZ MALIK, LISE TARNOW, PER HELLSTROM, GEORG DIMCEVSKI, J.C. PEZULLO, ROBERT VENUTI, LAURA SHAUGHNESSY, PHILIPPA CHARLTON, GORDANA KOSUTIC, RICHARD MCCALLUM, *Aarhus, Denmark, Manchester, United Kingdom, Copenhagen, Denmark, Stockholm, Sweden, Bergen, Norway, Washington, D.C., Durham, NC*

Hypothesis: TZP-102 ghrelin receptor agonist reduces symptoms of diabetic gastroparesis in both type 1 and type 2 diabetes.Objectives: To characterize TZP-102 effects on symptoms of gastroparesis in type 1 and type 2 diabetes. Methodology: Patients with diabetes, delayed GE, and moderate/severe upper gastrointestinal symptoms were randomized to 10, 20 or 40mg TZP-102 or placebo. Symptoms were evaluated by patient-reported symptom severity scales (0-5) on days 8, 15, 28 (treatment) and 42, 58 (follow up).Findings: 92 patients {females 65%; age 49.9 ± 11.9 years; 91% Caucasian; BMI 28.8 ± 5.1; 60% type 1; ~70% on insulin; HbA1c 8.3 ± 1.5%; PAGI-SYM 3.0 ± 0.8; breath test $t_{1/2}$ GE 193 ± 51 min} received treatment (22, 21, 23 and 26 patients received 10, 20, 40 mg TZP-102 and placebo, respectively). Significant improvements vs. placebo were observed in individual symptoms across all TZP-102 dose groups. However, the maximum improvement was achieved at the 20mg dose, with no additional benefit seen at the 40mg dose. Importantly, statistically significant improvement vs. placebo was observed with 20mg TZP-102 for each of the most prevalent symptoms for this patient population, and the magnitude of the effects was similar in type 1 and type 2 diabetic patients (see below).

TZP-102 End of Treatment Change from Baseline *over* Placebo* in Prevalent (>90% of Patients) Symptoms of Gastroparesis - 20mg Dose

Symptom	All patients (n=21)	p-value	Type 1 (n=10)	Type 2 (n=11)
Nausea	-1.0	0.029	-1.0	-0.9
Early satiety	-0.9	0.022	-0.9	-1.2
Postprandial fullness	-1.0	0.019	-1.4	-0.4
Bloating-stomach large	-0.9	0.018	-0.9	-0.8
Upper abdominal pain	-0.7	0.042	-0.7	-0.7

*Placebo n=26; type 1 =15; type 2=11Conclusion: TZP-102 significantly improves symptoms of gastroparesis in both type 1 and type 2 diabetic patients.

Supported by: Tranzyme Ltd.

952-P

Biologically Active Wound Dressing Improves Wound Healing in Diabetic db/db Mice

CHRISTOPH SCHÜRMANN, KERSTIN ENGELMANN-PILGER, TOBIAS HILDEBRANDT, MICHAEL MARK, THOMAS KLEIN, KATHARINA REIF, STEFAN FRANK, *Frankfurt, Germany, Biberach, Germany, Augsburg, Germany*

Diabetic ulcers are a significant clinical complication of diabetes and treatment options are limited. We have developed a novel Biologically Active Wound Dressing (BAWD) consisting of well-defined human keratinocytes grown on a perforated hyaluronic acid matrix. Here we investigated the effects of BAWD on wounds in a mouse model of diabetes. C57BL/6 *db/db* mice were wounded on their backs (6 full-thickness wounds, 5 mm in diameter). BAWD was applied to the wounds directly after injury. Representative controls were included. Wounds were isolated and analyzed histologically and by direct RNA sequencing at Day 10 post-injury. Wounds treated with BAWD exhibited a prominent advancement in wound closure. The wounds showed re-epithelialization from the wound margins, robust granulation tissue with high cellularity (Figure), and the presence of large numbers of newly formed blood vessels. By contrast, control wounds persisted in a severely impaired state without granulation tissue and blood vessel formation. The expression of human VEGF and IL-8 mRNA transcripts at Day 10 post-wounding suggested that the applied human keratinocytes were viable in murine wound tissue. Importantly, our data indicate that tissue regeneration was not dependent on the diabetic state of mice, as the BAWD-driven marked improvement occurred in the presence of a severely diabetic phenotype. In summary, this study of a novel treatment modality for diabetic ulcers suggests that BAWD stimulates wound repair in the presence of a severely diabetic phenotype despite the underlying pathophysiological processes.

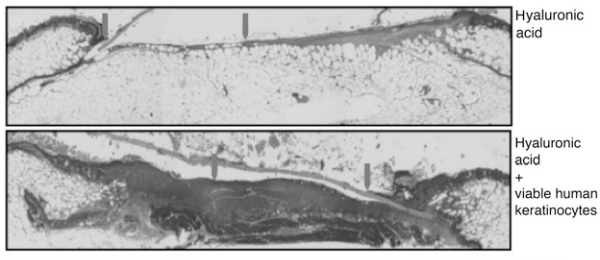


Figure: Induction of robust granulation tissue in wounds of diabetic mice by application of a keratinocyte-containing hyaluronic acid matrix. Blue: collagen staining; red: nuclei and cytoplasmic staining; red arrows: epithelial margins.

Supported by: Boehringer Ingelheim

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

953-P

Linagliptin Lowers Albuminuria on Top of Recommended Standard Treatment for Diabetic Nephropathy

PER-HENRIK GROOP, MARK COOPER, VLADO PERKOVIC, ANGELA EMSER, MAXIMILIAN VON EYNATTEN, HANS-JUERGEN WOERLE, *Helsinki, Finland, Melbourne, Australia, Sydney, Australia, Ingelheim, Germany*

Despite optimal therapy, people with type 2 diabetes (T2D) remain at high risk for kidney damage, manifest as albuminuria, and many develop progressive renal failure. Linagliptin, a DPP-4 inhibitor, has previously shown evidence of reducing albuminuria on top of telmisartan in mice. We explored the clinical effect of linagliptin on albuminuria in T2D patients with early diabetic nephropathy. Four randomized, double-blind, 24-week, placebo-controlled trials of linagliptin on no, mono, or dual oral glucose-lowering background therapy had data available for urinary albumin-to-creatinine ratio (UACR) and were pooled for analysis (n=2472). Participants were included in this analysis if they had: i) 30≤UACR≤3000 mg/g creatinine; ii) stable treatment with ACE/ARBs ≥4 weeks prior and during the trial; and iii) eGFR >30 mL/min/1.73 m². The endpoint was the percentage change in geometric mean UACR. In this analysis, 492 (19.9%) patients met UACR and eGFR thresholds of whom 46% received stable ACE/ARB therapy (linagliptin n=168; placebo n=59). Mean baseline HbA1c and median UACR were 8.2% vs 8.5% and 76 vs 78 mg/g creatinine for the linagliptin and placebo groups, respectively. After 24 weeks, placebo-corrected changes in HbA1c and FPG were -0.71% and -26 mg/dL, respectively (both p<.0001). Linagliptin significantly lowered adjusted UACR by 33% (95% CI: 22 to 42%; p<.05) with a between group difference vs placebo of -29% (-3 to -48%; p<.05). Overall, kidney function and blood pressure were unchanged although more patients on placebo received new anti-hypertensive drugs (17% vs 11% with linagliptin). Sensitivity analyses in patients not previously treated with RAS blockade (n=265) found similar results. Linagliptin may have kidney-protective properties beyond glucose-lowering effects. Further investigation of the potential kidney benefits is underway.

Supported by: Boehringer Ingelheim

954-P

The Effect of Metformin Therapy on Vitamin B12 Levels and Degree of Peripheral Neuropathy in Type 2 Diabetic Patients

JASNA KLEN, NEVENKA KIRIC, ANDREJ JANEZ, *Trbovlje, Slovenia, Ljubljana, Slovenia*

Chronic metformin use can results in vitamin B12 deficiency, which may present as a peripheral neuropathy and is often misdiagnosed as diabetic neuropathy. The objective of this study was to evaluate the presence of vitamin B12 deficiency, degree of peripheral neuropathy and the factors associated with serum vitamin B12 levels in a sample of metformin-treated Slovenian diabetic patients.We included 84 type 2 diabetic patients treated at least 4 years with metformin with a mean age of 63 ± 15 years and a mean BMI of 32.1 kg/m2. Serum concentrations of vitamin B12 were deteremined and biochemical deficiency was defined as serum B12 concentrations ≤150 pmol/L and borderline deficiency was defined as >150 to ≤250 pmol/L. The peripheral neuropathy was diagnosed according to the established protocol. Serum vitamin B12 levels were low (< 150 pmol/L) in 15 patients (17.8%) and possibly low (150 - 250 pmol/L) in 22 patients (26%). Serum vitamin B12 levels were negatively associated with age (B = -2.91; β= -0.161; p = 0.035) and duration of metformin use (B= -31.30; β= -0.16; p = 0.048). Lower values were associated with a higher degree of peripheral neuropathy (p = 0.002).The study suggests a high prevalence of vitamin B12 deficiency in metformin-treated type 2 diabetic patients. Older patients, patients with long-standing treatment with metformin are probably more prone to this deficiency. Lower B12 levels are associated with a higher degree of peripheral neuropathy.

955-P

Alendronate Prevents the Negative Effects of PPAR-γ Agonism on Bone Mass and Bone Strength at the Proximal Femur in the OVX Rat

SANJAY KUMAR, SUSAN Y. SMITH, SANDRA J. HOFFMAN, LORRAINE A. FITZPATRICK, RANA SAMADFAM, *Collegeville, PA, Senneville, QC, Canada, King of Prussia, PA*

Rosiglitazone (RSG) is a PPAR-γ agonist associated with bone loss and increased fracture risk. The objective of this study was to determine the effects of RSG on bone mass and bone strength at different sites and also to investigate if concomitant treatment with alendronate (ALN) prevents the RSG-induced loss of bone mass and strength in the OVX rat model. Nine month old rats were randomized to the following groups: SHAM, OVX vehicle, ALN (SC, 0.03mg/kg/twice weekly), RSG at two doses (PO, 3 or 10 mg/kg/d) or RSG10/ALN for 12 weeks. Treatment was initiated immediately after ovariectomy. We have previously published the effects of these treatments on bone mass and bone strength at the lumbar spine and femur diaphysis. Here we present the bone density and bone strength analysis at the proximal femur, a site clinically relevant to hip fracture. In addition, we present the whole body composition analysis (bone, muscle and fat). Treatment of OVX rats with RSG at 3 mg/kg/d, and to a greater extent at 10 mg/kg/d, decreased bone strength (up to 24%) and bone density parameters (up to 13%) at the proximal femur compared to OVX vehicle controls, statistically significant for peak load, DXA BMC and BMD at the high dose, and for DXA BMD at the low dose. Treatment with ALN prevented effects of RSG on bone mass in RSG/OVX-treated animals, consistent with slight increases in peak load and stiffness relative to RSG/OVX alone. The mean values for BMC, BMD and stiffness for ALN-treated RSG/OVX animals were higher compared to OVX vehicle controls. Whole body BMC and BMD were consistent with the findings at the proximal femur with values generally higher for ALN treated groups (alone or combined with RSG) compared to sham vehicle controls. Minimal effects were noted on soft tissue composition. Treatment of OVX rats with RSG further decreased parameters of bone mass and bone strength at the proximal femur compared to OVX controls, and that these effects were prevented by concomitant treatment with ALN.

956-P

Hospitalization in Patients With Type 2 Diabetes: A Retrospective Cohort Study

JAVARIA M. KHALID, MARTHA E. DAVIS, KRISTINA S. BOYE, BRADLEY CURTIS, MIREIA RALUY, ANDREW MAGUIRE, MATTHEW REANEY, *London, United Kingdom, Indianapolis, IN, Surrey, United Kingdom*

Hospitalization is the main contributor to total healthcare costs for people with type 2 diabetes (T2D). The aim of this study was to estimate the proportion of, and reasons for hospitalization among patients with T2D in England. This study used patient-level linked data from the UK General Practice. Research Database and the Hospital Episode Statistics (HES) data warehouse. Inclusion criteria were a diagnosis of T2D or a prescription for an oral antidiabetic drug (OAD) indicative of T2D.The study window was January 2006 to September 2011. The index date was the earlier of first T2D diagnosis or first OAD prescription. Data were sampled from index until the last data collection date for the practice, patient transfer, HES end date, end of study period, or death (whichever came first).An initial sample of 112,120 patients were identified of whom 62,515 (55.8%) had ≥ 1 hospitalization. Of these patients, 58,083 (92.9%) were followed for ≥ 12 months (mean follow-up time 3.5 (±1.6) yrs, median 4.3 yrs). A subset of 27,465 (47.3%) patients had ≥1 diabetes-related hospitalizations (DRH). Admitting diagnoses included: 34.9% due to renal failure (and its sequelae), 13.1% due to hypertension, 12.5% due to cataract and 1.3% due to hypoglycemia. Non-DRH were seen in 30,618 (52.7%) patients; the most frequent admitting diagnoses were atherosclerotic heart disease, anemia and "unspecified" illness. Patients with ≥1 hospitalization were older, had a longer duration of diabetes (yet better glycemic control) and lower Body Mass Index (BMI) compared to those without hospitalization.

Patients With a Diagnosis of T2D or OAD Prescription Indicative of T2D	≥1 Post-Index Hospitalization (Any Cause) A	No Hospitalization (Post-Index) B	All Patients C	*p*-value (A vs. B)*
Total Patients, N (%)	62,515 (55.8%)	49,605 (44.2%)	112,120 (100%)	
Male, N (%)	32,952 (52.7%)	28,174 (56.8%)	61,126 (54.5%)	ρ<0.001
Age, Mean (SD)	67.5 (13.5)	61.5 (13.5)	64.8 (13.8)	ρ<0.001
Years Since T2D Diagnosis, Mean (SD)	4.5 (2.7)	3.9 (2.5)	4.2 (2.6)	ρ<0.001
HbA1c value ≤ 6 months pre Index, Mean (SD)	7.5 (1.6)	7.7 (1.8)	7.6 (1.7)	ρ<0.001
BMI value ≤ 12 months pre Index, Mean (SD), Kg/m²	30.5 (6.4)	31.2 (6.4)	30.8 (6.4)	ρ<0.001
Mean(SD)/Median Days (IQR) Between Index and First Hospitalization	580(472)/463 (IQR: 176-902)	** T-tests and Z-tests (at the 0.01 significance level) were used to test for differences in means and proportions between groups, where appropriate.*		

Guided Audio Tour: Clinical Diabetes *(Posters 957-P to 964-P), see page 13.*

957-P

Treatment Patterns and A1C Reduction After Adding a 3rd Agent to 2 Oral Antidiabetic Drugs (OADs)

LIN XIE, STEVE ZHOU, WENHUI WEI, JOHN LING, ONUR BASER, PHILIP LEVIN, *Ann Arbor, MI, Bridgewater, NJ, Baltimore, MD*

Patients with type 2 diabetes mellitus (T2DM) failing to achieve glycemic control with 2 OADs may add a 3rd OAD (3OAD), GLP1 agonist (+GLP1), or insulin (+ins). This study assessed real-world treatment patterns and A1C outcomes in T2DM patients adding a 3rd drug to 2 OADs.Data were obtained from IMPACT®, a national managed care claim database, from 2000-2011. Index date is the addition of the 3rd drug (index drug). Descriptive 1- and 2-year (y) follow-up persistence (i.e., no switching/discontinuation of index drug) and A1C outcomes were examined, with patients grouped by index drug.51,771 patients (3OAD: 79.3%; +ins: 17.3%; +GLP1: 7.4%) had 2y follow-up data available with significant group differences at baseline. +GLP1 patients were youngest and had the lowest baseline A1C while +ins patients were oldest with the highest baseline A1C (mean baseline age: 55.9 y vs. 55.4 y vs. 52.8 y; men: 61.6% vs. 55.3% vs. 47.8%; A1C: 8.4% vs. 9.2% vs. 7.8%, for 3OAD vs. +ins vs. +GLP1, respectively, all $P<0.001$). Results on follow-up treatment patterns and A1C reduction from baseline are presented in the Table. This real-world study showed that most T2DM patients chose to add a third OAD after failing 2 OADs, and stayed on orals. Persistence was low among those adding GLP-1. For patients adding insulin to 2 OADs, 2y A1C reduction from baseline was higher in persistent patients. However, for 3OAD patients, those who switched to/added insulin or GLP1 therapy in y1 had higher A1C reduction than those who stayed on OADs. This data supports the calls for timely intensification and persistent use of insulin among T2DM patients who failed multiple OADs.

2-year treatment pattern	Total	Persistent in y1 and y2	Persistent for y1, but switched in y2	Switched in y1	Others: not filling any diabetes drug in last quarter of y1 or y2
3OAD, n (%)	41,052 (79.3)	29,576 (72.0)	3660 (8.9)	3627 (8.8)	4189 (10.2)
+Insulin, n (%)	6904 (13.3)	3942 (57.1)	618 (9.0)	1707 (24.7)	637 (9.2)
+GLP1, n (%)	3815 (7.4)	1360 (35.6)	661 (17.3)	1518 (39.8)	276 (7.2)
2-year A1C reduction from baseline: by treatment persistence * $P<0.05$; ** $P<0.01$; compared to patients persistent in y1 and y2					
3OAD, mean ± SD (n)	–0.64 ± 1.65 (4566)	–0.65 ± 1.57 (3437)	–0.59 ± 1.90 (412)	–0.92 ± 1.86 (348)**	–0.36 ± 1.88 (369)**
+Insulin, mean ± SD (n)	–0.88 ± 1.92 (547)	–0.99 ± 1.90 (320)	–0.93 ± 2.18 (51)	–0.59 ± 1.70 (143)*	–0.97 ± 2.45 (33)
+GLP, mean ± SD (n)	–0.33 ± 1.52 (376)	–0.48 ± 1.23 (132)	–0.27 ± 1.87 (60)	–0.23 ± 1.55 (160)	–0.38 ± 1.83 (24)

Supported by: sanofi-aventis

958-P

Effect of Needle Size on Nighttime Glucose Excursions in Obese Type 2 Diabetes Patients Treated With NPH Insulin at Bedtime

MACIEJ PAWLOWSKI, MALGORZATA RUTKOWSKA, LESZEK CZUPRYNIAK, ELEKTRA SZYMANSKA-GARBACZ, MALGORZATA SARYUSZ-WOLSKA, PIOTR GRZELAK, LUDOMIR STEFANCZYK, JERZY LOBA, *Lodz, Poland*

In a large group of type 2 diabetes patients NPH insulin given at bedtime fails to control fasting blood glucose, even when given in high dose. This problem frequently occurs in obese subjects, in whom insulin absorption from subcutaneous tissue might be impaired and may depend on the depth of the injection i.e. on the needle length. The effect of needle length on blood glucose control is poorly studied. The aim of this study was to assess the effect of using two various needle sizes on blood glucose excursions. We studied 17 obese subjects (mean [±SD] age 61.1±5.0 years, 11 women, BMI 35.5±4.4 kg/m2, diabetes duration 14.7±4.0 years, HbA1c 8.4±0.9%). All subjects were treated with basal-bolus regimen, including high dose of NPH insulin (43±9 IU) at bedtime. Subcutaneous fat tissue thickness assessed by ultrasound scanning was 2.6±0.8 cm. Glucose excursions were measured with with the Continuous Glucose Monitoring System (iPRO2, Medtronic, Minneapolis, USA) used for 5 consecutive days (4 nights), from Monday to Friday. For the first two days patients used 6 mm needle, and for the following days - 12.7 mm. Insulin injection site (abdominal skin) was unchanged.Injecting NPH insulin with a 12.7 mm needle was associated with significantly improved glycemia when compared to 6 mm needle: fasting plasma glucose was 131±19 vs 152±25 mg/dl (p=0.02), nighttime average glucose - 113.1±14.1 vs 136.9±30.7 mg/dl (p=0.04), and area under glucose curve was 7941±734 vs 9752±1651 (p=0.04), respectively. Coefficient of glycemia variation was similar when 12.7 or 6 mm needle was used (12.8±6.3 and 10.3±6.1, p=0.37, respectively)In conclusion, obese type 2 diabetes patients may benefit from using longer needles for NPH insulin injections as it may result in the reduction of fasting and nighttime average blood glucose, without adversely affecting glucose variability. Establishing whether this effect is long lasting and eventually may lead to HbA1c decrease requires further studies.

Supported by: Medical University of Lodz, 502-03/8-072-03/502-64-028; Medtronic Polska

959-P

Identification of Patients Suitable for Addition of Prandial Therapy Following Oral Agent and Insulin Treatment

CHARLES SHAEFER, TIMOTHY REID, ANDRES DIGENIO, ALEKSANDRA VLAJNIC, RONG ZHOU, MATTHEW RIDDLE, *Augusta, GA, Janesville, WI, Bridgewater, NJ, Cincinnati, OH, Portland, OR*

The benefits of adding prandial therapy to meet postprandial needs in patients not controlled on basal insulin are increasingly valued by primary care. Guidance is needed to identify patients not at goal on basal insulin who are suitable for prandial therapy. Whether identification of residual postprandial defects is best done through fasting plasma glucose (FPG) in addition to high A1C or through A1C alone is unknown. We aimed to clarify this by examining patient data where A1C was ≥7.0% despite systematically titrated insulin glargine or a comparator insulin/oral therapy added to prior therapy.From 63 insulin glargine clinical trials between 1997 and 2007, 6 adult type 2 diabetes studies met criteria of being randomized, controlled, gathering complete 7 point self-monitored blood glucose data, and titrating insulin over 24 weeks (N=1699). Baseline and 24-week data were examined in patients with endpoint A1C ≥7.0%. High FPG was defined as ≥130 mg/dL and high postprandial glucose (PPG) as ≥180 mg/dL 2 hours after any meal.Overall, 496 patients had an A1C ≥7.0% at Week 24. Of these, 340 had a high PPG at some point and were analyzed: 190 in the FPG <130 mg/dL and 150 in the FPG ≥130 mg/dL group (Table). The latter group had a higher Week 24 A1C and numerically more serious adverse and severe hypoglycemic events. In patients with A1C ≥7.0% after 24 weeks of basal insulin therapy, A1C appears a more inclusive indicator of PPG defects than FPG. A1C elevations may help clinicians identify patients most likely to benefit from addition of prandial therapy such as a rapid-acting insulin analog or a GLP-1 agonist.

Baseline and Week 24 Characteristics of Patients with A1C ≥7.0% and PPG ≥180 mg/dL

Characteristic	Patients with Week 24 A1C ≥7.0% N=340	Patients with Week 24 A1C ≥7.0% and Week 24 FPG <130 mg/dL N=190	Patients with Week 24 A1C ≥7.0% and Week 24 FPG ≥130 mg/dL N=150
Mean (SD) age, years	60.3 (9.7)	60.5 (9.3)	60.1 (10.2)
Men, n (%)	169 (49.7)	95 (50.0)	74 (49.3)
Mean (SD) T2DM Duration, years	9.6 (6.0)	9.9 (6.3)	9.3 (5.7)
Mean (SD) baseline weight, kg	85.7 (16.2)	84.1 (15.1)	87.8 (17.3)
Mean (SD) baseline/ Week 24 A1C, %	9.1 (1.0)/7.8 (0.8)	9.0 (0.9)/7.7 (0.6)	9.1 (1.0)/8.0 (0.9)
Mean (SD) Week 24 insulin dose, U/kg	0.47 (0.25)	0.45 (0.27)	0.49 (0.22)
Any serious adverse event, n (%)	26 (7.6)	12 (6.3)	14 (9.3)
Any severe hypoglycemic events, n (%)	6 (1.8)	1 (0.6)	5 (3.4)

Supported by: sanofi-aventis

For author disclosure information, see page 797.

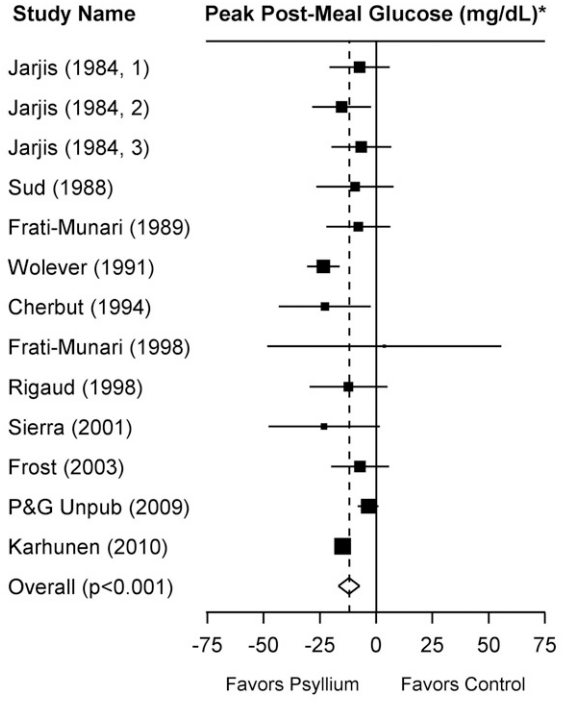
Guided Audio Tour poster ADA-Funded Research

960-P

Psyllium Husk Attenuates Peak Post-Prandial Glucose and Insulin Levels in Euglycemic Subjects: A Meta-Analysis of Randomized, Controlled Clinical Trials

ROGER D. GIBB, VICTOR HASSELBLAD, JOHNSON W. MCRORIE, DAVID D'ALESSIO, *Mason, OH, Durham, NC, Cincinnati, OH*

Psyllium husk, a natural, viscous, soluble fiber, is clinically proven to lower serum cholesterol, and is recognized to reduce the risk of cardiovascular disease. A meta-analysis of 13 clinical studies (12 published) that included 160 subjects was performed on randomized, controlled clinical studies that assessed the efficacy of psyllium for attenuating peak post-prandial glucose and insulin levels in euglycemic subjects. Clinical studies were identified through a literature search using key words synonymous with psyllium and glucose, and a review of unpublished clinical data on file at The Procter & Gamble Company. A random effects meta-analysis of the data showed that psyllium, dosed 1.7g to 23g (mean 10.2g) before a test meal, lowered peak post-prandial glucose by a mean (SE) of 12.1mg/dl (2.43mg/dl) relative to control (p<0.001, figure below). Psyllium also lowered post-prandial peak insulin levels by a mean (SE) of 131.6pmol/L (43.22pmol/L) relative to control (p=0.002). These data are comparable to the reductions in peak post-prandial glucose and insulin observed with acarbose 50mg in healthy subjects (7.3 - 11.8mg/dl and 148 - 223pmol/L, respectively)†. Psyllium was generally well-tolerated across doses with no serious adverse events. In conclusion, this meta-analysis showed that psyllium husk, a viscous, soluble fiber, significantly attenuates peak post-prandial glucose and insulin levels in euglycemic subjects.† Kageyama et al., Clin. Ther. 1997, 19(4):720-729.



*Mean and 95% CI

Supported by: Procter & Gamble

961-P

The Effect of High Dose Vitamin D Supplementation in People With Pre-Diabetes and Hypovitaminosis D

MAYER B. DAVIDSON, PETRA DURAN, MARTIN L. LEE, THEODORE C. FRIEDMAN, *Los Angeles, CA*

Hypovitaminosis D (<30 ng/mL) is a risk factor for diabetes and more frequent in those with pre-diabetes and diabetes. To determine if correcting hypovitaminosis D will beneficially affect insulin secretion and insulin action and the development of diabetes in people with pre-diabetes (FPG=110-125 mg/dL and/or 2-hr OGTT glucose = 140-199 mg/dL), 72 subjects (age 51.6 years ± 7.2 [SD], 56 females, 16 males, 60 Latinos, 12 African Americans) were randomized to receive for 1 year placebo or large weekly doses of vitamin D based on weight and baseline25-OH vitamin D levels. When serum levels ≥80 ng/mL were achieved, the dose was decreased by 20%. Vitamin D levels were measured at baseline, 1, 2, 3, 6, 9 and 12 months. A1C levels and OGTTs sampled at 0, 30, 60, 90 and 120 minutes were measured at baseline and every 3 months.Baseline vitamin D levels (ng/mL ± SD) were similar in 40 placebo subjects and 32 vitamin D subjects (22.5 ± 4.8 vs 21.3 ± 4.4) and in the vitamin D group rose to mean levels of 60-70 ng/mL by 2 months and persisted with no change in the placebo group. By a 2-way repeated measures ANOVA, there were no significant differences (P >0.05) between the 2 groups in FPG, OGTTs (glucose AUC), A1C levels, insulin secretion (HOMA-B, insulin AUC, Stumvoll's 1st and 2nd phase insulin secretion), insulin action (HOMA-IR, Matsuda index) or the disposition index (Matsuda index x insulin AUC/glucose AUC [ISS1-2]). By the chi square test for homogeneity, there was also no statistical difference between the placebo and vitamin D groups, respectively, in those developing diabetes (8% vs 9%) or reverting to normal (42% vs 44%) at 1 year.Vitamin D supplementation to high normal 25-OH vitamin D levels had no effect on glycemic parameters in those with pre-diabetes and hypovitaminosis D. To quote Thomas Huxley, "the great tragedy of science - the slaying of a beautiful hypothesis by an ugly fact."

962-P

Protocol-Based Transition from IV to SC Insulin Therapy More Effective Than Usual Care in Intensive Care Subjects With Hyperglycemia

BRESTA MIRANDA-PALMA, ALVARO PUIG, LUZ PRIETO, SYLVIA URBINA, LAUREN GOLDBERG, GHOSHEH YAZAN, SHARI MESSINGER, LUIGI MENEGHINI, *Miami, FL, Tallahassee, FL, Orlando, FL, Odessa, TX*

We compared glycemic control in hyperglycemic subjects in intensive care following transitioning from IV to SC insulin therapy under usual practice [prospective observation (OBS, N=50)] vs the implementation of an endocrinologist-led standardized treatment protocol based on concepts of basal/bolus insulin therapy [prospective intervention (INT, N=30)]. Eligible subjects had been on IV insulin for at least 48 hours and were receiving at least 20 units/day insulin infusion at the time of the transition.Blood glucose (BG) values were analyzed with a mixed model regression. Results refer to days 0-4, with day 0 being the day before the switch, day 1 being the day of the switch and days 2-4 referring to the following 3 days.Mean BG levels at baseline (day 0) in the INT and OBS groups were 164 and 144 mg/dl, respectively, and decreased to a significant degree in the INT group only, by the 3rd & 4th day following transition (140 & 120 mg/dl, respectively; p<0.05 vs baseline). On the other hand BG tended to increase in the OBS group after switching to SC therapy (171 & 172 mg/dl on the 3rd & 4th days, respectively; p=NS). The odds of being in BG range (70-150 mg/dl) were significantly higher in the OBS on the transition day, but higher in the INT on day 4. The odds of experiencing severe hyperglycemia (BG>180 mg/dl) were lower in the OBS group on the transition day, but lower in the INT in days 3 & 4. Subjects with a prior diagnosis of diabetes & higher bolus dose requirements had lower odds of being in target glycemic range and higher odds of experiencing severe hyperglycemia. The percent of values in the hypoglycemia range (BG<70 mg/dl) following transition to SC insulin was not significantly different between OBS and INT (1.3% versus 1.8%, respectively); no severe hypoglycemia (BG<40 mg/dl) was recorded.A protocol based basal/bolus intervention led by an endocrinologist team safely improved glycemic control in intensive care subjects transitioning to SC insulin therapy.

Supported by: Novo Nordisk

963-P

Continuous Intravenous Insulin Infusion May Affect QT Interval in Otherwise Healthy Patients With Type 1 Diabetes

ELEKTRA SZYMANSKA-GARBACZ, MALGORZATA SARYUSZ-WOLSKA, MACIEJ PAWLOWSKI, JERZY LOBA, LESZEK CZUPRYNIAK, *Lodz, Poland*

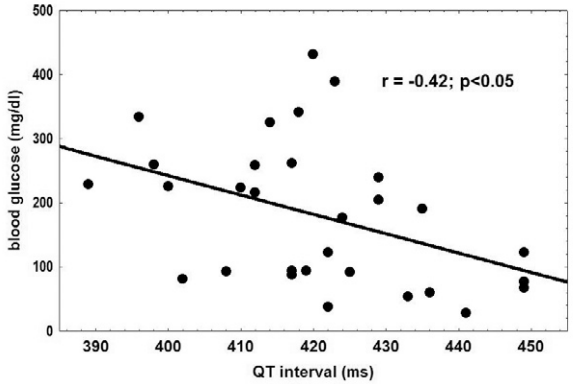
Poorly controlled Type 1 diabetes patients are occasionally hospitalized and treated with continuous intravenous insulin infusion (CIVII), which is associated with a significant risk of hypoglycemia, an acknowledged risk factor for cardiac arrhythmias. The aim of the study was to assess heart rhythm during CIVII. The study group comprised 15 Type 1 diabetes subjects (mean [±SD] age 32.6±10.7 years, diabetes duration 7.8±6.5 years, BMI 23.1±2.2 kg/m2, HbA1c 10.0±2.3%, pH 7.419±0.08, K+ 4.34±0.39 mmol/l) without macrovascular complications or autonomic neuropathy, using no QT-affecting medications. CIVII consisted of basal insulin infusion and three 90-min mealtime boluses per day. Capillary blood glucose was measured every 60-90 min, and the CIVII rate was adjusted accordingly so as to achieve near normoglycemia. In all subjects 24-hour ECG monitoring was performed during the second day of CIVII. Mean blood glucose during CIVII was 174±51 mg/dl (range 28-432 mg/dl). No clinically significant abnormalities in ECG monitoring were noted.

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

Mean QT interval was 422±14 ms. However, in the whole group there was a statistically significant correlation between QT interval during minimum and maximum blood glucose and these blood glucose values (r=-0.42, p<0.05, Fig. 1). Moreover, more insulin resistant subjects showed tendency to have longer QT interval (r=0.25; p=0.06) In conclusion, using CIVII in otherwise healthy Type 1 diabetes subjects may affect electrophysiological processes in the myocardium. This mode of treatment should be used with caution even in patients without cardiovascular disease.

Fig. 1. **The correlation between QT interval during minimum and maximum blood glucose and these blood glucose values during CIVII (two blood glucose values per each patient).**



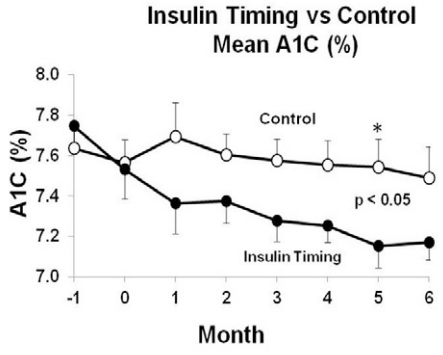
Supported by: Medical University of Lodz, Poland, Grant No. 502-18-848

964-P

Insulin Timing—A Beneficial Addition to Intensive Insulin Therapy in Type 1 Diabetes

ELIZABETH DURAN-VALDEZ, MARK R. BURGE, PAULA BRODERICK, LYNDA SHEY, VIRGINIA VALENTINE, RONALD SCHRADER, DAVID S. SCHADE, *Albuquerque, NM, Los Lunas, NM*

Purpose of Study:The treatment goal in T1D is to reduce A1C to ≤ 7.0% with minimal hypoglycemia.We investigated the possibility that "insulin timing" would improve A1C without incurring severe hypoglycemia. This approach is based on the concept of closely matching subcutaneous insulin absorption with meal induced glucose absorption to greatly reduce postprandial hyperglycemia.Methods: Forty healthy adult volunteers with T1D were randomly assigned for six months to one of two groups, a control group or an insulin timing group. The insulin timing algorithm altered the time when the meal dose of insulin was injected (MDI regimen) or infused (CSII regimen) from 30 minutes before the meal to 15 minutes after the meal as determined by the 30 minute premeal blood glucose.The control group continued their usual intensive insulin therapy regimen. Fasting blood samples were drawn for A1C and other glucose parameters each month. All subjects were questioned at each visit about the occurrence of serious hypoglycemia.Summary of Results: As shown in the figure, by 5 months individuals in the insulin timing group decreased their A1C by 0.59% compared to the control group which had a decrease of 0.05% (p<0.05). The greatest improvement in A1C was observed in individuals with the highest baseline A1C levels, p<0.001. No severe hypoglycemia occurred in either group.Conclusions: Insulin timing is a safe approach to improving A1C in individuals with type 1 diabetes. It is easy to learn, is associated with no additional cost, and does not increase the incidence of severe hypoglycemia. We recommend its addition to all intensive insulin therapy regimens.



965-P

Engineering and Characterization of an Aggregation- and Proteolysis-Resistant Long-Acting Fc-FGF21 Analog

RANDY HECHT, YUE-SHENG LI, JEONGHOON SUN, ED BELOUSKI, MICHAEL HALL, TODD HAGER, JUNMING YIE, WEI WANG, DWIGHT WINTERS, STEPHEN SMITH, LEI-TING TAM, ZHONGNAN SHEN, SHANAKA STANISLAUS, NARUMOL CHINOOKOSWONG, MARK MICHAELS, THOMAS BOONE, MURIELLE M. VÉNIANT, JING XU, *Thousand Oaks, CA*

Fibroblast growth factor 21 (FGF21) is a promising new drug candidate for the treatment of type 2 diabetes, dyslipidemia and obesity. The use of native FGF21 is, however, hindered by its short half-life, propensity to aggregate and susceptibility to *in vivo* degradation. Here we describe the generation and characterization of a long-acting FGF21 analog with improved resistance to aggregation and proteolysis. A human recombinant Fc-FGF21 protein was constructed by fusing the Fc domain of IgG1 via a 15 amino acid linker to an FGF21 variant. It was determined that fusing Fc at the N-terminus was superior to fusing Fc at the C-terminus, as the N-terminal fusion retained the βKlotho binding activity and exhibited a potency similar to that of native FGF21 in terms of FGF receptor activation and glucose reduction. Two specific mutations were introduced into FGF21 without compromising its biological activity. The replacement of a hydrophobic leucine residue at position 98, identified through computer-aided structure modeling, with a hydrophilic arginine (L98R) suppressed time- and temperature-dependent FGF21 aggregation. The substitution of proline to glycine at position 171 (P171G) eliminated a proteolytic degradation site identified when wild type FGF21 was administered in mice or cynomolgus monkeys. The clipping resulted in a loss of 10 amino acid residues at the C-terminus leading to inactivation of FGF21 bioactivity. The fusion molecule with the 2 point mutations, Fc-FGF21 (RG), demonstrated a significantly improved circulating half-life of 30 h in monkeys, as compared to 1 h for native FGF21 and 1.8 h for Fc-FGF21. A single administration of Fc-FGF21 (RG) in diabetic mice resulted in a sustained reduction of blood glucose and body weight for 5 to 7 days; whereas the effect of native FGF21 or Fc-FGF21 lasted only for 1 to 2 days. Our data demonstrated that Fc-FGF21 (RG) is a potent, aggregation- and proteolysis-resistant long-acting FGF21 analog.

Supported by: Amgen, Inc.

966-P

Clinical Proof of Concept With a Prototype mTOT Modulating Insulin Sensitizer

JERRY R. COLCA, JAMES T. VANDERLUGT, WADE J. ADAMS, JOANNE LIANG, RONG ZHOU, DAVID G. ORLOFF, *Kalamazoo, MI, Cincinnati, OH*

Pharmacology of TZDs may be mediated through a mitochondrial target (mTOT) while the side effects are mediated by the transcription factor PPARγ. If so, it should be possible to design molecules with preferential mTOT activity relative to PPARγ and thus with improved therapeutic profiles. Here we report on a phase 2b clinical trial in patients with type 2 diabetes treated with MSDC-0160, a prototype compound (an isomer of a pioglitazone metabolite). A total of 258 subjects (80% on stable metformin treatment; 20% treatment naïve) completed the trial per-protocol. The data were analyzed to compare three doses of MSDC-0160 to 45 mg pioglitazone and placebo (qd, double blind). Baseline characteristics were similar across treatment groups. Average starting HbA1c was 8.07% and FPG was 171.9 mg/dl. After 12 weeks of treatment, groups treated with 50 mg (N=48), 100 mg (N=52), and 150 mg (N=47) of MSDC-0160 had significant decreases in HbA1c (placebo-adjusted LS mean ± SEM) of -0.39 ± 0.175, -0.79 ± 0.171, and -0.86 ± 0.176, respectively (p<.0001). The decreases observed with the two higher doses were not different than with pioglitazone (-0.98 ± 0 .169; N=55). In contrast, there were marked between-treatment differences in effects on HMW adiponectin: increases of 40.2 ± 24.7%, 89.5 ± 24.3%, and 127.5 ± 24.9% for the 3 MSDC-0160 groups compared to an increase of 282.1± 23.89% for pioglitazone (difference p<0.0001). Fluid retention as evidenced by reduction in hematocrit, red blood cells and total hemoglobin was also 50% less in the MSDC-0160-treated groups. The differential induction of HMW adiponectin suggests a greater effect of pioglitazone on white adipose tissue. Consistent with this conclusion, unlike pioglitazone, no dose level of MSDC-0160 produced a significant reduction in circulating triglycerides, although treatment did increase HDL cholesterol. We conclude that it is feasible to achieve glucose lowering similar to pioglitazone while sparing activation of PPARγ with its associated adverse effects.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

967-P

Long-Term Glycemic Outcome of Short-Term Intensive Insulin Therapy in Newly Diagnosed Type 2 Diabetic Patients

LIEHUA LIU, MINHUA LIANG, JUAN LIU, XUESI WAN, JIANBIN LIU, WANPING DENG, AILING CHEN CHEN, YANBING LI, *Guangzhou, China*

Previous studies showed that short-term intensive insulin therapy could induce glycemic remission in newly diagnosed type 2 diabetic patients. However, long-term outcome was still uncertained.We investigated 59 patients (BMI, 25.0±3.7 kg/m2; age, 50.3±9.5 years) who were diagnosed as type 2 diabetes between Oct. 2001 and Aug. 2007 and sequently received short-term intensive insulin therapy. Euglycemia were achieved and maintained for 2 weeks. Measurements of fasting plasma glucose (FPG), 2h-postprandial glucose (2hPG) and an intravenous glucose tolerance tests were performed before and after the therapy with HOMA IR and Acute insulin response (AIR) calculated. Patients were then follow up at 3-months interval on diet and exercise alone. Remission was defined as FPG<7.0mmol/L and 2hPG<10mmol/L.Median follow-up period was 6.4 years. After the therapy, FPG and 2hPG decreased significantly (11.8±3.9 vs. 6.9±3.8 and 17.3±6.6 vs. 7.9±2.0mmol/L,respectively). Compared with baseline, AIR improved (0.1± 44.8 vs. 98.8±123.9mU/L·min, P<0.001) while HOMA IR decreased. 1-year and 2-year remission rate were 57.6% and 47.5% respectively, with a median remission time of 24.0 months (Fig.1). In logistic regression analysis, only increment of AIR after the therapy independently predicted long-term remission (≥3 years) after adjusted for HOMA IR and BMI (OR=1.02, 95%CI: 1.01-1.03, P=0.02).We conclude that short-term intensive insulin therapy can induce long-term glycemic remission with a median remission time of about 2 years. Recovery of AIR is a independent predictor of long-term remission.

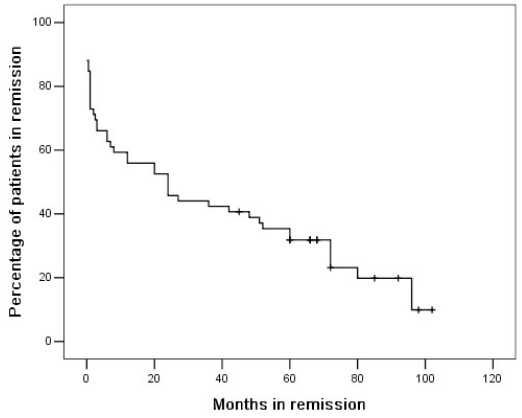


Figure 1. Kaplan-Meier curve for remission time after intensive insulin therapy.

968-P

WITHDRAWN

969-P

Linagliptin Modulates Immune Pathogenesis in RIP-B7.1 Transgenic (tg) Mice, an Experimental Model for Type 1 Diabetes

BERNHARD O. BOEHM, MICHAEL MARK, THOMAS KLEIN, ANDREA WISSMANN, ANDREAS SPYRANTIS, *Ulm, Germany, Biberach, Germany*

Dipeptidyl peptidase (DPP)-4 inhibitors block incretin degradation by DPP-4. We assessed whether the DPP-4 inhibitor linagliptin suppresses progression to hyperglycemia in an autoimmune diabetes mouse model (RIP-B7.1). As in humans, diabetes development in this model critically depends on activated CD8 T cells. Diabetes develops in RIP-B7.1 tg mice after a single intramuscular (i.m.) vaccination (vac) of proinsulin (PI) plasmid DNA. Linagliptin (3 mg/kg/d) or placebo were given orally for 1 wk before i.m. vac and continued for 6 wks. Vac A: Diabetes was induced using a PI-encoding plasmid resulting in an aggressive insulitis. Vac B: vac with insulin A-chain encoding plasmid resulted in a delayed diabetes development compared with vac A. With vac A (n=20 tg mice), diabetes incidence was 80% 5 wks after vac, whereas vac B (n=34) resulted in 79% incidence after 12 wks in placebo-treated mice. Linagliptin did not stop the aggressive insulitic process (vac A; n=20) but significantly delayed diabetes onset (80% incidence after wk 8 of follow-up [p<0.05] compared with 5 wks in placebo-treated mice). When a less aggressive insulitis was induced (vac B; n=16), linagliptin treatment again delayed onset and preserved β-cell function since diabetes incidence did not exceed 62% during 14 wks follow up (control mice: [n=34] 92% incidence wk 14; p<0.05). FACS and ELISPOT showed that islet antigen-specific CD8 T cells expressed high levels of IFN-γ with equal number in placebo- and linagliptin-treated mice. In the linagliptin-treated group, islet insulin content was partially preserved after diabetes onset. Serum levels of the regulatory cytokine IL-10 were significantly upregulated in linagliptin-treated mice. Our data suggest that DPP-4 inhibition can modulate T cell-mediated immune pathogenesis. Since linagliptin had no impact on the number of IFN-γ producing T cells, we suggest that DPP-4 inhibition predominantly alleviates cytokine-induced β-cell death.

Supported by: Centre of Excellence Metabolic Disorders, State Baden-Wuerttemberg, Germany

970-P

Reversal of Type 1 Diabetes by the Stem Cell Educator Therapy in Humans

YONG ZHAO, ZHAOSHUN JIANG, TINGBAO ZHAO, MINGLIANG YE, CHENGJIN HU, ZHAOHUI YIN, HENG LI, YE ZHANG, YALIN DIAO, YINGJIAN CHEN, XIAOMING SUN, MARY BETH FISK, RANDAL SKIDGEL, MARK HOLTERMAN, BELLUR PRABHAKAR, THEODORE MAZZONE, *Chicago, IL, Jinan, China, San Antonio, TX, Peoria, IL*

We developed a procedure for Stem Cell Educator therapy in which a patient's blood is circulated through a closed-loop system that separate lymphocytes from the whole blood and briefly co-cultures them with adherent human cord blood-derived multipotent stem cells (CB-SCs), and returns the educated lymphocytes (but not the CB-SCs) to the patient's circulation. In an open-label, phase1/phase 2 study, patients (n = 15) with T1D received one treatment with the Stem Cell Educator. Median age was 29 years (range, 15 to 41), and median diabetic history was 8 years (range, 1 to 21). Clinical findings demonstrate that a single treatment with the Stem Cell Educator provides lasting reversal of autoimmunity that allows regeneration of islet beta cells and improvement of metabolic control in individuals with long-standing T1D. During *in vitro* co-cultures, CB-SCs attached to interior surfaces in the device present secreted and cell-surface signaling molecules (e.g., nitric oxide and PD-L1) to passing lymphocytes, and only the autologous lymphocytes are returned to the subjects. Therefore, Stem Cell Educator therapy is very safe approach without any adverse events in all participants.We found that CB-SCs express autoimmune regulator (Aire). Knockdown of Aire indicate that Aire is involved in immune modulation and induction of immune tolerance following Stem Cell Educator therapy. Further mechanistic study from

non-obese diabetic (NOD) mice demonstrated that increased plasma TGF-beta1 may contribute to the formation of a "TGF-beta1 ring" around pancreatic islets that protects beta cells against infiltrating lymphocytes, providing a safe environment for promotion of beta cell regeneration.Thus, Stem Cell Educator therapy is safe, and in individuals with moderate or severe T1D, a single treatment with Stem Cell Educator therapy reverses autoimmunity and promotes regeneration of islet beta cells, without the safety and ethical concerns associated with conventional immune and stem cell-based approaches.

Supported by: JDRF, UIC CCTS Grant, Chinese Government Funding

971-P

Sitagliptin More Effectively Improved Left Ventricular Diastolic Function Compared With Bedtime NPH Insulin as Third-Line Agent in T2DM Patients

KÁTIA C. NOGUEIRA, ROSA FUKUI, DALVA M. ROCHA, MÁRCIA R. CORREIA, ROSA F. SANTOS, MEIVE FURTADO, JOSÉ L. ANDRADE, MARIA R. SILVA, *São Paulo, Brazil*

The main goal of diabetes treatment is to obtain normal glucose levels to prevent the diabetic complications. Left ventricular diastolic dysfunction (LVDD), the pre clinical signal of diabetic cardiomyopathy, is often observed in T2DM patients and tissue Doppler echocardiography (TDE) is a sensitive method for its early detection. This 24-wk study compared the effects of the dipeptidil-peptidase-4 inhibitor sitagliptin with bedtime NPH insulin (NPH) on blood pressure (BP) and left ventricular (LV) diastolic function in T2DM patients inadequately controlled with metformin and glibenclamide. Thirty-five patients with similar age, diabetes duration, BP, HbA1c and fasting glucose (FG) levels were randomized to receive sitagliptin (SITA group, n=18) or bedtime NPH insulin (NPH group, n=17) as additional treatment. Ambulatory BP monitoring and TDE were performed in 35 and 29 patients, respectively. HbA1c and FG fell similarly in the SITA group (HbA1c: 8.0 ± 0.6 to 7.3 ± 0.8%, p=0.001/ FG:136.5 ± 30.0 to 125.6 ± 33.4 mg/dl, p=0.037) and the NPH group (HbA1c: 8.1 ± 0.6 to 7.3 ± 0.7%, p=0.001/ FG:159.2 ± 38.0 to 111.6 ± 30.4 mg/dl, p<0.001). Systolic and diastolic BP did not change. Systolic function was normal in all patients, however 53% of SITA group and 64% of NPH group patients had LVDD. Sitagliptin promoted a greater improvement in LV diastolic function (40%) when compared with NPH (7.1%) (p=0.038, χ^2 test). Our study is the first to compare sitagliptin with bedtime NPH as a third-line agent on metabolic control, BP and cardiovascular function of T2DM patients. Sitagliptin and bedtime NPH were equally effective on glucose control. However, improvement in LV diastolic function was higher in the SITA group than in the NPH group, probably due to the increase in GLP-1 levels, which have been associated to beneficial cardiac effects. Therefore, sitaglipitin seems to be a promising drug for the prevention of diabetic cardiomyopathy.

Supported by: FAPESP

972-P

Efficacy and Safety of Lixisenatide in Elderly (≥65 yr) and Very Elderly (≥75 yr) Patients With Type 2 Diabetes: An Analysis from the GetGoal Phase 3 Program

DENIS RACCAH, PATRICK MIOSSEC, VIRGINIE ESPOSITO, ELISABETH NIEMOELLER, MEEHYUNG CHO, JOHN GERICH, *Marseille, France, Paris, France, Frankfurt, Germany, Rochester, NY*

The number of elderly people with T2DM is increasing due to improved life expectancy and managing elderly patients with T2DM can be challenging. The effect of age on the pharmacokinetics of lixisenatide was assessed in a study that included 18 elderly healthy subjects (age range 65-79 yr) and 18 young healthy subjects (age range 24-44 yr). The mean exposure after a 20 µg single dose was ~30% higher in elderly than in young subjects and the terminal half-life was prolonged ~1.6 times. C_{max} and t_{max} were comparable in both groups. To date, 612 elderly (≥65 yr) patients overall have been exposed to lixisenatide in Phase 2/3 clinical trials (567.9 patient-yr), including 59 very elderly (≥75 yr) patients (58.3 patient-yr). This analysis of 6 randomized, placebo-controlled Phase 3 trials assessed the efficacy (HbA_{1c}) and safety (overall AEs, GI events, hypoglycemia) of 20 µg QD lixisenatide in 379 patients ≥65 yr, including 48 patients ≥75 yr (436.5 and 49.1 patient-yr exposure, respectively) during the main 12-wk (GetGoal-Mono) or 24-wk (GetGoal-M, -F1, -S, -L, -L-Asia) treatment periods. The efficacy profiles were similar regardless of age, with comparable HbA_{1c} decreases in ≥65 yr *vs* <65 yr for lixisenatide in all 6 studies, and significantly greater decreases *vs* placebo in both age categories. In a pooled analysis of the 6 studies, the lixisenatide safety profile was also comparable regardless of age, with overall AE and GI event incidences in lixisenatide-treated patients of 72% and 43% (≥65 yr) *vs* 69% and 41% (<65 yr) and 73% and 46% (≥75 yr) *vs* 69% and 41% (<75 yr). The incidence of symptomatic hypoglycemic events varied depending on the background treatment and was usually comparable between lixisenatide and placebo and no relevant difference between age categories was observed. In conclusion, in this analysis, lixisenatide was shown to be effective and well tolerated in elderly and very elderly patients.

Supported by: sanofi-aventis

973-P

Albiglutide Significantly Lowers Glycemia in Japanese Patients With Type 2 Diabetes (T2D)

YUTAKA SEINO, NOBUYA INAGAKI, HAJIME MIYAHARA, INAHA OKUDA, MARK BUSH, FRED YANG, JUNE YE, CLAIRE HOLLAND, SUSAN JOHNSON, ERIC LEWIS, HIROMU NAKAJIMA, *Osaka, Japan, Kyoto, Japan, Tokyo, Japan, Research Triangle Park, NC, King of Prussia, PA*

This study examined the efficacy, safety, and optimal dose/schedule of albiglutide (ALBI), a long acting GLP-1 receptor agonist, in Japanese patients (pts) with T2D.This 16-week, Phase IIb, randomized, double-blind, placebo (pbo)-controlled trial enrolled pts who were either treatment naïve or washed out of 1 oral antidiabetic drug. Pts were randomized 1:1:1:1 to pbo, ALBI 30 mg weekly (QW), 15 mg QW, or 30 mg every other week (EOW). Primary endpoint was change from baseline in A1C vs pbo at wk 16.Demographics were similar across groups; baseline A1C was 8.5 ± 0.8% (National Glycohemoglobin Standardization Program equivalent). Randomization was stratified by prior therapy and A1C at wk –2. Each arm of the study showed statistically significant change from baseline in A1C vs pbo. The treatment effect of ALBI on A1C was: –1.55%, –1.10%, and –0.89% with 30 mg QW, 30 mg EOW, and 15 mg QW at wk 16, respectively. In the 30 mg QW, 30 mg EOW, and 15 mg QW arms, 63.0%, 39.6%, and 17.3% of pts achieved A1C < 7.4%, respectively, compared with 6.0% of pbo pts. There were generally significant decreases in FPG and 2 hr postprandial glucose. Also, there were generally significant increases in 2 hr postprandial insulin, C-peptide, and postprandial AUC for insulin. There were no meaningful changes in weight: week 16 change from baseline of –0.67 kg, pbo; +0.40 kg, 15 mg QW; –0.23 kg, 30 mg QW; –0.12, 30 mg EOW.The most frequently reported adverse event (AE) in all treatment arms was nasopharyngitis (20.3% overall). No serious AEs were related to study therapy; no deaths occurred. Nausea and vomiting were seen in < 5% of pts in all treatment arms, similar to pbo. Injection site reactions were most common with 30 mg QW (14.8%).Among those tested, 30 mg QW was the most effective ALBI regimen with regard to glucose lowering, although all showed efficacy. All regimens were safe and well tolerated.

974-P

LX4211, a Dual Inhibitor of SGLT2 and SGLT1 Enhances the Effects of Sitagliptin in Patients With Type 2 Diabetes Mellitus (T2DM)

BRIAN ZAMBROWICZ, IKE OGBAA, DAVID POWELL, PHILLIP BANKS, ANNE TURNAGE, KENNY FRAZIER, KRISTI A. BOEHM, JOEL FREIMAN, PABLO LAPUERTA, ARTHUR SANDS, *The Woodlands, TX*

Combination therapy is often required in patients with type 2 diabetes mellitus (T2DM) to achieve glycemic control. LX4211 is a potent inhibitor of SGLT1 in the gastrointestinal (GI) tract and SGLT2 in the kidney. Local SGLT1 inhibition has been shown to stimulate secretion of GI hormones that play a role in glycemic control and appetite suppression. In this mechanistic study, we investigated the pharmacodynamic (PD) effects of the combination of LX4211 plus sitagliptin, a DPP-4 inhibitor, compared to either agent alone.18 diabetic patients received single doses of either LX4211 (400 mg), sitagliptin (100 mg) or LX4211+sitagliptin on Days 1, 8, or 15 according to a balanced 3x3 crossover design with a 7-day washout period between each dosing day. PD parameters assessed included urinary glucose excretion (UGE), postprandial glucose (PPG), insulin, peptide YY (PYY), and total and active glucagon-like peptide 1 (GLP-1).All patients completed the study. There were no serious adverse events, deaths or discontinuations due to adverse events. The drug combination differed from sitagliptin for the PD parameters below. Data are presented as $AUC_{0\text{-last}}$ adjusted means, except for UGE.LX4211 and sitagliptin, combined, significantly increased both active and total GLP-1 as compared to sitagliptin alone, and produced substantial reductions in PPG with lower endogenous insulin levels. LX4211 and sitagliptin appear to have complementary mechanisms of action that may provide a novel approach to combination therapy for T2DM.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

PD Parameter	Treatment Group		
	LX4211	Sitagliptin	LX4211 + Sitagliptin
UGE (g/24hr)	92.2	7.5	83.9
Difference from combo*	*-8.2†† (-24.8, 8.4)*	*76.4 (59.8, 93.0)*	
Insulin (uM•hr/mL)	479.2	623.4	547.3
Difference from combo*	*68.1† (2.3, 133.9)*	*-76.1† (-141.9, -10.3)*	
PPG (mg•hr/L)	2366.7	2412.8	2209.6
Difference from combo*	*-157.0† (-312.9, -1.2)*	*-203.2† (-359.0, -47.3)*	
PYY (pmol•hr/L)	404.3	208.9	247.5
Difference from combo*	*-152.8†† (-187.1, -118.5)*	*43.6† (9.3, 77.9)*	
GLP-1 total (pmol•hr/L)	161.9	105.9	135.8
Difference from combo*	*-26.1†† (-38.8, -13.3)*	*29.9†† (17.2, 42.6)*	
GLP-1 active (pmol•hr/L)	69.2	128.8	167.4
Difference from combo*	*98.2†† (80.9, 115.4)*	*38.6†† (21.3, 55.9)*	

* estimated difference between combination and single dose drug adjusted means (95% CL)
p-values reflect differences in adjusted means between the combination of LX4211+Sitagliptin and each drug given as a single dose
†† p<0.001, † p<0.05

975-P

Releasing Volume and Managing Ligand-Binding: The Resolution of TZD-Induced Cardiac Hypertrophy

CHERNG-SHYANG CHANG, PEI-JANE TSAI, YAU-SHENG TSAI, *Tainan, Taiwan*

Thiazolidinediones (TZDs), including rosiglitazone (Rosi) and pioglitazone (Pio), are PPARγ agonists used clinically to treat hyperglycemia associated with diabetes mellitus. Despite the evidence that TZDs prevent cardiac hypertrophy via an intrinsic cardiac pathway, it has been reported that TZDs caused cardiac hypertrophy in animal models, and increased risk of congestive heart failure in humans. Plasma volume expansion, a TZDs side effect, has been demonstrated to be mediated via renal PPARγ activation. Thus, we test whether TZD-induced cardiac hypertrophy is primarily due to volume overload through a PPARγ dependent pathway. We released TZD-induced volume overload by feeding mice diuretic furosemide (Furo), and examined the PPARγ dependency on either PPARγ haploinsufficient (*Pparg*$^{+/-}$) mice or ligand-binding deficient (*Pparg*$^{L/+}$) mice. We found that Furo effectively attenuated Rosi-induced volume overload, cardiac hypertrophy, apoptosis, and Erk1/2 activation without affecting glucose-lowering efficiency of Rosi. Although Furo blunted Rosi-induced upregulation of contractile and hormonal genes of heart, none of Rosi-reprogrammed metabolic genes was reversed by Furo. Thus, despite the direct effect of PPARγ activation on metabolic genes in heart, release of plasma volume ameliorated Rosi-induced cardiac hypertrophy, associated with attenuation of hypertrophic genes and signals. While the dosage was 4-fold higher of Rosi, we found that Pio cause volume overload and cardiac hypertrophy, and those were also blunted by Furo. Besides, *Pparg*$^{L/+}$ but not *Pparg*$^{+/-}$ is associated with attenuation of Rosi-induced volume overload and cardiac hypertrophy, suggesting that those effects require the intact ligand-binding ability of PPARγ. Our work has identified the causative link of TZD-PPARγ-volume overload-cardiac hypertrophy axis, and provided the evidence that co-treatment with Furo and managing ligand-binding ability can prevent the cardiac side effect of TZDs.

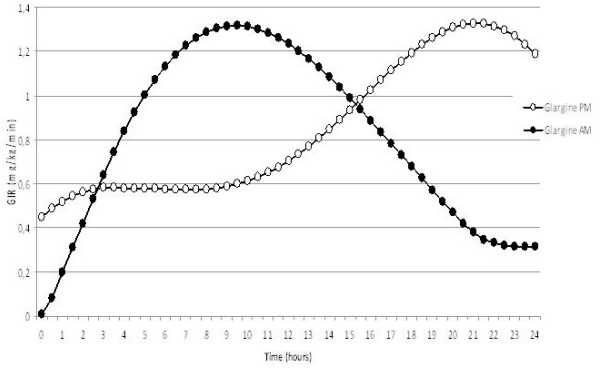
Supported by: NSC-98-2320-B-006-009-MY3

976-P

Different Effects of Insulin Glargine Given Morning vs. Evening in T2DM

FRANCESCA PORCELLATI, PAOLA LUCIDI, PATRIZIA CIOLI, STEFANIA MARZOTTI, ANNA MARINELLI ANDREOLI, GEREMIA B. BOLLI, CARMINE G. FANELLI, *Perugia, Italy*

Basal insulin glargine (GLA) is usually given once daily no matter if in the evening or in the morning. However, no study has directly compared pharmacokinetics and pharmacodynamics (PK/PD) of GLA administered at different times of day. Aim of this cross-over study was to evaluate PK/PD of GLA in persons with type 2 diabetes (T2DM), during a 24h euglycemic glucose clamp, where GLA was given s.c., either at 10 PM or at 10 AM (0.4 U/kg). Data from 7 out of 10 subjects studied, are here reported (mean±SD: age 66.9±6.5 yrs; BMI 28±3.3 kg/m^2; A1C 7.2±0.8%, known diabetes duration 17.4±10.4 yrs). Total activity (GIR_AUC$_{0\text{-}24h}$) was similar in the two studies (1177±761, 1151±667 mg/kg, AM vs PM respectively, p=0.8), but AUC$_{0\text{-}12h}$ was greater in 10 AM vs 10 PM study (678±407 vs 374±292 mg/kg, p=0.005), whereas the opposite was observed for AUC$_{12\text{-}24h}$ (499 ±366 vs 777 ±450 mg/kg, 10 AM and 10 PM, respectively, p=0.027). FFA were greater in the 10 AM vs 10 PM study (AUC$_{0\text{-}24h}$ 9.16 ±1.94 vs 7.52 ±1.96 mmol/L/h, p<0.002) primarily reflecting higher values in the 12-24 h time period. In conclusions PD of insulin GLA differs depending on the time of administration with morning injection showing greater activity in the initial 12 out of 24 hours in contrast to evening administration with greater activity in the second 12 hours. Since PK of GLA was similarly flat in the 2 studies, the different PD could be consequence of nycthoemeral changes in insulin sensitivity. In T2DM, evening better than morning GLA, counteracts the dawn phenomenon on glucose/lipid metabolism enhancing insulin activity beyond 24 h.



977-P

Oral Salmon Calcitonin Attenuates Hyperglycemia and Preserves Pancreatic Islet Structure and Function in Zucker Diabetic Fatty Rats

MICHAEL FEIGH, KIM HENRIKSEN, KIM VIETZ ANDREASSEN, ANITA V. NEUTZSKY-WULFF, CHRISTINA HANSEN, JAN ERIK HENRIKSEN, HENNING BECK-NIELSEN, CLAUS CHRISTIANSEN, MORTEN A. KARSDAL, *Herlev, Denmark, Odense, Denmark*

Oral delivery of the peptide hormone salmon Calcitonin (sCT) possessed glucoregulatory effects in diet-induced obese rats. In this study, we describe a proof of concept study in the Zucker diabetic fatty (ZDF) rat, a model of type 2 diabetes, investigating the effects of oral sCT on diabetic hyperglycemia and exploring the mode of actions by which it may protect against type 2 diabetes. Male ZDF rats were treated with oral sCT (0.5, 1.0 or 2 mg/kg) or oral vehicle twice daily from age 8 to 18 weeks. Attenuation of diabetic hyperglycemia and preservation of pancreatic function and islet morphology were evaluated. Oral and intraperitonal glucose tolerance testing (OGTT and IPGTT, respectively) was performed and levels of gut and pancreatic hormones were measured. Oral sCT dose-dependently prevented fasting and fed hyperglycemia and reduced HbA1C levels by 1.7% during the first 5 weeks of treatment in ZDF rats ($p < 0.01$). At the end of the study period, oral sCT by dose decreased diabetic hyperglycemia by approximately 9 mmol/l and sustained a 1.7% reduction in HbA1C ($p < 0.01$). Oral sCT treatment sustained plasma levels of insulin ($p < 0.01$) and decreased plasma levels of glucagon ($p < 0.01$) in the basal state compared to vehicle. Interestingly, plasma levels of incretin hormones glucagon-like-peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)were not influenced by oral sCT treatment. Furthermore, oral sCT dose-dependently reduced total glucose excursions during both OGTT ($p < 0.001$)and IPGTT ($p < 0.01$), although more pronounced during the OGTT. Lastly, pancreatic beta-cell morphology was normalized in high dose oral sCT treated rats. Oral salmon Calcitonin attenuated development of diabetic hyperglycemia in ZDF rats by influencing glucose absorption, exerting a direct insulinotropic and glucagonostatic action and by preserving pancreatic function and islet morphology.

Supported by: Danish Research Foundation (Den Danske)

978-P

LX4211 Increases Serum GLP-1 and PYY Levels After Oral Glucose Challenge in Mice by Inhibiting SGLT1-Mediated Intestinal Glucose Absorption

DAVID R. POWELL, MELINDA SMITH, SHARON ZHAO, JENNIFER GREER, ANGELA HARRIS, CHRISTOPHER DACOSTA, ARTHUR SANDS, BRIAN ZAMBROWICZ, ZHI-MING DING, *The Woodlands, TX*

LX4211, a dual SGLT1/SGLT2 inhibitor, is designed to block renal glucose (G) reabsorption by inhibiting SGLT2 and intestinal (GI) G absorption by inhibiting SGLT1. Increased GI G levels secondary to SGLT1 inhibition should trigger release of GI hormones such as glucagon-like peptide (GLP)-1 and peptide YY (PYY). We asked if oral G increases levels of cecal G and serum GLP-1 and PYY in mice treated with LX4211, and if these findings are recapitulated in SGLT1 or SGLT2 knock out (KO) mice. Wild-type (WT) mice raised on G-containing diet received vehicle or LX4211 (60 mg/kg) by gavage; 30

min later these mice, along with SGLT1 and SGLT2 KO and WT littermate mice raised on G-free diet, received a G-containing meal (9.2 g G/kg, 2.5 g protein/kg, 0.6 g fat/kg) by gavage and were studied 3 hr later (Table 1).

Table 1

Mice	Cecal G (mg)	Total GLP-1 (pM)	Active GLP-1 (pM)	PYY (ng/ml)
WT + Vehicle	1.2 ± 0.4	55 ± 2	7.2 ± 0.6	0.9 ± 0.1
WT + LX4211	18.9 ± 2.2***	161 ± 15***	16.3 ± 2.1***	2.2 ± 0.3**
SGLT1 WT	0.1 ± 0.1	36 ± 4	2.7 ± 0.2	1.0 ± 0.1
SGLT1 KO	16.7 ± 5.4*	158 ± 14***	12.5 ± 3.8*	2.2 ± 0.6*
SGLT2 WT	0.7 ± 0.5	52 ± 2	7.0 ± 0.1	1.6 ± 0.1
SGLT2 KO	0.7 ± 0.4	53 ± 4	7.1 ± 0.4	1.3 ± 0.1

Values are mean ± SE; N > 4; unpaired t test. * p<0.05; ** p<0.01; *** p<0.001

Also, 30 min after receiving vehicle or LX4211 (60 mg/kg) by gavage, WT mice were gavaged different G doses; total GLP-1 AUC was then estimated over the next 6 hr (Table 2).

Table 2

Treatment	GLP-1 AUC 0-6 hr (nM x min)			
Vehicle	18 ± 3	19 ± 1	29 ± 4	25 ± 4
LX4211	42 ± 4	59 ± 6	84 ± 12**	160 ± 36***
	(G dose 2 g/kg)	(G dose 4 g/kg)	(G dose 6 g/kg)	(G dose 8 g/kg)

Values are mean ± SE; N = 5; ANOVA followed by Bonferroni-Dunn post-hoc test. ** p < 0.01; *** p < 0.001

Oral G increased levels of GI G and serum GLP-1 and PYY in LX4211-treated mice, findings that were recapitulated in SGLT1, but not SGLT2, KO mice. These data suggest that LX4211 increases serum GLP-1 and PYY levels after an oral G challenge by inhibiting GI SGLT1.

979-P

Effect of BLX-1002 in a Rat Model of Non-Alcoholic Fatty Liver Disease

JEYAMURUGAN MOOKKAN, JAYANARAYANAN KULATHINGAL, MALLIKARJUN S. JAJI, VIJAYARAJ DEVISINGH, NAGARAJ M. KULKARNI, NAVINRAJESH B., GAJENDRA SINGH, GOPALAN B., SHRIDHAR NARAYANAN, *Chennai, India*

Non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome, which is strongly associated with obesity. No pharmacologic therapy has conclusively proved to be effective for the treatment of this disease. In present investigation effect of BLX-1002 a novel small molecule was evaluated on obesity and hepatic steatosis using supranutritional diet induced nSTZ rat model of NAFLD.Neonatal Streptozotocin (STZ) treated male rat fed with high fat diet (60 Kcal %) and fructose (40%) in drinking water for 90 days to induce NAFLD. After the induction period the animals were divided into different groups and treated with vehicle, BLX -1002 at 1, 3 and 10 mg/kg for 48 days p.o. Body weight was monitored daily. At the end of the experiment animals were sacrificed, organs collected and liver samples subjected to histopathological examination.The animals treated with BLX-1002 at 3 and 10 mg/kg showed reduction in body weight (10 mg/kg, P<0.05) and in fat pad weight .The histopathology examination of liver revealed that, BLX-1002 at 10 mg/kg (P<0.05) produced marked reduction in hepatocellular vacuolation (steatosis).In conclusion, these data demonstrate the remarkable effect of BLX-1002 not only on hepatic steatosis but also on body weight and fat pad weight, suggesting that, this compound may be an attractive therapy for NAFLD. Phase II trials of BLX-1002 in NAFLD subjects is planned.

980-P

Ultrastructural Visualisation of Insulin Degludec Multi-Hexamers in the Subcutaneous Depot In Vivo Supports a Unique Mechanism of Protraction

TORBEN SEESTED, SVEND HAVELUND, IB JONASSEN, THOMAS HOEG-JENSEN, CHARLES PYKE, ERICA NISHIMURA, *Måløv, Denmark*

Insulin Degludec (IDeg) is a novel basal insulin engineered to form a depot of soluble multi-hexamers at the injection site from which there is a slow and steady absorption into the circulation to provide an ultra-long half-life of over 24 hours.In the present study we visualise at the ultra-structural level the *in vivo* depot formation of IDeg multi-hexamers in the subcutis following injection of the clinical formulation.IDeg or NPH insulin (120 nmol/20U) was subcutaneously injected in the neck of anesthetized pigs. After 10 minutes, a biopsy of the injection site was fixed in paraformaldehyde and embedded in epoxy resin. Micrographs from ultra-thin sections revealed the presence of thread-like structures, measuring approximately 5-20 nm in width. The size and shape of these thread-like structures resemble that of IDeg multi-hexamers previously observed by *in vitro* electron microscopy. Immuno-gold labelling was performed using 2 antibodies directed against the insulin backbone and 2 antibodies specific for the acylated linker on IDeg. When applied to separate tissue blocks, all 4 antibodies showed the same pattern of immuno-reactivity, confirming the presence of IDeg in the thread-like structures located in the subcutis. Anti-insulin antibodies pre-absorbed with insulin and a non-relevant antibody showed no gold labelling over the thread-like structures.In contrast to IDeg, large (~200-500 µm in width) crystalline, rod-like structures were observed after injection of NPH. Immuno-gold reactivity was only observed with the two antibodies directed against the insulin backbone.These data visualize the formation of IDeg multi-hexamers at the injection site and support IDeg's unique mechanism of protraction.

981-P

12-Week Treatment With Glucagon Receptor Antagonist LY2409021 Significantly Lowers HbA1c and is Well Tolerated in Patients With T2DM

CHRISTOF KAZDA, PARAG GARHYAN, RONAN P. KELLY, CHUNXUE SHI, CHAY NGEE LIM, HAODA FU, MARK DEEG, *Suresnes, France, Indianapolis, IN, Singapore, Singapore, Ellicott City, MD*

T2DM pathophysiology is characterized by dysregulated glucagon secretion. LY2409021 (LY) is a potent, selective glucagon receptor antagonist that lowers glucose. This double-blind, Phase 2 study examined the margin between LY efficacy and safety by comparing mean changes in HbA1c and liver aminotransferases at 3 dose levels; other measures of glycemic control and safety were evaluated. Pts (18-70 y) with T2DM (HbA1c 6.5-10%) naïve to antidiabetic medications or taking a stable Met dose were randomized to LY 10 mg (n=17), 30 mg (n=34), 60 mg (n=26) or placebo (n=10) QD for 12 weeks. At baseline, mean HbA1c for LY 10 mg (8.0%), 30 mg (7.5%), and 60 mg (7.6%) were similar to placebo (7.8%). At 12 weeks, HbA1c LS mean change from baseline showed all LY dosages improved glycemic control (10 mg: -0.83%, P=.030; 30 mg: -0.65%, P=.042; 60 mg: -0.66%, P=.051) in contrast to placebo (0.11%). Secondary efficacy measures (eg, 7-pt SMBG) supported superiority of LY over placebo. No significant changes in TGs, LDL-c, HDL-c, weight, or BP were observed. Dose-dependent increases in fasting glucagon, ALT, AST, and total GLP-1 were observed; these returned to baseline on washout of LY. Pts exposed at endpoint to LY 10 mg showed no significant ALT or AST changes; LY 30 and 60 mg were associated with mean increases ranging from 3.7 to 19.9 U/L. Total, direct, and indirect bilirubin, fasting insulin, and active GLP-1 were unchanged vs. placebo. Eight of 85 pts reported hypoglycemic events, 4 of which were confirmed. Incidence of hypoglycemia was not dose dependent; no severe events were reported. AE frequency was similar with active treatment and placebo. This study demonstrates that glucagon receptor antagonism with LY substantially lowers HbA1c. Increases in aminotransferases were evident at higher doses without elevated bilirubin or other signs or symptoms of liver injury. The efficacy, safety, and tolerability profile of LY in pts with T2DM supports further clinical development.

982-P

Diet-Oil, a Pro-Drug for the GPR 119 Receptor Agonist, 2-Oleoyl-Glycerol, Increases the Secretion of Incretin Hormones in Patients With Type 2 Diabetes

METTE J. MANDØE, KATRINE B. HANSEN, FILIP K. KNOP, JENS J. HOLST, HARALD S. HANSEN, *Copenhagen, Denmark, Gentofte, Denmark*

Diet-oil (1,3-di-butyryl-2-oleoyl-glycerol) is a precursor for the naturally occurring ligand, 2-oleoyl-glycerol (2-OG), which is a ligand for the G protein-coupled receptor GPR119, and causes release of the insulinotropic and glucagonostatic hormone, glucagon-like peptide-1 (GLP-1), from L cells in healthy subjects. The liberation of 2-OG from diet-oil is thought to occur more distally in the gut than 2-OG from olive oil (trioleoylglycerol). Because the density of L cells increases in the distal gut, diet-oil might generate a greater GLP-1 response than olive oil. 2-OG also stimulates release of glucose-dependent insulinotropic polypeptide (GIP)Diet-oil (and olive oil) were administered orally to 13 Caucasian patients with type 2 diabetes (8 males, age: 62±3 years (mean±SEM), body mass index: 30.4±2.5 kg/m^2, fasting plasma glucose: 8.9±1 mM, HbA_1c: 6.9±0.4%) in a randomized, single-blinded cross-over study. The subjects were given 3 different meals on 3 different days: 200 g grated carrot, 200 g grated carrot + 20 g olive oil, or 200 g grated carrot +10.7 g diet-oil. Theoretically, the two oil regimes both result in formation of 7.7 g 2-OG during digestion. Total GLP-1 and GIP were measured in plasma.Olive oil and diet-oil resulted in significantly ($P \leq 0.01$) greater postprandial GLP-1 and GIP responses [GLP-1: incremental area under curve (iAUC) 845 and 710 pM×180 min, $P = 0.41$; GIP: 4337 and 2926 pM×180 min, $P = 0.08$] compared to the carrot meal (386 pM×180 min and 874 pM×180 min).Diet-oil enhanced secretion of GLP-1 and GIP (compared to carbohydrate alone) to almost the same extent as olive oil, although olive oil liberates not only 2-OG but in addition 2 oleic acid molecules, which may also stimulate incretin secretion. Thus, diet oil is more effective as incretin releaser than olive oil per unit of energy content and could be useful for dietary intervention.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

983-P

Efficacy and Safety of Once-Daily Lixisenatide in Type 2 Diabetes Insufficiently Controlled With Basal Insulin ± Metformin: GetGoal-L Study

MATTHEW RIDDLE, PHILIP HOME, MICHEL MARRE, ELISABETH NIEMOELLER, LIN PING, JULIO ROSENSTOCK, *Portland, OR, Newcastle, United Kingdom, Paris, France, Frankfurt, Germany, Dallas, TX*

This was a double-blind, multicenter study in people with Type 2 diabetes (T2D) previously treated with basal insulin ± metformin [NCT00715624]. Participants were randomized to add lixisenatide 20 µg (LIXI) or placebo (PBO) QD (morning). Demographics at baseline were well balanced: mean T2D duration was 12.5 yr, BMI 32.1 kg/m^2, A1C 8.4 %. Previous insulin therapy (mean 55 U/day) included glargine (50%), NPH (40%), detemir (9%), premix (2%). In cases of screening A1C ≤7.5 %, insulin was to be reduced 20% at randomization to limit hypoglycemia, with the subsequent aim of maintaining stable dosage and no titrations were allowed except for hypoglycemia. The primary endpoint was A1C reduction with LIXI *vs* PBO at Week 24 (LOCF analysis). LIXI significantly reduced A1C, 2-h PPG after standardized breakfast, and body weight *vs* PBO (Table). More LIXI *vs* PBO patients achieved A1C <7.0 % (28% *vs* 12%; p<0.0001). Insulin dose at endpoint was decreased more with LIXI *vs* PBO (-5.6 U *vs* -1.9 U; p=0.012). Incidence of AEs and serious AEs was 73.5% and 3.7% with LIXI *vs* 68.3% and 4.2% with PBO. Discontinuation due to AEs (mainly GI events) was 7.6% with LIXI and 4.8% with PBO. Comparable proportions of LIXI *vs* PBO patients had ≥1 hypoglycemic event (27.7% *vs* 21.6%); 4 cases (1.2%) of severe hypoglycemia occurred in the LIXI group, none with PBO. In conclusion, in uncontrolled T2D with non-optimized basal insulin ± metformin, once-daily LIXI improved glycemic control (despite reduction of insulin dose) and reduced body weight. AEs were mainly gastrointestinal and transitory.

Efficacy parameters in mITT population		Lixisenatide (N=327)	Placebo (N=166)
A1C (%)	Mean baseline ± SD LS mean ± SE change from baseline LS mean difference vs placebo	8.39 ± 0.86 –0.74 ± 0.09 –0.36 (–0.55 to –0.17); p=0.0002	8.38 ± 0.83 –0.38 ± 0.11
2-hour post-breakfast plasma glucose (mmol/l)*	Mean baseline ± SD LS mean ± SE change from baseline LS mean difference vs placebo	16.44 ± 4.29 –5.54 ± 0.47 –3.81 (–4.70 to –2.93); p<0.0001	15.85 ± 3.71 –1.72 ± 0.54
Body weight (kg)	Mean baseline ± SD LS mean ± SE change from baseline LS mean difference vs placebo	87.4 ± 20.0 –1.80 ± 0.25 –1.28 (-1.80 to -0.75); p<0.0001	89.1 ± 21.0 –0.52 ± 0.29
Safety parameters in safety population, N (%)			
Symptomatic hypoglycemia**		91 (27.7%)	36 (21.6%)
Nausea		86 (26.2%)	14 (8.4%)
Vomiting		27 (8.2%)	1 (0.6%)
Diarrhea		24 (7.3%)	9 (5.4%)

*After a standardized meal test; **Event with clinical symptoms with either plasma glucose <3.3 mmol/L or prompt recovery after carbohydrate administration if no plasma glucose measurement was available; mITT=modified intention to treat; SD=standard deviation; LS=least squares; SE=standard error

Supported by: sanofi-aventis

984-P

Saxagliptin Improves Glucose Tolerance but Fails to Improve Survival in a Murine Model of Dilated Cardiomyopathy

ARPITA KALLA VYAS, LAUREN B. AERNI-FLESSNER, MARIA PAYNE, PATRICK Y. JAY, PAUL W. HRUZ, *St. Louis, MO*

Glucagon-like peptide 1 (GLP-1) agonists improve myocardial function in the setting of chronic heart failure. Endogenously produced GLP-1 peptide (7-36) is normally rapidly cleaved by dipeptidyl peptidase 4 (DPP4) to the 9-36 peptide which does not possess anti-hyperglycemic activity but may have direct effects on cardiac function. To elucidate the effect of increased endogenous GLP-1 during heart failure progression, the DPP4 inhibitor saxagliptin or vehicle was administered by daily oral gavage to female TG9 mice, a model of dilated cardiomyopathy generated by cardiac-specific overexpression of cre recombinase, starting at day of life 42, which is just prior to the development of cardiac dysfunction. Saxagliptin treatment inhibited DPP4 activity >90% and increased GLP-1 levels 4-fold following a 2 gm/kg glucose load but did not affect fasting GLP-1 levels. There was no difference in food intake or body weight between groups. At 56 days of age, oral glucose tolerance was improved in saxagliptin-treated mice versus vehicle-treated animals (AUC0-120 1340 ± 46 and 1501 ± 43 min · mmol/L, respectively, p<0.015). There was no significant difference in the quantitative insulin sensitivity check index. Myocardial 2-deoxyglucose uptake, GLUT4 expression, and activation of both AKT and AMPK were also unchanged. Saxagliptin treatment had no effect on left ventricular brain naturetic peptide message, cardiac contraction, or survival (80.7 ± 4.3 days) compared to vehicle-treated mice (79.6 ± 3.6 days, p = 0.46). DPP4 inhibition, in contrast to the effect of GLP-1 agonists, has a moderate effect on glucose tolerance in TG9 mice but does not significantly alter survival in the setting of progressive congestive heart failure. Taken together, these data demonstrate that improved glucose tolerance is not sufficient to alter cardiac function and survival and suggest that glucose-independent effects may contribute to the benefit of GLP-1 agonists in heart failure treatment.

985-P

Muscle Oxygenation Measured With Near Infrared Spectroscopy in Diabetic Patients

FRANCESCO TECILAZICH, JOSHUA A. SAMUELS, MICHAEL NEIDRAUER, LEONID ZUBKOV, ELISABETH S. PAPAZOGLOU, ARISTIDIS VEVES, *Boston, MA, Philadelphia, PA*

There is very limited information regarding muscle oxygenation in diabetes (DM), mainly due to the lack of reliable non-invasive techniques. We have employed a new technique that employs Diffuse Near Infrared Spectroscopy (DNIRS) to identify changes in the level of muscle oxygenation during endothelium-dependent and -independent vasodilation in the macrocirculation of DM patients. We studied healthy control subjects [group C, n=4, age 65 ± 5 years] and DM patients (DM, n=22, age 59 ± 2). All subjects underwent a complete physical examination. Neuropathy was assessed by neuropathy disability score (NDS) and vibration perception threshold (VPT). We performed continuous measurements of oxygenated hemoglobin (O_2Hb), deoxygenated hemoglobin (HHb) and hemoglobin O_2 saturation (satO_2) in the thenar muscle at resting conditions, during the occlusion of the brachial artery and the following reactive hyperemia [Flow Mediated Dilation (FMD)] and Nitroglycerin Induced Dilation (NID). The resting O_2Hb, HHb and satO_2 at baseline were similar among the 2 groups. All the spectroscopic measurements of tissue oxygenation during FMD were also similar among the 2 groups. However, the average of the continuous measurements of O_2Hb and satO_2 from 4 to 8 minutes after the administration of nitroglycerin were higher in the DM group when compared to the C (66.6 um ± 16.8 vs 45.3 ± 8.3, p=0.057; and 57% ± 6 vs 48% ± 6, p<0.05 respectively). HHb levels were similar between the two groups. Strong associations were observed between the spectroscopy measurement satO_2 and FMD (r=-0.53, p<0.04), NDS (r=0.51, p<0.04) and VPT (r=0.48, p<0.05); and between the O_2Hb and NDS (r=0.46, p<0.05). We conclude that DNIRS can reliably measure muscle oxygenation. Furthermore, DM especially in the presence of neuropathy, adversely affects the peripheral uptake of oxygen during NID, probably due to the presence of arterial-venous shunting.

Supported by: NIH (1R21DK082987)

986-P

Renoprotective Effects of the DPP-4 Inhibitor Linagliptin in db/db Mice

YULIYA SHARKOVSKA, MARKUS ALTER, CHRISTOPH REICHETZEDER, OLEG TSUPRYKOV, THOMAS KLEIN, BERTHOLD HOCHER, *Berlin, Germany, Potsdam, Germany, Biberach, Germany*

Diabetic nephropathy is the main cause of end-stage renal disease. This study investigated the effects of linagliptin on diabetic nephropathy in severe insulin-resistant and *db/db* mice as a model for diabetic nephropathy. Male diabetic C57BL/6 *db/db* mice (10 weeks) were divided into 3 groups and treated for 12 weeks with vehicle (n=10), linagliptin 3 mg/kg/d (n=8), or the angiotensin-converting enzyme (ACE) inhibitor enalapril 20 mg/kg/d (n=10). Heterozygous *db/+* mice treated with vehicle were used as controls (n=8). Levels of glucose, triglycerides, and insulin were analyzed in serum and urine samples. Renal histology (glomerulosclerosis, tubulointerstitial fibrosis) and expression of the sialoglycoprotein podocalyxin (a marker of podocyte integrity in the glomeruli) were evaluated at study end. At 22 weeks, *db/db* mice showed significantly higher levels of fasting plasma glucose, insulin, and triglycerides, and increased body weight compared with *db/+* mice (all p<0.01). Linagliptin and enalapril had limited effects on fasted or postprandial glucose levels. However, histology analysis showed that tubulointerstitial fibrosis and glomerular mesangial matrix expansion were reduced almost to control levels in both treatment groups compared with *db/db* vehicle-treated mice (both p<0.05). Podocalyxin expression in *db/db* vehicle-treated mice was significantly reduced compared with *db/+* controls (1.59±0.2 vs. 2.65±0.1; p<0.001). Mice treated with linagliptin and enalapril had significantly higher podocalyxin expression compared with *db/db* vehicle-treated mice (2.3±0.2 and 2.4±0.2, respectively, vs. 1.59±0.2; both p<0.05). This study suggests that linagliptin protects podocytes from injury and may therefore be efficacious in the treatment of diabetic nephropathy independent of its effect on glucose homeostasis. The renoprotective effect of linagliptin in this model is as effective as treatment with an ACE inhibitor, the current gold standard for treatment of diabetic nephropathy.

Supported by: Boehringer Ingelheim

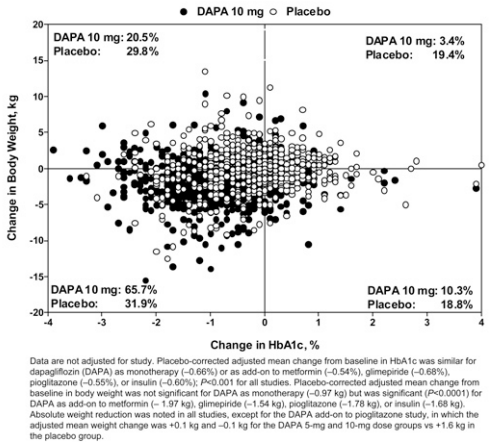
987-P

Exploration of the Relationship of Reduction in HbA1c and Body Weight by Dapagliflozin in Patients With T2DM: Pooled Analysis of 5 Clinical Trials

ELISE HARDY, AFSHIN SALSALI, CATRIN WESSMAN, LI WEI, TRACI MANSFIELD, SHAMIK PARIKH, *Wilmington, DE, Princeton, NJ, Mölndal, Sweden*

Dapagliflozin (DAPA), a sodium glucose cotransporter 2 (SGLT2) inhibitor, decreases both plasma glucose and body weight through the common mechanism of urinary glucose excretion. We analyzed the distribution of change from baseline to week 24 in HbA1c and body weight in individual patients pooled from 5 of the core DAPA phase 3 placebo-controlled clinical trials to explore a potential relationship between the 2 variables. Patients with T2DM received DAPA 10 mg/d (N=690) or placebo (N=689) for 24 wk as monotherapy (NCT00528372) or as add-on to metformin (NCT00528879), glimepiride (NCT00680745), pioglitazone (NCT00683878), or insulin (NCT00673231). Analysis of HbA1c and body weight excluded data after rescue (LOCF). In these studies, DAPA 10 mg/d produced mean placebo-corrected changes from baseline in HbA1c of -0.54% to -0.68% and of -1 to -2 kg for body weight. Mean (95% CI) change from baseline in spot urine glucose/creatinine ratio pooled across the 5 studies for DAPA 10 mg/d (including data after rescue) was 34.6 g/g (32.1 g/g, 37.0 g/g), compared with placebo -1.4 g/g (-2.8 g/g, -0.1 g/g). Approximately one third more patients treated with DAPA compared with placebo (65.7% vs. 31.9%, respectively) achieved reductions in both HbA1c and body weight based on unadjusted data for individual patient responses to treatment (Figure). In conclusion, the majority of patients receiving DAPA 10 mg/d as monotherapy or as add-on therapy to commonly used diabetes medications achieved reductions in both HbA1c and body weight, consistent with a common mechanism for both parameters.

Proportion of Patients with Reduction in Body Weight and Reduction in HbA1c



Data are not adjusted for study. Placebo-corrected adjusted mean change from baseline in HbA1c was similar for dapagliflozin (DAPA) as monotherapy (–0.66%) or as add-on to metformin (–0.54%), glimepiride (–0.68%), pioglitazone (–0.55%), or insulin (–0.60%); $P<0.001$ for all studies. Placebo-corrected adjusted mean change from baseline in body weight was not significant for DAPA as monotherapy (–0.97 kg) but was significant ($P<0.0001$) for DAPA as add-on to metformin (– 1.97 kg), glimepiride (–1.54 kg), pioglitazone (–1.78 kg), or insulin (–1.68 kg). Absolute weight reduction was noted in all studies, except for the DAPA add-on to pioglitazone study, in which the adjusted mean weight change was +0.1 kg and –0.1 kg for the DAPA 5-mg and 10-mg dose groups vs +1.6 kg in the placebo group.

Supported by: Bristol-Myers Squibb and AstraZeneca

988-P

Glycemic Control and Hypoglycemia Prevalence According to Gender: An Analysis of RCT Data

ALEXANDRA KAUTZKY-WILLER, LANA KOSI, ROMAN MIHALJEVIC, JAY LIN, EDWARD WANG, *Vienna, Austria, Flemington, NJ, Bridgewater, NJ*

Small observational studies have suggested that females with type 2 diabetes (T2DM) have a reduced improvement in A1C levels and a greater hypoglycemia risk than males. The aim of this analysis was to determine glycemic control and hypoglycemia prevalence according to gender in insulin-naïve patients with T2DM. Intent-to-treat populations, who received insulin for 24-36 wk, were pooled from 6 randomized clinical trials. Baseline and endpoint A1C and demographics were measured. Severe hypoglycemia was defined as specified in each trial. Female (mean A1C, 9.0%; age, 56.9 y; duration of diabetes, 9.8 y) and male patients (mean A1C, 8.9%; age 57.5 y; duration of diabetes, 10.1 y) were started on insulin. Baseline BMI and insulin dose-to-weight ratio were higher in females than in males (Table). A1C levels fell significantly in both genders ($P<0.001$), and there was a significant difference in A1C reduction between genders (Table). Fewer females achieved a target A1C of < 7%. Severe and severe nocturnal hypoglycemia was higher in females, and at endpoint, females had significantly higher insulin dose-to-weight ratio than males. However, the insulin dose increase was lower in females. The results show that females had a smaller reduction in A1C levels, a higher prevalence of severe hypoglycemia and a greater insulin dose-to-weight ratio than males. This suggests that clinicians may have been more inclined to give more insulin to females to try and improve glycemic control. These observations emphasize previous small observational studies where a reduced improvement in A1C and a higher hypoglycemia risk were observed in females.

	Gender		*P* Value[a]
	Female (n = 1251)	Male (n = 1349)	
BMI at baseline, kg/m²	28.7 (5.3)	28.0 (4.9)	0.002
A1C at baseline,	9.0 (1.0)	8.9 (1.0)	0.054
SDΔ A1C,	-1.22 (1.18)	-1.36 (1.19)	0.002
SDA1C < 7% at endpoint, %	26.5	33.0	< 0.001
Insulin dose at baseline, U	13.8 (8.1)	13.6 (8.1)	0.375
Insulin dose at endpoint, U	34.3 (22.4)	36.8 (27.4)	0.012
Insulin dose at baseline, U/kg	0.20 (0.12)	0.16 (0.10)	< 0.001
Insulin dose at endpoint, U/kg	0.47 (0.27)	0.42 (0.27)	< 0.001
Patients with ≥ 1 hypoglycemic event			
Severe, n (%)	41 (3.3)	25 (1.9)	0.021
Severe nocturnal, n (%)	28 (2.2)	8 (0.6)	< 0.001

[a]Comparison between genders

Supported by: sanofi-aventis

989-P

LGD-6972, a Potent, Orally-Bioavailable, Small Molecule Glucagon Receptor Antagonist for the Treatment of Type 2 Diabetes

ERIC G. VAJDA, SCOTT C. POTTER, JAMES M. FUJITAKI, RAJA K. REDDY, PAUL D. VAN POELJE, YONG-HEE LEE, IAN HENDERSON, LIN ZHI, KEITH B. MARSCHKE, *La Jolla, CA*

In patients with type 2 diabetes (T2DM), inappropriately elevated levels of glucagon exacerbate the hyperglycemic state by stimulating hepatic glucose production. Small molecule glucagon receptor (GCGR) antagonists suppress fasting plasma glucose and hemoglobin A1C levels in T2DM patients, and have the potential of providing an effective treatment for T2DM either alone or in combination with other anti-diabetic agents. LGD-6972 is a novel small molecule GCGR antagonist with high affinity (IC_{50} 5.0 nM) for binding to human GCGR. In primary human hepatocytes stimulated with 0.1 nM glucagon, LGD-6972 potently inhibited cAMP and glucose production with EC_{50} values of 0.46 and 11 nM, respectively. LGD-6972 inhibited cAMP production in primary monkey hepatocytes (EC_{50} 0.7 nM), but was less active in mouse and rat hepatocytes (EC_{50} of 150 nM and 103 nM, respectively). LGD-6972 is highly selective for GCGR with minimal activity on GLP-1 and GIP receptors. In the glucagon-challenged rat and monkey, single oral doses of LGD-6972 markedly suppressed the peak hyperglycemic response. In db/db mice, a single oral administration lowered blood glucose in a dose-dependent manner with a minimum efficacious dose of 3 mg/kg, and daily oral administration of 30 mg/kg resulted in sustained reductions in blood glucose for 28 days. LGD-6972 displayed high systemic exposure (Cmax >1 µg/ml at 3 mg/kg p.o.), low clearance rates (≤ 2 mL/min/kg) and moderate to long terminal half-life (8 - 46 h), with oral bioavailability of 47%, 36%, 57% and 20% in mice, rats, dogs and monkeys, respectively. LGD-6972 demonstrated a favorable profile in multiple ADME assays without any safety issues regarding genotoxicity, hERG channel or CYP P450 inhibition, and was safe and well tolerated in 14-day rat and monkey toxicity studies. Further development of LGD-6972 is underway and should provide a promising new agent to suppress glucagon action and improve glycemic control in T2DM patients.

990-P

GKM-001, a Glucokinase Modulator With Liver-Directed/Pancreas-Sparing Action Improves Glucose Control in Rodent Models of Diabetes Without Hypoglycemia Risk or Tachyphylaxis

KASIM A. MOOKHTIAR, DHANANJAY UMRANI, SUHAS TAMBE, PRASAD SHITOLE, VISHAL KOTHARI, ANIL DESHPANDE, SIDDHARTHA DE, DEBNATH BHUNIYA, NARAYANAN HARIHARAN, *Pune, India*

Glucokinase (GK) regulates glucose homeostasis through dual control of insulin secretion in pancreas and glucose disposal in liver. Though GK activators have shown anti-hyperglycemic effects in animals and in T2D patients, hypoglycemia, due to their dual action of increased hepatic glucose disposal and pancreatic insulin release, is a concern. GKM-001 was designed to selectively target liver GK and spare pancreas GK and, thereby, lower hypoglycemia risk. Previously, the liver-directed/pancreas-sparing action of GKM-001

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

was demonstrated by glycogen accumulation in rat hepatocytes, absence of insulin secretion in rat islets and increase in glucose infusion rate during a hyperglycemic clamp in rats, without change in plasma insulin levels. In this report, GKM-001 was investigated for glucose control in Zucker *fa/fa* rats and DIO mice, and for any hypoglycemia potential in normoglycemic rats and mice.GKM-001 dose-dependently improved glucose tolerance acutely in Zucker *fa/fa* rats, with no change in insulin levels. This improvement in glucose control was sustained over 25 days of dosing. These observations were also seen in DIO mice, where GKM-001 alone, and in combination with metformin or sitagliptin, dose-dependently improved glucose tolerance over 4 weeks. The combined effect with metformin and Sitagliptin was better than with GKM-001 alone. No change in body weight or feed intake was seen in either study. Furthermore, no hypoglycemia was seen in normoglycemic rats or mice at doses ≥ 10-fold over efficacious dose.These data demonstrate that GKM-001: 1) lowers glucose levels acutely and after multiple days of treatment, 2) does not promote insulin secretion, and 3) shows no evidence of tachyphylaxis for glucose lowering or hypoglycemia risk. These data are also consistent with its liver-directed/pancreas sparing action. GKM-001 is currently in clinical development for the treatment of T2D.

991-P

LX4211, a Dual Inhibitor of SGLT1/SGLT2, Increases GLP-1 and PYY in Healthy Subjects Regardless of Dose Timing Relative to Breakfast; GLP-1 Elevations are Greatest when Dosed Just Prior to Breakfast

IKE OGBAA, DAVID POWELL, PHILLIP BANKS, ANNE TURNAGE, KENNY FRAZIER, KRISTI A. BOEHM, JOEL FREIMAN, ARTHUR SANDS, BRIAN ZAMBROWICZ, *The Woodlands, TX*

LX4211, a dual inhibitor of SGLT1 and SGLT2, has repeatedly improved glycemic control with a favorable gastrointestinal (GI) safety profile. Therapeutic LX4211 effects may be mediated, in part, by modulation of glucose absorption/incretin stimulation in the GI tract; it is important to explore the effect of dosing relative to meals on these parameters.12 healthy subjects were sequestered and randomly assigned (2 placebo:10 LX4211). LX4211 was dosed for 7 days, to a steady state, then administered at 5 different times with respect to meals, using a Latin Square design balanced for first order carryover effects. Pharmacodynamic (PD) parameters sensitive to SGLT1 inhibition, including GLP-1 and PYY, (GI hormones associated with glycemic control and satiety), were measured as was urinary glucose excretion (UGE), a PD parameter sensitive to SGLT2 inhibition. Safety was evaluated throughout the study.Results across dosing times relative to Day -1 are presented. All regimens produced significant elevations of GLP-1 relative to Day -1. There were significant differences in GLP-1 between dosing 1-hour and just prior to breakfast, favoring the latter. All adverse events (AE) were mild and infrequent; no AEs were drug-related. No hypoglycemia or diarrhea occurred.

The effect of LX4211 on UGE, an SGLT2-associated PD parameter, remained consistent across all dosing times; increases in the SGLT1-associated PD parameter GLP-1 (total and active) was greatest when dosing occurred just prior to the breakfast.

Days 8-12, change from Day -1[a]:

Dose Schedule→ / PD Variable↓	Prior to Breakfast: 1 hr (A) N=12	0.5 hr (B) N=12	Immediately prior (C) N=12	p-value between groups
SGLT2 effects:				
UGE, g mean change, (95% CI)	33.62 † (30.68, 36.55)	37.19 † (34.25, 40.12)	34.06 † (31.12, 37.00)	NS
SGLT1 effects:				
PYY, pmol•hr/L $AUC_{0\text{-last}}$, (95% CI)	106.75 † (73.77, 139.74)	122.80 † (89.81, 155.78)	127.16 † (94.18, 160.15)	NS
GLP-1 total, pmol•hr/L $AUC_{0\text{-last}}$, (95% CI)	6.93 (-2.15, 16.01)	17.21 † (8.13, 16.29)	25.92 † (16.84, 35.00)	A vs C*
GLP-1 active, pmol•hr/L $AUC_{0\text{-last}}$, (95% CI)	7.87 †† (0.82, 14.92)	16.23 † (9.18, 23.28)	19.13 † (12.07, 26.18)	A vs C**

[a] $AUC_{0\text{-last}}$ were calculated from 15-minutes to 13-hours postdose
NS = not significant
† p≤0.001 vs Day -1 within group
†† p≤0.05 vs Day -1 within group
* p≤0.005 – favoring dosing immediately prior to breakfast vs 1 hr prior to breakfast
** p≤0.01 – favoring dosing immediately prior to breakfast vs 1 hr prior to breakfast

992-P

One-Year Safety, Tolerability and Efficacy of Vildagliptin in Patients With Type 2 Diabetes Mellitus and Moderate or Severe Renal Insufficiency

WOLFGANG KOTHNY, MAGGIE WANG, QING SHAO, PER-HENRIK GROOP, VALENTINA LUKASHEVICH, *East Hanover, NJ, Helsinki, Finland*

We previously reported vildagliptin 24 week safety and efficacy from a large randomized study in patients with moderate or severe renal impairment [RI, glomerular filtration rate (GFR) ≥30 to <50 mL/min/1.73m^2 and <30 mL/min/1.73m^2]. We are now reporting the 1-year safety and efficacy in 369 patients with type 2 diabetes mellitus (T2DM) and moderate or severe RI who entered the 28-week extension phase. The study population comprised 122 and 89 patients with moderate RI and 94 and 64 patients with severe RI randomized to vildagliptin 50 mg qd and placebo, respectively, with the majority of patients receiving background insulin therapy (72% and 82% for moderate and severe RI, respectively). In patients with moderate RI, similar proportions of patients experienced any AE (84 vs. 85%), any SAE (21 vs. 19%), any AE leading to discontinuation (5 vs. 6%) and death (1 vs. 0%) with vildagliptin and placebo, respectively. This was also true for patients with severe RI: AEs (85 vs. 88%), SAEs (25 vs. 25%), AEs leading to discontinuation (10 vs. 6%) and death (3 vs. 2%). GFR was slightly reduced in both treatment groups.. The data showed that vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo in patients with T2DM and moderate or severe RI during 1-year observation. Further, as shown in the table, a clinically relevant and statistically significant decrease in HbA1c was maintained throughout one year of treatment with vildagliptin as compared to placebo.

ANCOVA results for change in HbA1c (%) from baseline to rescue-censored Week 52 endpoint by renal impairment severity and treatment

				Difference in adjusted mean change (Vilda-Placebo)		
Treatment	**n**	**Baseline mean (SE)**	**Adjusted mean change (SE)**	**Mean (SE)**	**95% CI**	**P-value**
Renal impairment: Moderate						
Vilda 50mg qd	111	7.82 (0.09)	-0.57 (0.12)	-0.44 (0.15)	(-0.74,-0.14)	<0.01*
Placebo	76	7.77 (0.11)	-0.14 (0.14)			
Renal impairment: Severe						
Vilda 50mg qd	87	7.72 (0.10)	-0.81 (0.21)	-0.73 (0.19)	(-1.11,-0.36)	<0.01*
Placebo	59	7.48 (0.14)	-0.08 (0.22)			

Supported by: Novartis Pharmaceuticals Corporation

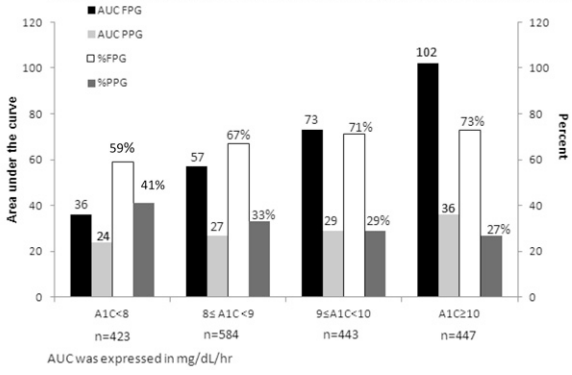
993-P

Challenging Monnier: Postprandial (PPG) vs. Fasting (FPG) Hyperglycemia by A1C Level Following Basal or Premixed Insulin Intervention

JULIO ROSENSTOCK, ANDRÉ J. SCHEEN, HENRY SCHMITT, HONGHUA H. JIANG, TIBOR IVANYI, *Dallas, TX, Liège, Belgium, Brussels, Belgium, Indianapolis, IN, Budapest, Hungary*

Monnier's cross-sectional study in non-insulin treated Type 2 Diabetes (T2D) showed greater contributions of PPG vs FPG to overall hyperglycemia at lower A1C. However, as shown recently, following basal insulin intervention both FPG and PPG contributed significantly even at A1C <7%.Relative 24h contributions of PPG and FPG to overall hyperglycemia calculated from 7-point glucose profiles (area under the curve (AUC) for FPG between 100 mg/dL and fasting glycemia and for PPG above the line projected from fasting glycemia) were analyzed from DURABLE study [T2D on ≥ 2 OAD's, randomized to once-daily insulin glargine (G) or twice daily insulin lispro mix 75/25 (LM75/25)]. At baseline, with increasing A1C, contributions of FPG to total AUC moved from 59 to 73% and PPG from 41 to 27% (Figure).

Figure: AUC FPG vs. AUC PPG at Baseline for all Randomized Patients (N=1897)



ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

Table: Baseline and Endpoint A1C, PPG and FPG AUC, for LM and G

	A1C<8%LM, G	A1C8<9%LM, G	A1C9<10%LM, G	A1C≥10%LM, G
Mean A1C baseline (%)	7.5, 7.6	8.5, 8.4*	9.4, 9.4	10.9, 10.8
Mean A1C endpoint (%)	6.7*, 6.8	7.0, 7.2	7.4, 7.4	7.8, 7.9
A1C<7%	72%*, 62%	52%*, 43%	37%, 31%	30%, 25%
Baseline PPG AUC (% total AUC, mg/dL/hr)	24, 24 (40%, 42%)	28, 27 (34%, 32%)	30, 28 (31%, 28%)	37, 35 (28%, 25%)
Endpoint PPG AUC (% total AUC)	19*, 25 (57%, 67%)	23*, 31 (56%, 67%)	22*, 29 (48%, 64%)	23*, 37 (49%, 66%)
Baseline FPG AUC (% total AUC)	37, 36 (60%, 58%)	55, 58 (66%, 68%)	72, 75 (69%, 72%)	98, 106 (72%, 75%)
Endpoint FPG AUC (% total AUC)* p<0.05 for difference between LM and G	14, 13 (43%, 33%)	19, 15* (44%, 33%)	24, 17* (52%, 36%)	27, 22* (51%, 34%)

Both LM and G lowered total and FPG AUC but only LM lowered PPG AUC (Table). Both insulins increased PPG % to AUC (48-67%) but FPG still contributed at all A1C levels (33-52%). In conclusion, at baseline, FPG AUC predominated at all A1C quartiles, with a relevant role of PPG at lower A1C. Insulin alters the relative contributions of PPG and FPG and its choice needs to be individualized according to glycemic goal and intensity of regimen chosen.

Supported by: Eli Lilly and Company

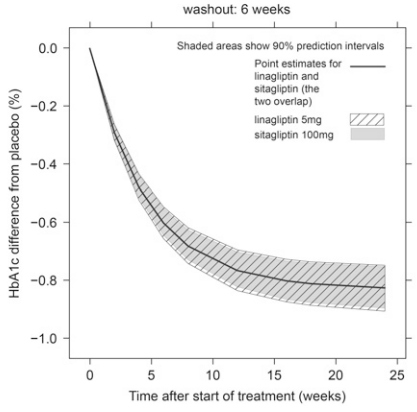
994-P

A Novel Model-Based Meta-Analysis to Estimate Comparative Efficacies of Two Drugs: An Example Using the DPP-4 Inhibitors Linagliptin and Sitagliptin in Type 2 Diabetes Mellitus

JORGE L. GROSS, JAMES ROGERS, DANIEL POLHAMUS, WILLIAM GILLESPIE, SANJAY PATEL, CHRISTIAN FRIEDRICH, YAN GONG, BRIGITTA MONZ, ALEXANDER STAAB, SILKE RETLICH, *Porto Alegre, Brazil, Tariffville, CT, Bracknell, United Kingdom, Biberach, Germany, Ingelheim, Germany*

A model-based meta-analysis (MBMA) approach was used to estimate comparative efficacies of two drugs that have not been compared directly. A comparison of the efficacy of linagliptin and sitagliptin in type 2 diabetes (T2D) treatment was used as an example. The analysis comprised a systematic review of double-blind, placebo-controlled, randomized trials ≥12 weeks' duration, investigating the efficacy of linagliptin or sitagliptin as HbA1c changes in adults with T2D and HbA1c >7.0%, irrespective of background medication. A total of 25 trials (10 linagliptin, 15 sitagliptin) were included, giving longitudinal data from 11,234 subjects. A Bayesian model was fitted (Markov chain Monte Carlo method). The final model described HbA1c levels as a function of time, dose, baseline HbA1c, washout status/duration, and race. Other covariates showed no major effect on model parameters and, so, were not included in the final model. For the indirect comparison, a population of 1000 patients was simulated from the model with a racial composition reflecting the average distribution in the linagliptin trials and a baseline HbA1c of 8.0%. Simulations showed both linagliptin 5mg and sitagliptin 100mg reduced HbA1c by 0.8% (placebo-adjusted) at week 24, indicating similar efficacy.This model seems a valid approach for indirect drug comparisons when head-to-head trials are not available. The results show virtually indistinguishable efficacies of linagliptin and sitagliptin in HbA1c reduction in people with T2D.

Figure: Estimated drug effects on HbA1c



Supported by: Boehringer Ingelheim

995-P

Vildagliptin Combined With Insulin Reduces HbA1c Without Increasing Risk of Hypoglycemia and Weight Gain in Patients With Type 2 Diabetes Mellitus

VALENTINA LUKASHEVICH, PLAMEN KOZLOVSKI, JAMES FOLEY, WOLFGANG KOTHNY, *East Hanover, NJ, Basel, Switzerland*

We previously reported that vildagliptin 50 mg bid (Vilda) added to insulin (INS) monotherapy in patients with type 2 diabetes mellitus (T2DM) provided 0.3% reduction in HbA1c vs. placebo (Pbo) with reduced risk of hypoglycemia (HYPO). The efficacy results were confounded by a high dose INS (>80U/daily) regimen suppressing endogenous INS secretion.We now report a 24-week study to assess the efficacy and safety of Vilda added to stable basal or pre-mixed INS, with or without concomitant metformin (MET) in patients with inadequately controlled T2DM with HbA1c 7.5% -11%. After a 2-week screening period patients were randomized to Vilda (N=228) or Pbo (N=221). Patients had mean age of 59 years and T2DM duration of 13 years, the mean dose of INS 40.9 U/day and about 40% of patients received INS monotherapy.Vilda significantly reduced HbA1c compared to Pbo in the overall population and sub-groups with or without MET (Table 1). Overall Vilda was safe and well tolerated with no weight gain. Incidences of HYPO (8.4% vs. 7.2%) and severe HYPO (0.9% in both groups) were similarly low in Vilda and Pbo groups despite the substantially greater HbA1c reduction with Vilda. Increased HYPO limits the efficacy of oral hypoglycemic agents in combination with INS. Vilda not only significantly lowered the HbA1c but also did not increase the risk of HYPO presumably due to a GIP mediated counter-regulatory glucagon effect.

Table 1. ANCOVA results for change in HbA1c (%) from baseline to study endpoint* (Full analysis set)

				Difference in adjusted mean change (Vilda-Placebo)		
Treatment	**n**	**Baseline mean (SE)**	**Adjusted mean change (SE)**	**mean (SE)**	**(95% CI)**	**P-Value**
Full-analysis set						
Vilda 50mg bid	221	8.80 (0.07)	-0.77 (0.08)	-0.72 (0.10)	(-0.92, -0.52)	<0.001*
Placebo	215	8.84 (0.07)	-0.05 (0.08)			
Full-analysis set (Insulin + metformin)						
Vilda 50mg bid	133	8.78 (0.08)	-0.98 (0.09)	-0.63 (0.12)	(-0.86, -0.39)	<0.001*
Placebo	134	8.80 (0.08)	-0.35 (0.09)			
Full-analysis set (Insulin)						
Vilda 50mg bid	88	8.84 (0.12)	-0.60 (0.19)	-0.84 (0.19)	(-1.21, -0.47)	<0.001*
Placebo	81	8.90 (0.11)	0.24 (0.20)			

* censored by the start of major changes in insulin background therapy

Supported by: Novartis Pharmaceuticals Corporation

996-P

Anti-Atherosclerotic Activity of Lixisenatide in ApoE Knockout Mice

HANS-LUDWIG SCHÄFER, THOMAS HÜBSCHLE, HANS-PAUL JURETSCHKE, ULRICH WERNER, *Frankfurt, Germany*

The ApoE knockout (KO) mouse develops atherosclerotic plaques with morphology resembling human atherosclerosis. This model was used to investigate the effects of chronic lixisenatide treatment on atherosclerotic plaque formation. Male ApoE KO mice (B.129P2-apoe ^{tm1Unc}/J) were treated for 16 weeks by continuous infusion *via* subcutaneous osmotic minipumps (ALZET™). Animals received 3.6 µg/mouse/day for the first 4 weeks and 5.04 µg for the subsequent 12 weeks. ApoE KO control mice received the same volume of placebo. Untreated mice from the background strain (C57BL6/J) were used as a second, healthy control. Total serum cholesterol and blood glucose were significantly reduced by lixisenatide both during (-41% and -10% Day 35) and at the end of treatment (-42% and -13% Day 112). The decrease in total serum cholesterol was related to a decrease in atherogenic non-HDL fractions. Treatment with lixisenatide had no significant effect on relative liver weight, hepatic cholesterol, triglyceride or phospholipid concentrations at study end. After 16 weeks of lixisenatide treatment, three methodologically independent measures (invasive [macroscopic and histology] and non-invasive [USPIO-based MRI imaging]) were used to quantify atherosclerotic plaque formation. When compared with the wildtype background, ApoE KO mice receiving placebo developed atherosclerotic lesions at the total inner surface of the aorta and the aortic root semilunar valve region of the heart. In contrast, lixisenatide treatment resulted in a significant reduction of atherosclerotic plaque formation by ~30% relative to placebo in all three methods. Lixisenatide significantly reduced atherosclerotic lesions at the total inner surface of the aorta and aortic root semilunar valve

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

region by 27% (oil red staining), 29% (Movat-Pentachrome staining) or 30% (USPIO-based MRI imaging). Thus, lixisenatide showed beneficial effects on non-HDL cholesterol, which was associated with a robust anti-atherosclerotic activity in ApoE KO mice.

Supported by: sanofi-aventis

997-P

LX4211, a Dual SGLT1/SGLT2 Inhibitor Shows a Favorable Gastrointestinal and Genitourinary Safety Profile in Type 2 Diabetes Mellitus (T2DM) Patients and Healthy Subjects

JOEL FREIMAN, GUI-LAN YE, IKE OGBAA, KRISTI A. BOEHM, ANNE TURNAGE, KENNY FRAZIER, ARTHUR SANDS, BRIAN ZAMBROWICZ, *The Woodlands, TX*

Selective SGLT2 inhibitors are designed to treat T2DM by blocking glucose reabsorption by the kidney, resulting in urinary glucose excretion. An increased incidence of genitourinary (GU) infections is a concern with these agents. Because patients with genetic mutations in SGLT1 experience glucose-galactose malabsorption, most SGLT inhibitors selectively inhibit SGLT2 to avoid theoretical risk of diarrhea resulting from SGLT1 inhibition. In clinical trials to date, LX4211, a potent dual inhibitor of SGLT1 and SGLT2, has shown both significantly improved glycemic parameters and a favorable gastrointestinal (GI) safety profile. This overview of LX4211 clinical studies evaluates the occurrence of adverse events (AEs) that may be associated with the pharmacologic action of LX4211.LX4211 was studied at single and multiple doses in healthy subjects and patients with T2DM (Figure 1) at doses ranging from 5 to 500 mg/day. LX4211 safety was assessed through AEs collected from the first dose to 30 days after the last dose. Relevant AEs were reviewed for each study.Of the 12 AEs of diarrhea, 5 occurred on LX4211 out of 1090 person days (PD), 3 with metformin out of 18 PD, and 4 with LX4211+metformin out of 18 PD. All resolved within 1 day and were generally mild. There were no episodes of hypoglycemia, with no deaths, serious AEs, or AEs leading to discontinuation. No GU infection was reported in any LX4211-treated subject.In clinical studies to date, LX4211 is well-tolerated with no evidence of clinically significant hypoglycemia, diarrhea, or GU infections.

Figure 1. Overview of Adverse Events[a]

LX4211 Dose, number of subjects	Diarrhea	Constipation	Nausea	Vomiting	UTI	Bacteriuria	Polyuria	Genital infection	Pruritus genital
	Gastrointestinal				Urinary			Genital	
Healthy Subjects									
LX4211.101	A placebo-controlled, double-blind, randomized, single ascending-dose and multiple ascending-dose study								
Placebo, n=24	0	0	1	0	0	0	0	0	0
5-100 mg, n=42	1	0	1	1	0	0	0	0	0
150-500 mg, n=30	0	0	0	0	0	0	1	0	0
LX4211.103	A single-center, randomized, open-label, 3-period, 3-treatment, crossover study to assess the pharmacokinetics, drug interaction of LX4211 and metformin when administered concurrently in healthy subjects (single-dose)								
400 mg, n=18	1	1	0	0	0	0	0	0	0
Metformin 1000 mg, n=18	3	1	0	0	0	0	0	0	0
LX4211 + Metformin, n=18	4	0	1	0	0	0	0	0	0
LX4211.104	A single-center, randomized, double-blind, placebo-controlled, multiple-dose study to assess the safety, tolerability, and PD of various dosing schedules of LX4211 relative to meals in healthy subjects								
Placebo, n=2	0	0	0	0	0	0	0	0	0
400 mg, n=10	0	0	0	0	0	0	0	0	0
Type 2 Diabetic Patients									
LX4211.102	A single-center, open-label, randomized, three-way crossover study designed to assess 2 oral formulations of LX4211 (solid tablet and liquid) in subjects with type 2 diabetes. Two tablet strengths of LX4211 (50 mg and 150 mg) and 1 oral solution (10 mg/mL) given to achieve 300 mg of LX4211 at each dose								
Tablet (2 x 150 mg), n=12	0	1	0	0	0	0	0	0	0
Tablet (6 x 50 mg), n=12	0	0	0	0	0	0	0	0	0
Oral solution (300 mg), n=12	1	2	0	0	0	0	0	0	1
LX4211.201	A 28 days, single-center, randomized, double-blind, placebo-controlled study in subjects with type 2 diabetes mellitus								
Placebo, n=12	0	2	2	1	0	0	0	0	0
150 mg, n=12	1	3	2	1	0	1	0	0	1
300 mg, n=12	1	2	1	0	0	0	1	0	0

[a] Data are presented as number of subjects experiencing the AE

998-P

Ipragliflozin (ASP1941), a Novel SGLT2 Inhibitor, Demonstrates Beneficial Effects on Nonalcoholic Fatty Liver Disease in Animal Models

EIJI KUROSAKI, TOSHIYUKI TAKASU, SHUNJI YAMAZAKI, KUMI KOIDE, NORIAKI MAEDA, ANN HASTINGS, QUN LI, *Ibaraki, Japan, Leiderdorp, The Netherlands*

Nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH), is closely linked to metabolic diseases, such as obesity and diabetes. Ipragliflozin (ASP1941) is a novel sodium glucose cotransporter 2 (SGLT2) inhibitor, which is in clinical development for the treatment of type 2 diabetes mellitus (T2DM). Ipragliflozin has been shown to increase urinary glucose excretion, and reduce hyperglycemia and body weight in patients with T2DM. The aim of this study was to investigate the effects of ipragliflozin on NAFLD in 3 animal models.1. Obese diabetic KK-A^y mice showed elevated hepatic triglyceride (TG) content. After 2-week treatment, ipragliflozin (3 mg/kg, once daily) reduced hepatic TG content (34.8 vs 52.8 mg/g tissue vehicle group; $P < 0.05$).2. The choline-deficient and amino acid-defined (CDAA) diet-induced rat model of NASH showed hepatic TG accumulation, fibrosis, and mild inflammation. After 5-week treatment, ipragliflozin (3 mg/kg, once daily) prevented hepatic TG accumulation (188 vs 290 mg/g tissue vehicle group; $P < 0.05$) and fibrosis, but not inflammation. Pioglitazone (10 mg/kg, once daily) also prevented fibrosis, but did not prevent hepatic TG accumulation or inflammation.3. The methionine- and choline-deficient (MCD) diet-induced rat model of NASH showed hepatic TG accumulation, inflammation, and fibrosis. After 16-week treatment, ipragliflozin (3 mg/kg, once daily) prevented inflammation and fibrosis, but not hepatic TG accumulation.In conclusion, ipragliflozin reduced hepatic TG content in KK-A^y mice, prevented hepatic TG accumulation and fibrosis in CDAA-diet rats, and inflammation and fibrosis in MCD-diet rats. These positive findings support future clinical studies in patients with NAFLD.

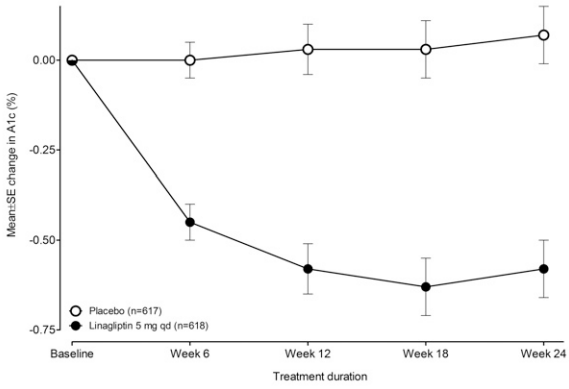
999-P

Efficacy and Safety of Linagliptin as Add-On Therapy to Basal Insulin in Patients With Type 2 Diabetes

HANNELE YKI-JARVINEN, SANTIAGO DURÁN-GARCIA, SABINE PINNETTI, SUDIPTA BHATTACHARYA, SANDRA THIEMANN, SANJAY PATEL, HANS-JUERGEN WOERLE, *Helsinki, Finland, Seville, Spain, Biberach, Germany, New York, NY, Storrs, CT, Ingelheim, Germany, Bracknell, United Kingdom*

This multicenter, randomized, placebo-controlled, phase 3 study evaluated the efficacy and safety of the DPP-4 inhibitor linagliptin as add-on therapy to basal insulin alone or in combination with metformin and/or pioglitazone in patients with type 2 diabetes. A total of 1261 patients inadequately controlled on insulin glargine, insulin detemir, or NPH insulin were randomized to receive either linagliptin 5 mg qd or placebo for at least 52 weeks. The primary efficacy endpoint was the mean change in A1C from baseline to Week 24, during which time the basal insulin dose remained stable. This predefined interim analysis incorporates all safety and tolerability data up to the interim timepoint (mean exposure: linagliptin, 304 days; placebo, 296 days). Mean (SD) baseline characteristics were similar in the linagliptin vs placebo groups: age, 59.7 (9.9) vs 60.4 (10.0) yrs; BMI, 30.8 (5.4) vs 31.2 (5.0) kg/m^2; A1C, 8.3% (0.9%) both; basal insulin dose, 41.6 (31.9) vs 40.1 (27.3) IU/day. The placebo-adjusted mean change in A1C from baseline to Week 24 was -0.65% (p<0.0001; Figure). The overall frequency of adverse events (linagliptin, 71.8%; placebo, 72.5%) and hypoglycemia (linagliptin, 25.7%; placebo, 27.3%) were similar in both groups. Mean (SE) body weight did not change significantly from baseline (linagliptin, -0.17 (0.11) kg; placebo, +0.13 (0.12) kg; p=0.07). In conclusion, the addition of linagliptin to patients inadequately controlled on basal insulin therapy achieved significant and clinically meaningful improvements in glycemic control without weight gain and no additional risk of hypoglycemia.

Figure. Mean change in A1C over time. Full analysis set (LOCF analysis)



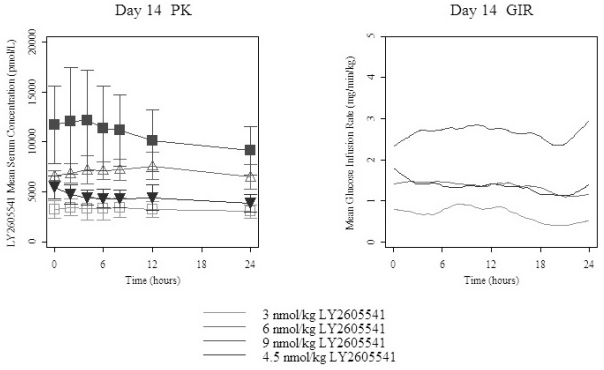
Supported by: Boehringer Ingelheim

1000-P

Steady-State Pharmacokinetics (PK) and Glucodynamics (GD) of the Novel, Long-Acting Basal Insulin LY2605541 Dosed Once-Daily (QD) in Patients With Type 2 Diabetes Mellitus (T2DM)

TIM HEISE, DANIEL C. HOWEY, VIKRAM P. SINHA, SIAK LENG CHOI, KENNETH F. MACE, *Neuss, Germany, Indianapolis, IN*

The basal insulin LY2605541 (LY) is PEGylated insulin lispro designed to have a large hydrodynamic size which delays insulin absorption and reduces clearance, resulting in prolonged duration of action.This parallel group, open-label, dose escalation study examined the PK and GD of LY after multiple-dose administration. Fixed-doses of LY (3-9 nmol/kg) were given QD for 14 days to insulin-treated patients with T2DM (N=32 [30M/2 F; 8 patients per arm]; mean [SD] age, 56 [6] yrs; BMI, 31.0 [2.4] kg/m^2; HbA1c, 7.8 [0.4] %). A 24-h euglycemic glucose clamp was conducted on Days 1 and 14.Pharmacokinetic steady state was achieved within 7-10 days and the peak to trough fluctuation was <1.5 which translated to a nearly "peakless" glucose infusion rate at steady state and a duration of action of at least24 h [Figure]. Based on AUC, there was a gradual build up of mean LY concentrations (8.4-fold higher vs. single dose). Across dose levels $t_{1/2}$ ranged from 44.7-75.5 h (~ 2-3 days). As steady state was achieved there were dose-dependent reductions in the prandial insulin dose and in fasting blood glucose, which decreased to 60-100 mg/dL across dose levels. The nocturnal glucose control between 3 am and 9 am was unchanged. No severe or prolonged hypoglycemia was reported. Mild hypoglycemia was the most common adverse event.In this Phase 1 study of fixed LY doses without titration, LY was well-tolerated and demonstrated a flat PK and GD profile accompanied by glucose normalization, prandial insulin dose reduction, and no severe hypoglycemia.



1001-P

Comparative Study of Sitagliptin With Pioglitazone for Strict Glycemic Control: The COMPASS Study

MASAHIRO TAKIHATA, AKINOBU NAKAMURA, KAZUKI TAJIMA, TAKAHARU INAZUMI, YUMIKO KOMATSU, HARUKA TAMURA, SYUNSUKE YAMAZAKI, YOSHINOBU KONDOU, MASAYO YAMADA, MARI KIMURA, YASUO TERAUCHI, *Yokohama, Kanagawa, Japan, Fujisawa, Kanagawa, Japan, Chigasaki, Kanagawa, Japan*

No randomized trials that compare sitagliptin and pioglitazone in patients with type 2 diabetes have been published. The aim of this study is to compare sitagliptin and pioglitazone with respect to the efficacy and safety in Japanese type 2 diabetic patients. Subjects who had been inadequately controlled (HbA1c 6.9-9.4%) with metformin and/or sulfonylurea were eligible for recruitment. A total of one hundred thirty patients were enrolled. These subjects were ramdomly assigned to sitagliptin group (sitagliptin 50 mg/day) or pioglitazone group (pioglitazone 15 mg/day) and were followed up for 24 months. At 16 weeks, if HbA1c was > 6.9%, the dose of sitagliptin and pioglitazone should be increased up to 100mg/day and 30mg/day, respectively. Adverse effects such as hypoglycemia, gastrointestinal symptom and pedal edema were monitored during this study. One hundred ten patient (sitagliptin group: 55, pioglitazone group: 55) completed the 24-week follow-up. There were no statistically significant differences in baseline characteristics between these two groups. At 0 week, mean HbA1c were 7.48 ± 0.67% vs. 7.40 ± 0.62%. At 8, 16 and 24 weeks, variation of HbA1c were -0.69 ± 0.42% vs. -0.26± 0.55% (p<0.001), -0.89 ± 0.58% vs. -0.49 ± 0.58% (p<0.001), and -0.86 ± 0.63% vs. -0.57 ± 0.68% (p=0.027), respectively. Liver function (AST, ALT, gamma-GTP, ChE) was improved in both groups. In sitagliptin group, surrogate marker for cardiovascular event, such as hs-CRP, PAI-1, IL-6, were not altered, but in pioglitazone group, hs-CRP was significantly decreased (p=0.044). In sitagliptin group, hypoglycemia (2 patients, 3.5%) and gastrointestinal symptom (3 patients, 5.3%) were observed. In pioglitazone group, hypoglycemia (2 patients, 3.5%) and pedal edema (38 patients, 66.7%) were observed. In conclusion, sitagliptin was not only safer but more effective than pioglitazone in Japanese type 2 diabetic patients who had been treated with metformin and/or sulfonylurea.

1002-P

Glucagon Receptor Antagonist LY2409021 Does Not Impede Recovery From Insulin Induced Hypoglycemia in Patients With T2DM

RONAN P. KELLY, CHAY NGEE LIM, EDWARD PRATT, MEI TENG LOH, MARK DEEG, HAODA FU, SHERRY CUI, PARAG GARHYAN, *Singapore, Singapore, Indianapolis, IN, Austin, TX*

In patients (pts) with T2DM, glucagon receptor blockade improves hyperglycemia by inhibiting hepatic glucose output. It is unknown if an appropriate physiologic response to hypoglycemia is preserved in the presence of a glucagon receptor blockade. LY2409021 (LY) is a selective and potent glucagon receptor antagonist. The primary objective of this study was to determine if recovery from hypoglycemia in pts with T2DM is delayed by administration of LY vs. placebo (PB); the responses of counter-regulatory hormones under these conditions were also examined. This single-site, single-dose, subject-blind study enrolled 13 Asian pts (21 to 65 years) with T2DM (HbA_{1c} ≤11.0%), half of whom were taking metformin (Met) (n=7). Pts were randomized to 1 of 2 treatment sequences and received PB or 1 dose of 90-mg LY (a dose expected to achieve near maximal glucagon receptor blockade) 12 hrs before insulin infusion to achieve hypoglycemia (blood glucose ≈40 mg/dL). With LY vs. PB, the LS mean insulin load required to achieve hypoglycemia was 1920 pmol/kg vs. 2170 pmol/kg. Mean time to recovery from hypoglycemia to a blood glucose ≥63 mg/dL was similar between LY and PB, and among pts taking Met and not taking Met (Table). During hypoglycemia, mean glucagon levels were 2 to 3 fold higher after LY than after PB. The AUC and C_{max} of epinephrine, norepinephrine, cortisol, and growth-hormone responses to hypoglycemia were similar between groups. No deaths or serious adverse events occurred during the study. LY does not impede recovery from insulin-induced hypoglycemia in pts with T2DM.

Mean Time to Recovery From Hypoglycemia

	Overall		Met*		No Met	
	LY N=12	PBN=12	LYN=6	PBN=6	LYN=6	PBN=6
LS mean time to recovery (minutes)	58.19	53.45	51.40	52.65	65.87	54.26
Mean ratio	1.09		0.98		1.21	
90% CI	0.88, 1.35		0.71, 1.33		0.90, 1.64	
P-value	0.4928		0.8916		0.2720	

Abbreviations: CI=confidence interval, LS=least squares, LY=LY2409021, Met=metformin, PB=placebo.

*One patient taking Met was not included in the analysis due to lack of post-baseline data.

1003-P

Assessment of Hepatic Glycogen Using Magnetic Resonance Spectroscopy: Implications for Bihormonal Artificial Pancreas

JESSICA R. CASTLE, YU CAI, MARK WOODS, RHONDA MUHLY, MATTHEW BREEN, JOSEPH EL YOUSSEF, W.K. WARD, *Portland, OR*

Glucagon has been successfully incorporated into a bi-hormonal artificial endocrine pancreas device to reduce hypoglycemia. We wish to better understand if persons with type 1 diabetes are able to respond normally to repeated small doses of glucagon and if repeated doses deplete hepatic glycogen. In this study, a custom carbon/proton magnetic resonance coil was developed and validated in subjects without diabetes using magnetic resonance spectroscopy (MRS) on an ultra-high resolution (7 Tesla) MRI to non-invasively measure hepatic glycogen.Five healthy adult subjects participated. Subjects underwent carbon-13 (^{13}C) MRS the morning of the first study day after having breakfast. Subjects were then fasted for 24 hours and instructed to avoid vigorous activity. Water and other calorie-free drinks were allowed ad lib. Subjects returned the following morning for a second ^{13}C MRS procedure. Subjects were then given a standardized meal containing 800 calories and 120 grams of carbohydrate. Four hours later, subjects underwent a third ^{13}C MRS procedure.Hepatic glycogen, as measured by ^{13}C MRS, fell consistently after the 24 hour fast (46 ± 18% of baseline values, p = 0.002 vs. baseline, mean ± SD). Hepatic glycogen values also rose consistently four hours after a high carbohydrate meal (67 ± 14% of baseline values, p = 0.01 vs. fasting values) and were significantly below baseline

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

values (p = 0.02).Using an ultra-high resolution non-invasive 7 Tesla MRI technique consistently detected the rise and fall of hepatic glycogen with feeding and fasting. This technique will be valuable in assessing hepatic glycogen in persons with type 1 diabetes before and after repeated doses of subcutaneous glucagon in an artificial pancreas system. With such data, the pattern of glucagon delivery can be designed to minimize the probability of glycogen depletion.

Supported by: M.J. Murdock Charitable Trust, JDRF

1004-P

The Efficacy and Safety of Imeglimin as Add-On Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy

PASCALE FOUQUERAY, VALDIS PIRAGS, SILVIO INZUCCHI, CLIFFORD J. BAILEY, GUNTRAM SCHERNTHANER, MICHAELA DIAMANT, HAROLD E. LEBOVITZ, *Lyon, France, Riga, Latvia, New Haven, CT, Birmingham, United Kingdom, Vienna, Austria, Amsterdam, The Netherlands, New York, NY*

Imeglimin is the first in a new Tetrahydrotriazine-containing class of oral anti-hyperglycemic agents (the glimins). Preclinical studies suggest that it reduces glucose through effects on both insulin secretion and insulin action. This 12-week Phase II study assessed the efficacy, safety and tolerability of imeglimin as add-on therapy in patients with type 2 diabetes (T2D) inadequately controlled with metformin (Met) alone.This multicenter, randomized, double blind, placebo controlled, parallel group study compared imeglimin (1500mg BID) with placebo (PBO) added to a stable dose of Met (1500-2000mg per day) in 156 patients with T2D and A1C 7.5-10.0%. The primary end point was change in A1C vs PBO. Secondary end points included fasting plasma glucose (FPG), fasting insulin, and the pro-insulin/insulin ratio, a marker of β-cell function.Imeglimin+Met reduced A1C (LS mean) from baseline to week 12 by 0.65% compared with a reduction of 0.21% with PBO+Met (*P<0.001*). Imeglimin+Met reduced FPG (LS mean) from baseline to week 12 by 0.91 mmol/L compared with an increase of 0.36 mmol/L with PBO; *P <0.001*. Imeglimin treatment reduced the pro-insulin/insulin ratio by 7.5 compared with an increase of 11.81 with PBO; between-group difference 19.31, *P<0.007*). A significantly greater proportion of responders achieved a decrease in A1C >0.5% (63.6% with imeglimin vs. 36.4% with PBO (*P=0.001*), and 14.3% of patients achieved A1C < 7% with imeglimin compared with 3.8% in the PBO group (*P=0.04*). The incidence of treatment-emergent adverse events (TEAEs) was similar between treatment groups. Met-imeglimin treatment-related TEAEs were mild and mainly gastrointestinal in nature. No serious adverse events were observed in the Met-imeglimin treatment group.We conclude that imeglimin represents a potential new approach to the treatment of patients with T2D inadequately controlled with Met alone, since it lowers A1C and may improve beta-cell function.

1005-P

Defining Criteria for the Introduction of Liraglutide Using the Glucagon Stimulation Test In Patients With Type 2 Diabetes

YOSHINOBU KONDO, JOE NAGAKURA, MASAYO KIMURA, SHINOBU SATOH, *Kanagawa, Japan*

Liraglutide enhances glucose-dependent insulin secretion from pancreatic β-cells. Thus, preservation of β-cell function is required for effective liraglutide action in patients with type 2 diabetes. However, the criteria for effective introduction of liraglutide based on β-cell function have not yet been clarified.The β-cell function of patients with type 2 diabetes treated with insulin was evaluated by the glucagon stimulation test and measurement of the 24-h urinary C-peptide (U-CPR) before switching to liraglutide monotherapy. Liraglutide was started at 0.3 mg/day and titrated up to 0.9 mg/day. The efficacy of liraglutide was determined by whether glycemic control was maintained or improved from baseline after liraglutide monotherapy for 12 weeks.Liraglutide was effective in 50 of 76 patients. There was no difference in baseline HbA1c, body mass index, the duration of diabetes, insulin dose requirements before introduction of liraglutide and fasting C-peptide (F-CPR, 1.42 ± 0.81 ng/mL vs. 1.08 ± 1.07 ng/mL, p = 0.12) between liraglutide-effective and ineffective groups. The change in HbA1c was –1.19 ± 1.78 % in the effective group, +0.48 ± 0.65 % in the ineffective group (p = 0.0016). C-peptide 6 min after intravenous glucagon stimulation (CPR6, 3.71 ± 3.06 ng/mL vs. 2.11 ± 1.88 ng/mL, p = 0.026) and C-peptide index (CPI: 100 × F-CPR(ng/mL)/Fasting plasma glucose(mg/dL), 1.33 ± 0.83 vs. 0.88 ± 0.52, p = 0.013) were higher in the effective group. U-CPR did not differ between groups (65.5 ± 49.3 μg/day vs. 55.8 ± 40.0 μg/day, p = 0.41). Body weight decreased in both groups but did not differ between the groups (–1.66 ± 3.66 kg vs. –1.67 ± 1.92 kg, p = 0.99).In receiver operating characteristic analysis, the cutoff value for effective introduction of liraglutide was 2.5 ng/mL for CPR6, and 1.02 for CPI.Evaluation of β-cell function by CPR6 and CPI allows effective introduction of liraglutide to patients with type 2 diabetes.

1006-P

WITHDRAWN

1007-P

WITHDRAWN

ADA-Funded Research Guided Audio Tour poster

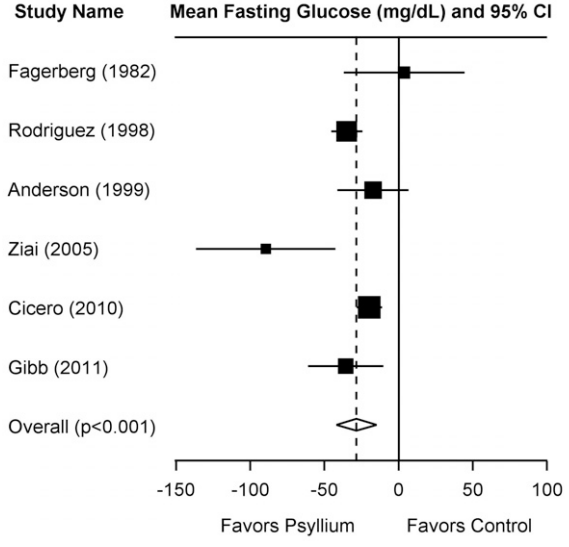
For author disclosure information, see page 797.

1008-P

Psyllium Husk Lowers Fasting Glucose and HbA1c in Populations With Elevated Fasting Blood Glucose: A Meta-Analysis of Randomized, Controlled Clinical Studies

ROGER D. GIBB, VICTOR HASSELBLAD, RICHARD S. SURWIT, JOHNSON W. MCRORIE, MARK N. FEINGLOS, *Mason, OH, Durham, NC*

Psyllium husk is a natural, viscous, soluble fiber that is clinically proven to lower serum cholesterol, and recognized to reduce the risk of cardiovascular disease. A meta-analysis was performed on randomized, controlled, parallel design, clinical studies that assessed the efficacy of psyllium for lowering fasting glucose and HbA1c in subjects with elevated fasting blood glucose levels (mean > 100mg/dl). Studies were identified by literature search, review of reference lists, and review of the clinical trial database at The Procter & Gamble Company. Six clinical studies (5 type-2 diabetes; 1 metabolic syndrome) that included 378 subjects were selected and meta-analyzed using a random effects model. All 5 studies in type-2 diabetics included patients being treated with stable doses of oral hypoglycemic agents. The meta-analysis showed that psyllium, dosed 7.0g/day (3.5g bid) to 15.0g/day (5.0g tid) (mean 10.0g/day) before meals for 6 weeks to 6 months, reduced fasting glucose by a mean (SE) of 28.5mg/dl (6.94; p<0.001) and HbA1c (%) by a mean (SE) of 0.74 (0.21; p<0.001), versus control. Psyllium was generally well-tolerated across doses with no serious adverse events. In conclusion, the meta-analysis shows that psyllium husk significantly lowers both fasting glucose and HbA1c in subjects with elevated fasting glucose levels.



Supported by: Procter & Gamble

1009-P

Sitagliptin More Effectively Achieves a Composite Endpoint of A1C Reduction, No Body Weight Gain, and Lack of Hypoglycemia in Patients With Type 2 Diabetes and Renal Insufficiency Compared to Glipizide

JUAN CAMILO ARJONA FERREIRA, SAMUEL S. ENGEL, HUA GUO, GREGORY T. GOLM, CHRISTINE MCCRARY SISK, KEITH D. KAUFMAN, BARRY J. GOLDSTEIN, *Rahway, NJ*

Sulfonylureas improve glycemic control but are associated with a propensity to cause body weight (BW) gain and an increased risk of hypoglycemia (HYPO). This analysis of data from a 54-week clinical trial in patients (pts) with type 2 diabetes mellitus (T2DM) and moderate or severe chronic renal insufficiency (RI) compared sitagliptin (SITA) to glipizide (GLIP) on a composite endpoint consisting of glycemic control (reduction in A1C >0.5%), no BW gain, and no HYPO. Pts (N=423) were randomized 1:1 to SITA or GLIP. The dose of SITA was 50 mg q.d. for pts with moderate RI and 25 mg q.d. for pts with severe RI. The dose of GLIP was initiated at 2.5 mg/day and electively titrated (based on level of glycemic control) to a maximum of 20 mg/day; GLIP dose could also be reduced or interrupted as considered appropriate to reduce or prevent HYPO. At Week 54, LS mean changes from baseline in A1C were -0.76% in the SITA group and -0.64% in the GLIP group, demonstrating non-inferiority of SITA compared to GLIP. In the present analysis, pts with both A1C and BW measurements at both baseline and at Week 54 were included. The composite endpoint was achieved in a significantly greater proportion of pts with SITA (35.7% of 140 patients) vs. GLIP (14.2% of 148 patients), with a between-group difference of 22.1% (95% CI: 12.4, 31.9). The odds ratio for achieving the composite endpoint was 3.4 (95% CI: 1.9, 6.2). In subgroups of pts by baseline A1C (≥8.0% or <8.0%) similar proportions achieved the composite endpoint with SITA (38.5% and 34.1%, respectively). With GLIP, more pts with A1C at baseline ≥8.0% achieved the composite endpoint (25.0%) relative to those with A1C at baseline <8.0% (7.6%). In conclusion, SITA and GLIP provided similar degrees of clinically important glycemic efficacy, but significantly more pts in the SITA group achieved an A1C reduction of >0.5% without HYPO and without an increase in BW.

1010-P

Efficacy and Safety of Lixisenatide Once Daily Versus Placebo in Patients With Type 2 Diabetes Insufficiently Controlled on Pioglitazone (GetGoal-P)

MICHEL PINGET, RONALD GOLDENBERG, ELISABETH NIEMOELLER, ISABEL MUEHLEN-BARTMER, RONNIE ARONSON, *Strasbourg, France, Ontario, ON, Canada, Frankfurt, Germany, Toronto, ON, Canada*

GetGoal-P was a randomized, double-blind, placebo-controlled, multicenter study comparing efficacy and safety of lixisenatide 20 µg once daily (QD) *vs* placebo in patients with T2DM insufficiently controlled by ≥30 mg/day pioglitazone ± metformin [NCT00763815]. The primary objective was to assess the absolute HbA_{1c} reduction with lixisenatide *vs* placebo at Week 24 (main treatment period). At baseline, mean age was 55.8 yr, mean diabetes duration 8.1 yr, mean HbA_{1c} was 8.1% and mean BMI was 33.9 kg/m^2. Lixisenatide QD produced significantly greater HbA_{1c} reduction *vs* placebo (Table) and a greater proportion of patients achieved HbA_{1c} <7.0% (52% lixisenatide *vs* 26% placebo; p<0.0001). Significantly fewer patients on lixisenatide required rescue therapy (3.8% *vs* 11.3% on placebo). Overall, lixisenatide was well tolerated, with a similar proportion of AEs and serious AEs (72.4% and 2.5% in the lixisenatide group *vs* 72.7% and 1.9% in the placebo group). Only 6.5% of lixisenatide and 5.0% of placebo patients discontinued due to AEs at Week 24, mainly due to GI events (Table). Symptomatic hypoglycemia rates were low in both groups (Table). There were no cases of severe hypoglycemia in either group. In conclusion, in T2DM patients insufficiently controlled on pioglitazone ± metformin, lixisenatide 20 µg QD significantly improved glycemic control with a low risk of hypoglycemia and was well tolerated over 24 weeks.

Efficacy parameters in mITT population		Lixisenatide 20 µg QD (N=320)	Placebo (N=159)
HbA_{1c} (%)	Mean baseline ± SD LS mean ± SE change from baseline LS mean difference vs placebo	8.08±0.91 -0.90±0.09 -0.56 (-0.73 to -0.39); p<0.0001	8.05±0.78 -0.34±0.10
Fasting plasma glucose (mmol/L)	Mean baseline ± SD LS mean ± SE change from baseline LS mean difference vs placebo	9.14±2.15 -1.16±0.19 -0.84 (-1.21 to -0.47); p<0.0001	9.12±2.19 -0.32±0.22
Body weight (kg)	Mean baseline ± SD LS mean ± SE change from baseline LS mean difference vs placebo	92.8±23.0 -0.21 ± 0.32 -0.41 (-1.03 to 0.20); p=0.1864	97.0±25.8 +0.21±0.36
Safety parameters (safety population)			
N (%) of patients with symptomatic hypoglycemia*		11 (3.4%)	2 (1.2%)
N (%) of patients with nausea		76 (23.5%)	17 (10.6%)
N (%) of patients with diarrhea		23 (7.1%)	17 (10.6%)
N (%) of patients with vomiting		22 (6.8%)	6 (3.7%)

*Event with clinical symptoms with either plasma glucose <3.3 mmol/L or prompt recovery after oral carbohydrate administration if no plasma glucose measurement was available

Supported by: sanofi-aventis

1011-P

Safety of Dapagliflozin in Clinical Trials for T2DM

AGATA PTASZYNSKA, KRISTINA M. JOHNSSON, ANNE MARIE APANOVITCH, JENNIFER E. SUGG, SHAMIK J. PARIKH, JAMES F. LIST, *Princeton, NJ, Mölndal, Sweden, Wilmington, DE*

Dapagliflozin (DAPA) an SGLT2 inhibitor lowers blood glucose by increasing renal glucose excretion. Data were pooled from the short-term double-blind periods of 12 placebo (PBO)-controlled trials (>4500 patients). Adverse events (AEs) were slightly more common with DAPA vs PBO; serious AEs and discontinuations due to AEs were balanced across groups. Hypoglycemia was more common with DAPA vs PBO; in individual studies imbalances were only observed when DAPA was combined with sulfonylurea or insulin. Genital infections and UTI were more common with DAPA vs PBO with imbalances less marked for UTIs. Mean changes in systolic/diastolic BP were -4.0/-2.0 vs -0.9/-0.5 mmHg for DAPA vs PBO without increases in measured

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

orthostatic hypotension (3.9% vs 3.7% for DAPA vs PBO). AEs of volume depletion (hypotension/dehydration/hypovolemia) were seen in 0.4% for PBO vs 0.6-1.2% for DAPA. AEs of renal impairment/failure were balanced across groups (0.9% for PBO vs 0.9-1.4% for DAPA). Minor changes in serum electrolytes were seen with DAPA, with small increases in serum Mg and P. To screen for rare events, all DAPA doses from 19 Phase 2b/3 trials were reviewed. Incident rates for malignancies were similar for DAPA (1.4%) vs control (1.3%); breast and bladder cancer events were more common with DAPA. Elevated liver laboratory tests were seen in 4.4% vs 4.2% for DAPA vs control. CV death, MI, stroke or hospitalization for unstable angina were similar for DAPA vs control, (HR 0.82; 95% CI: 0.583, 1.152). Trends in CV events and specific malignancies will be further evaluated in a randomized CV outcomes trial and complementary observational studies.

Safety summary, Short-term double-blind PBO-controlled pool

	% patients			
	PBO (N=1393)	DAPA 2.5mg (N=814)	DAPA 5mg (N=1145)	DAPA 10mg (N=1193)
≥ 1 AE	56.9	60.6	61.9	61.5
≥ 1 serious AE	3.3	4.5	3.5	3.5
Deaths, n (%)	1 (0.1)	1 (0.1)	2 (0.2)	3 (0.3)
Serious AE leading to disc.	0.8	0.6	0.8	0.8
AE leading to disc.	2.5	2.2	2.8	3.2
Hypoglycemia leading to disc.	0	0	0	0
≥ 1 hypoglycemia	8.0	16.3	11.4	10.7
UTI	3.7	3.6	5.7	4.3
Genital infection	0.9	4.1	5.7	4.8

Supported by: Bristol-Myers Squibb/AstraZeneca

1012-P

Event Rate Assessment of Myocardial Infarction and Stroke for Pioglitazone Relative to Insulin

ALFONSO PEREZ, CARLOS VALLARINO, GREGORY FUSCO, HUIFANG LIANG, MORGAN BRON GREEN, SUDHAKAR MANNE, VENKATESH HARIKRISHNAN, GUIANDRE JOSEPH, SHAWN YU, *Deerfield, IL*

Little data are currently available directly comparing the risk of cardiovascular (CV) events in type 2 diabetes mellitus patients receiving pioglitazone (PIO) or insulin mainly as third-line therapies. A retrospective cohort study using i3 InVision Data Mart was conducted to assess event rates of myocardial infarction (MI) and stroke in new users of PIO or insulin. Key outcomes were incident cases of a composite of MI and stroke requiring hospitalization. Kaplan-Meier curves were generated for these outcomes based on adjustment with inverse probability weights derived from propensity scores. Hazard ratios (HR) for PIO versus insulin and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. A total of 56,536 type 2 diabetes patients (PIO: 38,588; insulin: 17,948) aged ≥45 years were selected from May 1, 2000 to June 30, 2010 (mean follow-up: 2.2 years for PIO and 1.9 years for insulin). For the composite of MI and stroke, the incidence rate was lower for PIO; the HR for PIO versus insulin was 0.44 (95% CI [0.39, 0.50], p<0.0001). Over the first 6 years, incidence rates of the composite of MI and stroke were greater in the insulin group than in the PIO group. When compared individually, the risks of MI and stroke were both significantly lower in the PIO group: the HR versus insulin for MI was 0.49 (95% CI [0.41, 0.57], p<0.0001), and for stroke was 0.37 (95% CI [0.31, 0.45], p<0.0001). In the analyses by gender, age, congestive heart failure, pre-index antidiabetic and lipid-altering medication use, PIO lowered the risk of the composite of MI and stroke in every subgroup compared with insulin. The results suggest that pioglitazone significantly reduces the risk of MI and stroke requiring hospitalization compared with insulin.

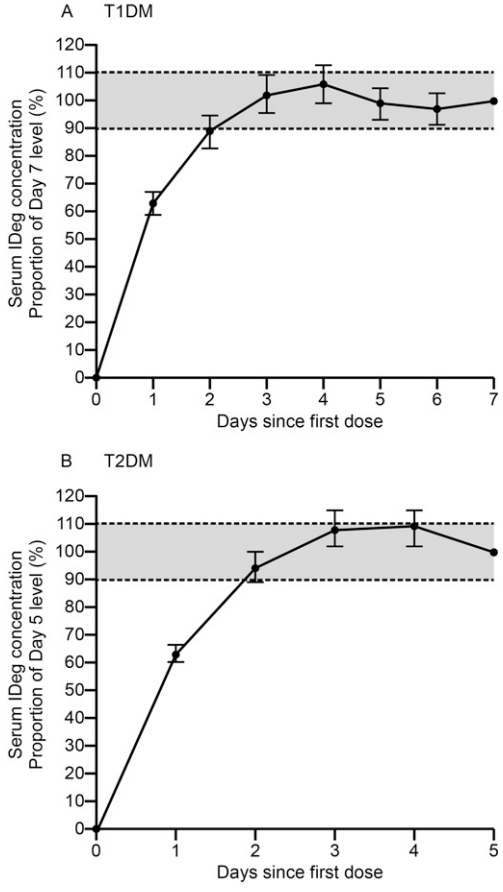
1013-P

Steady State Is Reached Within Two to Three Days of Once-Daily Administration of Ultra-Long-Acting Insulin Degludec

TIM HEISE, LESZEK NOSEK, HANS-VEIT COESTER, CARSTEN ROEPSTORFF, STINE SEGEL, NATHAN LASSOTA, HANNE L. HAAHR, *Neuss, Germany, Søborg, Denmark, Aalborg, Denmark*

The objective of basal insulin therapy is to ensure continuous insulin coverage throughout the 24 hrs of the day. Insulins with a duration of action of 24 hrs or less are in once daily regimens characterized by action profiles with periods of low action rising to a peak/plateau followed by a decline. Such profiles will only provide partial basal coverage implying clinical challenges in ensuring consistent glucose control throughout 24 hrs. Insulin degludec (IDeg) has a duration of action extending beyond 42 hrs leading to a flat and stable action profile at steady state. It is important for clinical evaluation at initiation and titration of treatment to estimate the time to reach steady state with IDeg.In two randomized, double-blind trials, subjects with type 1 and 2 diabetes (T1DM/T2DM; n=66/49; age 37/59 yrs, BMI 25/30 kg/m^2, A1C 8.1/7.6 %) received IDeg at 0.4, 0.6 or 0.8 U/kg for 8 (T1DM) or 6 (T2DM) days. Blood samples were taken before each dosing to determine the serum IDeg concentration on each day relative to the serum IDeg concentration before dosing on Day 7 (T1DM) or 5 (T2DM). The clinically relevant time to steady state was estimated as time from first dose until serum IDeg trough concentrations exceeded 90% of the final plateau level.For all subjects, independent of dose or type of diabetes, steady state was reached after 2-3 days of IDeg dosing. At steady state, exposure of IDeg was unchanged from day to day.In conclusion, steady-state kinetics were observed with stable serum IDeg concentrations reached within 2-3 days of once-daily dose administration with no further increase in exposure thereafter.

Fig 1. Relative serum IDeg trough concentrations (estimated ratios and 95% CIs) during initiation of once-daily dosing in subjects with T1DM (A) and T2DM (B).



Supported by: Novo Nordisk A/S

Clinical Diabetes/ Therapeutics POSTERS

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

1014-P

Efficacy and Safety of Dapagliflozin as Monotherapy for Type 2 Diabetes Mellitus in Japanese Patients

KOHEI KAKU, SATOSHI INOUE, OSAMU MATSUOKA, ARIHIRO KIYOSUE, HARUNA AZUMA, NOBUYA HAYASHI, TAKUTO TOKUDOME, ANNA MARIA LANGKILDE, SHAMIK PARIKH, *Okayama, Japan, Osaka, Japan, Tokyo, Japan, Mondal, Sweden, Wilmington, DE*

Dapagliflozin (DAPA) is a selective SGLT2 inhibitor that increases urinary glucose excretion and is under development as treatment for type 2 diabetes (T2DM). This multicenter, randomized, double-blind, placebo-controlled, parallel-group study was designed to assess the efficacy and safety of DAPA monotherapy in Japanese T2DM patients with inadequate glycemic control with diet or exercise. Patients (n=279) were randomized to receive DAPA (1 mg, 2.5 mg, 5 mg or 10 mg) or placebo (PBO) QD for 12 weeks. The primary end point was change from baseline (BL) in HbA1c (BL 8.07 ± 0.72%) at week 12. Additional end points included change from BL in fasting plasma glucose (FPG: BL 161.9 ± 29.9 mg/dL) and body weight (BW: BL 68.61 ± 14.06 kg). Significant reductions from BL were seen with all doses of DAPA vs PBO in HbA1c, FPG, and BW (Table). The frequency of adverse events (AE) was higher with DAPA (40.7%-53.8%) vs PBO (38.9%). All AEs were mild or moderate in intensity. Hypoglycemia events were infrequent (DAPA: 0%-1.9%, PBO: 1.9%). The frequency of signs and symptoms suggestive of urinary tract and genital infections was low with both DAPA (0%-3.8%, 0%-1.8%) and PBO (1.9%, 0%). No AEs of pyelonephritis, hypotension, dehydration, or hypovolemia or significant changes in serum electrolytes were observed. In conclusion, compared with PBO, DAPA improved glycemic control and reduced BW with a low risk of hypoglycemia over 12 weeks in Japanese T2DM patients with inadequate glycemic control.

	Adjusted mean change from BL at week 12 (SEM)				
		DAPA			
	PBO (N=54)	1 mg/QD (N=59)	2.5 mg/QD (N=56)	5 mg/QD (N=58)	10 mg/QD (N=52)
HbA1c %	0.35 (0.07)	-0.12 (0.07)[a]	-0.10 (0.07)[a]	-0.37 (0.07)[a]	-0.44 (0.07)[a]
HbA1c % PBO subtracted		-0.47 (0.10)	-0.45 (0.10)	-0.72 (0.10)	-0.79 (0.10)
FPG mg/dL	9.5 (3.4)	-16.6 (3.4)[a]	-20.0 (3.3)[a]	-23.5 (3.3)[a]	-31.9 (3.5)[a]
BW kg	-0.1 (0.19)	-1.3 (0.2)[a]	-1.2 (0.2)[a]	-2.1 (0.2)[a]	-1.9 (0.2)[a]

[a]*P*<0.0001 for comparison vs PBO; ANCOVA model including treatment group and BL.N = number of subjects in full analysis who took ≥ 1 dose of double-blind study medication.

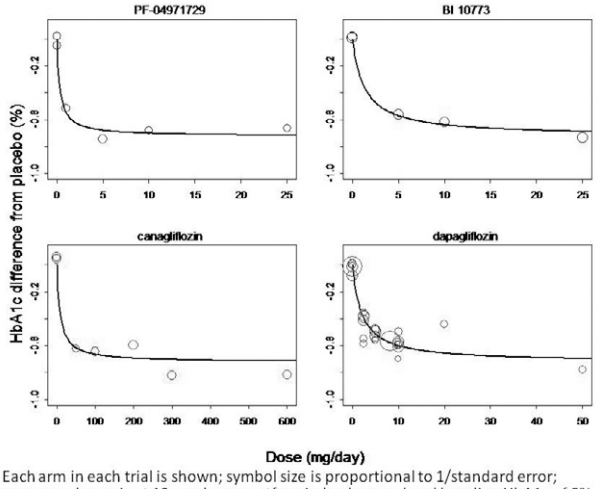
Supported by: AstraZeneca and Bristol-Myers Squibb

1015-P

Model-Based Meta-Analysis of the HbA1c Lowering Effect of PF-04971729, a Sodium Glucose Co-Transporter-2 Inhibitor (SGLT2i), in Comparison With Other SGLT2i and Anti-Diabetic Agents (ADA)

JAAP MANDEMA, KEVIN SWEENEY, STEVEN TERRA, VAISHALI SAHASRABUDHE, *Menlo Park, CA, Groton, CT, Cambridge, MA*

PF-04971729 is a potent, selective SGLT2i in development for treatment of type 2 diabetes mellitus (T2DM). Since there is growing recognition of the need for comparative effectiveness of various ADA, a model was developed to quantify time course of dose vs HbA1c response of PF-04971729 relative to other ADA including SGLT2i, DPP4 inhibitors (DPP4i), GLP-1 agonists (GLP1), sulfonylureas (SU), thiazolidinediones (TZD), and metformin. A systematic literature review yielded 153 randomized controlled trials representing >67000 T2DM patients and 21 drugs. PF-04971729 data were obtained from a 12-week, randomized, placebo-controlled study in T2DM patients on metformin background. The model indicated that SGLT2i have the fastest onset time for HbA1c lowering followed by DPP4i, metformin, SU, TZD and GLP1. A significant loss of effect over time was predicted for all drug classes except SGLT2i and TZD. There was no significant difference in maximal effect (Emax) across ADA within a class; however, Emax was dependent on baseline HbA1c and time (Emax = -0.70% [95% CI -0.62 to -0.78] for SGLT2i at 12 weeks at baseline HbA1c of 8%). The figure illustrates model-estimated and observed dose response for various SGLT2i. Estimated differences in HbA1c lowering between PF-04971729 25 mg and top doses of other SGLT2i ranged from -0.11 to -0.01%. This analysis offers a quantitative framework to leverage external data and thus enables an indirect comparison of novel ADA with existing treatments.



Each arm in each trial is shown; symbol size is proportional to 1/standard error; response shown is at 12 weeks on metformin background and baseline HbA1c of 8%

1016-P

Effect of Pioglitazone on 15-Epi-Lipoxin A4 in Patients With Type 2 Diabetes

ABSALON GUTIERREZ, PADMA SATHYANARAYANA, SOMASEKHAR KONDURU, YUMEI YE, YOCHAI BIRNBAUM, MANDEEP BAJAJ, *Houston, TX*

Arachidonic acid-derived eicosanoids (lipoxins and 15-epilipoxins) have a major role in resolution of inflammation. 15-epi-lipoxin A4 (15-epi-LXA4) is a lipid mediator with strong anti-inflammatory and inflammation-resolving effects. We examined the effect of pioglitazone therapy on plasma 15-epi-LXA4 in patients with type 2 diabetes (T2DM). Twenty five T2DM patients (Age=56 ± 2 y, BMI=33 ± 1.8, HbA1C=7.8 ± 0.3 %) not on thiazolidinedione therapy for at least 12 months were randomized to receive either pioglitazone 15 mg/day (n=13) for two months (PIO 15) or pioglitazone 15 mg/day for one month followed by a dose escalation to 30 mg/day for an additional one month (PIO 30)(n=12). After 2 months, PIO 15 increased plasma 15-epi-LXA4 levels (0.63±0.06 to 1.05±0.08 ng/mL, p<0.01) and adiponectin levels (6.4±0.3 to 10.1±0.7 µg/mL, p<0.001) and decreased fasting plasma glucose (FPG) (125±8 to 105±9 mg/dL, p<0.05), free fatty acids (FFA) (414±46 to 320±37 µmol/L, p=0.05) and HOMA-IR (5.3±0.4 to 4.0±0.4, p<0.02). Body weight (Δ=0.2 kg) and HbA1c (7.4±0.2 to 7.1±0.2%) did not change significantly. PIO 30 treated patients had similar increase in plasma 15-epi-LXA4 (0.64±0.10 to 1.08±0.09 ng/mL, p<0.01), and decrease in plasma FFA (423±43 to 317 ±41 µmol/L, p<0.05) despite a greater increase in plasma adiponectin (6.5±0.4 to 15.5±0.7 µg/mL, p<0.001) and a greater reduction in HbA1c (8.6±0.5 to 7.4±0.2%, p<0.01), FPG (158±16 to 120±10 mg/dL, p<0.02), and HOMA IR (6.6.±0.8 to 4.4±0.4, p<0.005). Furthermore, PIO 30 treated patients had a significant increase in body weight (Δ=1.7 kg, p<0.02). Conclusion**:** In T2DM, low dose pioglitazone (15 mg/day) increases 15-epi-lipoxin A4 and adiponectin levels in the absence of significant changes in body weight. Dose escalation of pioglitazone to 30 mg/day is associated with a similar increase in 15-epi-lipoxin A4 despite a greater increase in plasma adiponectin concentrations and improvement in insulin resistance and glycemic control and is associated with weight gain.

1017-P

Efficacy and Safety of Linagliptin in Elderly Patients (≥ 70 Years) With Type 2 Diabetes

ANTHONY BARNETT, HOLGER HUISMAN, RUSSELL JONES, MAXIMILIAN VON EYNATTEN, SANJAY PATEL, HANS-JUERGEN WOERLE, *Birmingham, United Kingdom, Alkmaar, The Netherlands, Bracknell, United Kingdom, Ingelheim, Germany*

Management of type 2 diabetes in the elderly patient is frequently complicated by comorbidities, polypharmacy, and vulnerability to adverse effects of drugs. This phase 3 placebo-controlled study evaluated linagliptin over 24 weeks in patients with type 2 diabetes, aged ≥70 years, insufficiently controlled despite metformin and/or sulfonylurea and/or insulin therapy. A total of 241 patients (74.9±4.3 years) were randomized to linagliptin 5 mg qd or placebo. Baseline HbA1c was 7.82% and 7.70%, respectively. Metformin, sulfonylurea, or insulin were taken by 84.9%, 57.6%, and 21.0% of all patients, respectively. After 24 weeks, placebo-adjusted mean change in HbA1c with linagliptin was –0.64% (95% CI: –0.81 to –0.48; p<0.0001)

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

(Figures 1 and 2). Drug-related adverse events were experienced by 21.0% and 13.9% of linagliptin and placebo patients, respectively. Hypoglycemia occurred in 24.1% and 16.5% of patients (odds ratio, 1.683; 95% CI: 0.811 to 3.493; p=0.1625). Events predominantly occurred on the background of insulin and/or sulfonylurea. Management of type 2 diabetes in the elderly patient with linagliptin was well tolerated and achieved clinically meaningful improvements in glycemic control without an excess risk of hypoglycemia.

Figure 1. Adjusted mean change in HbA1c (%±SE) over time – FAS (LOCF)

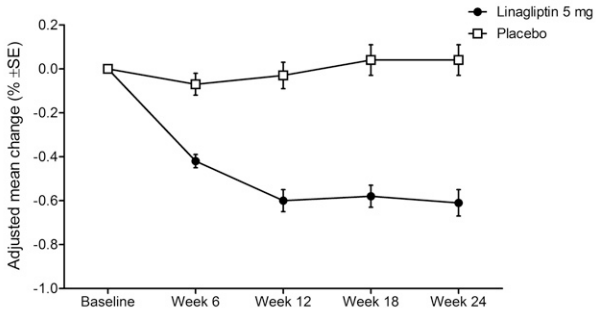
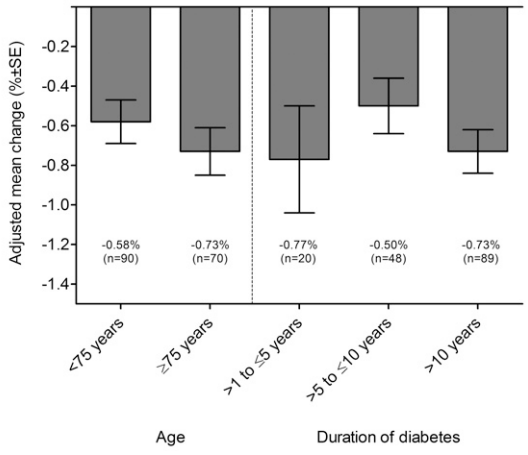


Figure 2. Placebo-adjusted mean change in HbA1c after 24 weeks with linagliptin – FAS (LOCF)



Supported by: Boehringer Ingelheim

1018-P

The Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitor Empagliflozin has a Durable Effect on the Restoration of Glucose Homeostasis by Preserving Beta-Cell Mass in Zucker Diabetic Fatty Rats

JACOB JELSING, NIELS VRANG, MICHAEL MARK, ERIC MAYOUX, THOMAS KLEIN, *Hørsholm, Denmark, Biberach, Germany*

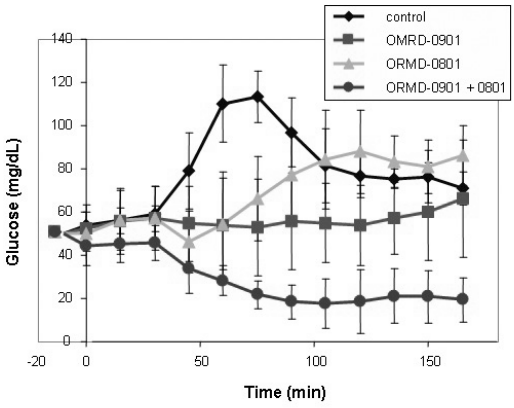
Empagliflozin, a potent, selective sodium glucose cotransporter-2 inhibitor, is a promising approach for treatment of type 2 diabetes mellitus. This study investigated the durability of the effect of empagliflozin on glucose homeostasis and beta-cell mass. The effect of 4 and 8 weeks' treatment with empagliflozin was compared to that of glibenclamide (a sulphonylurea) and liraglutide (a long-acting GLP-1 analog), agents with insulin-dependent mechanisms of action. Male Zucker Diabetic Fatty (ZDF) rats were continuously treated for 8 weeks once daily with empagliflozin (3 mg/kg po), glibenclamide (3 mg/kg po) or liraglutide (0.2 mg/kg sc). Fed blood glucose and insulin were measured weekly with a semi-fasted oral glucose tolerance test (OGTT) after 4 or 8 weeks of dosing. Empagliflozin and liraglutide led to marked improvement in fed glucose and insulin levels and HbA_{1c}, while glibenclamine was ineffective. The effect of liraglutide on fed glucose and insulin levels was less pronounced at week 8 compared to week 4, but the effect of empagliflozin remained stable throughout the study. Empagliflozin improved glucose and insulin levels during both OGTTs, while the effect of liraglutide was less pronounced in OGTT at week 8 compared to week 4. Beta-cell mass was significantly higher in empagliflozin- and liraglutide-treated rats at week 4, and remained higher only in empagliflozin-treated rats at week 8. . The overall improvement in glucose control directly correlated to beta-cell mass and insulin level.The data demonstrate that empagliflozin exerts very powerful effects on glucose homeostasis and beta-cell mass in male ZDF rats which remain stable, while those of liraglutide diminish over time. The results suggest that the insulin-independent anti-diabetic effect of SGLT-2 inhibitors may provide better durability of efficacy compared with other treatments.

1019-P

Concomitant Oral Insulin and Exenatide Therapies Significantly Curb Postprandial Glucose Excursions in Pigs

ROY ELDOR, EHUD ARBIT, YAEL GREENBERG-SHUSHLAV, MIRIAM KIDRON, *Jerusalem, Israel, Kfar Ha'Oranim, Israel*

Glucagon-like peptide-1 (GLP-1) stimulates glucose-dependent insulin secretion, and insulin biosynthesis, while inhibiting glucagon secretion and gastric emptying. Taken together with its restorative effect on β-cell sensitivity, GLP-1 and its analogues are suggested to bear therapeutic potential in regulating Type 2 Diabetes Mellitus (T2DM). A combination therapy of insulin and GLP-1 may be of value in simultaneously addressing the multiple metabolic targets of T2DM pathogenesis and in curbing progression of the disease and comorbidities. To assess such a concomitant treatment regimen, fasting pigs were treated with oral insulin (ORMD-0801) and/or oral exenatide (ORMD-0901) capsules thirty minutes prior to caloric intake. Blood glucose concentrations were monitored over the ensuing four hours. Preprandial delivery of ORMD-0901 fully prevented a rise in glucose concentrations following food intake (p=0.002). Similarly ORMD-0801 curbed the glucose excursions observed in nontreated pigs (p=0.086). A sharp, synergistic effect was imparted by simultaneous delivery of both ORMD-0901 and ORMD-0801, as expressed by blood glucose reductions to >50% of mean baseline values, and to concentrations 5.2-fold lower than mean peak values measured in control animals at ~75 min after feeding (p<0.0001). Coadministration of oral insulin and oral exenatide are hereby shown to better control postprandial blood glucose profiles than each drug individually. These favorable effects are proposed to result from improved coverage of a wider range of metabolic pathways stimulated upon food ingestion.



1020-P

Population Pharmacokinetic (PK) Analysis of Albiglutide in a Phase IIb Study in Japanese Patients With Type 2 Diabetes

MARK A. BUSH, CHARLES SMITH, PRAPOCH (KENG) WATANALUMLERD, FRED YANG, HAJIME MIYAHARA, *Research Triangle Park, NC, Richmond, VA, King of Prussia, PA, Tokyo, Japan*

Albiglutide (ALBI) is a long-acting GLP-1 receptor agonist in Phase III development for treatment of type 2 diabetes. This analysis characterized the population PK of ALBI in Japanese patients with type 2 diabetes as part of a Phase IIb study. Patients received ALBI 15 mg or 30 mg weekly (QW), 30 mg every other week (EOW), or placebo via subcutaneous injection for 16 weeks. The primary endpoint of the study was change from baseline in glycosylated hemoglobin A1C vs placebo at week 16: –1.55%, –1.10%, and –0.89% with 30 mg QW, 30 mg EOW, and 15 mg QW, respectively. Population models were developed using NONMEM software to characterize the PK profile of ALBI and to identify significant covariates affecting ALBI PK. The final PK model was evaluated using bootstrapping and the visual predictive check. A total of 159 patients receiving ALBI were included in the PK analysis. ALBI PK was well described by a 1-compartment model with first order absorption and elimination. ALBI was associated with extended absorption and elimination half-lives (≈1.9 days and ≈5.6 days, respectively, for a typical patient). Age

and weight were significant predictors of ALBI apparent clearance (CL/F). Weight was a significant predictor of ALBI apparent volume of distribution (V/F). CL/F increased by 0.82 mL/h/kg body weight and decreased by 0.354 mL/h/year of age. V/F increased by 136 mL/kg body weight.

Pharmacokinetic Parameter	Final Estimate	95% Bootstrap Confidence Interval	Inter-individual Variability (CV%)
$CL/F\ (mL/h) = \theta_{CL} + \theta_{CL\text{-}age} \times (age - 59) + \theta_{CL\text{-}weight} \times (weight - 67.2)$			24.1%
θ_{CL}	47.8	45.5, 49.9	
$\theta_{CL\text{-}age}$	–0.354	–0.661, –0.181	
$\theta_{CL\text{-}weight}$	0.820	0.621, 0.992	
$V/F\ (mL) = \theta_{V} + \theta_{V\text{-}weight} \times (weight - 67.2)$			19.8%
θ_{V}	9340	8710, 10000	
$\theta_{V\text{-}weight}$	136	99.1, 178	
Ka (h^{-1})	0.0154	0.0134, 0.0183	36.2%

θ_{CL} population estimate of CL/F for a typical patient; $\theta_{CL\text{-}age}$, effect of age (years) on CL/F; $\theta_{CL\text{-}weight}$, effect of weight (kg) on CL/F; θ_{V} population estimate of V/F for a typical patient; $\theta_{V\text{-}weight}$, effect of weight (kg) on V/F; Ka, first-order absorption rate constant.

1021-P

Uncontrolled Hypertension in Patients With Type 2 Diabetes Mellitus (T2DM) and Chronic Kidney Disease (CKD), a Pooled Analysis of the National Health and Nutrition Examination Surveys (NHANES), 1999–2008

ROBERT STELLHORN, CHERYL NESLUSAN, MANEESHA MEHRA, *Raritan, NJ*

The objective of this analysis was to profile patients with T2DM and CKD, with specific consideration of uncontrolled hypertension. Data from the NHANES for the years 1999-2008 was examined. Analysis was based on patients with T2DM (Diagnosed with diabetes and >= 25 years of age at the time of DM diagnosis). In addition, only patients with a valid serum creatinine test result were included in the study cohort. CKD stages were based on the classification system used by the National Kidney Foundation. Uncontrolled hypertension was defined as having either a systolic or diastolic blood pressure reading above 130/80 respectively.The final sample consisted of 2,181 patients with T2DM. The mean age of the cohort was 63 years, 50.9% were male and the mean diabetes duration was 10.1 years. Almost half (45.2%) of the patients were identified as having some form of CKD. Mean age and HbA1c for CKD patients was higher than patients without CKD; median HbA1c was similar in the two groups. The proportion of patients with uncontrolled hypertension was higher among patients with CKD vs. those without CKD (60.9% vs. 49.9%). Although current use of antihypertensive medication was higher in T2DM patients with CKD vs. those without CKD, a significantly larger proportion of these patients had uncontrolled hypertension (65.4% vs. 56.4%).These results demonstrate the need for strategies to improve blood pressure control among patients with T2DM, particularly in those patients with comorbid CKD.

Characteristics of patients with T2DM (NHANES 1999-2008)	No CKD	CKD Total	P-value
N	1195	986	
Percent	54.8%	45.2%	
Mean Age at Examination	60.7	65.6	< 0.0001
% Male	48.4%	54.0%	0.0094
% T2DM patients with Uncontrolled Hypertension	49.9%	60.9%	< 0.0001
% taking Antihypertensive	63.9%	76.8%	< 0.0001
% T2DM patients on Antihypertensive	56.6%	71.5%	< 0.0001
% Uncontrolled Hypertension	56.4%	65.4%	0.0006

Supported by: Janssen Global Services, LLC

1022-P

Canagliflozin (CANA), a Sodium Glucose Co-Transporter 2 Inhibitor, Improves Glycemic Control and Reduces Body Weight in Subjects With Type 2 Diabetes (T2D) Inadequately Controlled With Metformin (MET) and Sulfonylurea (SU)

JOHN WILDING, CHANTAL MATHIEU, FRANK VERCRUYSSE, KEITH USISKIN, LING DENG, WILLIAM CANOVATCHEL, *Liverpool, United Kingdom, Leuven, Belgium, Beerse, Belgium, Raritan, NJ*

CANA, a novel inhibitor of the sodium-glucose co-transporter 2, is being developed for the treatment of patients with T2D. In this randomized, double-blind, placebo (PBO)-controlled, Phase 3 study, subjects with T2D inadequately controlled with MET + SU (N=469; age 56.7 y; A1c 8.1%; fasting plasma glucose [FPG] 9.5 mmol/L; body mass index 33.0 kg/m^2) received CANA 100 or 300 mg or PBO. At 26 weeks, A1c was significantly reduced with CANA 100 mg (8.1% to 7.2%) and CANA 300 mg (8.1% to 7.0%) versus PBO (8.1% to 7.9%) (P<0.001). Both CANA doses improved FPG, proportion of subjects reaching A1c <7% and reduced body weight versus PBO (P<0.001). Incidences of adverse events (AEs) (CANA, 59.7%; PBO, 63.5%), serious AEs (CANA, 3.5%; PBO, 5.8%), and AE-related discontinuations (CANA, 5.8%; PBO, 3.2%) were similar among groups. Higher rates of AEs consistent with genital mycotic infections were seen with CANA versus PBO: 18.7% vs 3.8% (females) and 4.9% vs 1.3% (males), respectively. A low incidence (≤3%) of AEs reflective of osmotic diuresis (eg, pollakiuria) or lowered plasma volume (eg, postural dizziness) was seen, but these led to few discontinuations. Rates of urinary tract infections were similar among groups. More CANA-treated subjects had ≥1 hypoglycemia episode (28.8% vs 15.4%), but the number of severe hypoglycemic events was very low (≤1 per group). In summary, CANA provided glycemic improvement, reduced body weight, and was well tolerated in subjects with T2D inadequately controlled with MET + SU.

Table. Summary of Efficacy Endpoints (PBO-Adjusted) at Week 26 (LOCF)

Parameter	CANA 100 mg	CANA 300 mg
% Δ A1c	–0.71[a]	–0.92[a]
% of subjects reaching A1c <7%	25.2[a]	38.6[a]
Δ FPG, mmol/L	–1.24[a]	–1.92[a]
% Δ Body weight	–1.4[a]	–2.0[a]
Δ Systolic BP, mmHg	–2.24	–1.62
% Δ HDL-C	2.6	3.5
% Δ Triglycerides	–6.2	–3.1

LOCF, last observation carried forward; ANCOVA, analysis of covariance. Δ = PBO-adjusted least squares mean changes from baseline using ANCOVA. [a]P<0.001 vs PBO.

Supported by: Janssen Research and Development, LLC

1023-P

Contrasting Weight Changes With LY2605541, a Novel Long-Acting Insulin, and Insulin Glargine Despite Similar Improved Glycemic Control in T1D and T2D

SCOTT J. JACOBER, JULIO ROSENSTOCK, RICHARD M. BERGENSTAL, MELVIN J. PRINCE, YONGMING QU, JOHN M. BEALS, *Indianapolis, IN, Dallas, TX, Minneapolis, MN*

The basal insulin analog LY2605541 (LY) is a PEGylated insulin lispro designed to have a large hydrodynamic size which delays insulin absorption and reduces clearance, resulting in prolonged duration of action. Improved glycemic control with insulin generally results in weight gain. However, once-daily LY showed glycemic control comparable with or superior to insulin glargine (GL), and resulted in weight loss compared with weight gain with GL.In a 12-wk, randomized, open-label study (N=288), patients (pts) with T2D lost 0.6 kg with LY and gained 0.3 kg with GL (resulting in a treatment difference of -0.84 kg, p<.01). Weight loss was more common with LY than GL (57% v 40%, p=.01) and loss of ≥5% body weight was more frequent with LY than GL (5% vs 0%; respectively, p=.03) with no correlation between baseline BMI and mean weight change. Higher insulin doses correlated with less weight loss with LY (p<.01) and greater weight gain with GL (p<.01). There was no correlation between hypoglycemia rate and weight change with LY (p=.28).In a randomized, open-label, 2x2 crossover study of 8 wk LY or GL (N=137), pts with T1D lost 1.2 kg with LY and gained 0.7 kg with GL (resulting in a treatment difference of -1.9 kg, p<.01). Weight loss was more common during LY treatment (66% v 40%, p<.01) as was loss of ≥5% body weight (12% vs 1%; p<.01) with no correlation between weight and baseline BMI or dose for either insulin. Prandial insulin dose decreased (0.23 U/kg/d to 0.19 U/kg/d) with LY and increased to 0.24 U/kg/d with GL (between-treatment p<.01). More mild gastrointestinal (GI) adverse events were reported with LY, but LY-treated pts with GI events had less weight loss (0.84 kg) than those without (1.33 kg). There was no correlation between hypoglycemia rate and weight change with LY (p=.65).In summary, improved glycemic control with long-acting basal insulin analog LY is associated with weight loss that is not dependent on baseline BMI or rate of hypoglycemic events.

Supported by: Eli Lilly and Company

1024-P

The Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitor Empagliflozin Improves Insulin Sensitivity in db/db Mice in a Dose-Dependent Manner

MATTHIAS KERN, NORA KLÖTING, ERIC MAYOUX, MICHAEL MARK, THOMAS KLEIN, MATTHIAS BLÜHER, *Leipzig, Germany, Biberach, Germany*

Empagliflozin is a potent, selective sodium glucose cotransporter-2 (SGLT-2) inhibitor that is in development for the treatment of type 2 diabetes. It has been demonstrated that multiple daily doses of empagliflozin lower blood

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

glucose levels and improve glucose tolerance in diabetic Zucker diabetic fatty rats. However, the effects of chronic renal glucose re-absorption inhibition with empagliflozin on insulin sensitivity are not known.Therefore, we determined the effects of long-term (8 weeks) treatment with empagliflozin on whole body insulin sensitivity in *db/db* mice (n=45) using euglycemic-hyperinsulinemic clamps.*db/db* mice treated with either 10 or 30 mg/kg/day empagliflozin showed a significant dose-dependent decrease in HbA_{1c} of 27% and 35%, respectively (p<0.001) compared to vehicle. Improved glycemia by empagliflozin treatment was also demonstrated in intraperitoneal glucose tolerance tests (p<0.0001). The glucose disposal rate (GDR) was significantly improved in the 10 mg/kg and 30 mg/kg empagliflozin-treated groups (5.9 mg/kg/min and 8.0 mg/kg/min, respectively) compared to placebo (1.9 mg/kg/min) (p<0.001). In addition, insulin-mediated suppression of hepatic glucose production was significantly higher in the 10 mg/kg and 30 mg/kg empagliflozin-treated groups (13.1 mg/kg/min and 8.4 mg/kg/min, respectively) compared to placebo (26.3 mg/kg/min) during the clamp. A dose-dependent reduction in liver triglyceride content, as well as in circulating triglycerides and free fatty acids, was observed in empagliflozin-treated mice.In conclusion, long term inhibition of SGLT-2 with empagliflozin significantly improved insulin sensitivity in *db/db* mice, suggesting that glucose excretion and associated reduction of glucotoxicity with empagliflozin contribute to improved glycemic control and insulin sensitivity in insulin resistant states.

1025-P

Insulin Degludec is Superior to Sitagliptin in Improving Glycemic Control in Insulin-Naïve Patients With Type 2 Diabetes

ATHENA PHILIS-TSIMIKAS, STEFANO DEL PRATO, ILHAN SATMAN, ANUJ BHARGAVA, MALA DHARMALINGAM, TRINE V. SKJØTH, SØREN RASMUSSEN, ALAN J. GARBER, *La Jolla, CA, Pisa, Italy, Istanbul, Turkey, Des Moines, IA, Bangalore, India, Bagsvaerd, Denmark, Houston, TX*

The efficacy and safety of ultra-long-acting insulin degludec (IDeg) was compared to sitagliptin (Sita), a DPP-4 inhibitor, in a 26-week, open label trial. In all, 458 insulin-naïve adults with type 2 diabetes (mean age: 56 yrs, diabetes duration: 7.7 yrs, A1C 8.9%) were randomized (1:1) to once-daily IDeg or Sita (100 mg orally) as add-on to stable treatment with 1 or 2 OADs (metformin, sulphonylurea, glinides or pioglitazone). IDeg was dosed between wake-up and bedtime based on individual day-to-day preference. The completion rate was 76% in both treatment arms. At 26 weeks, IDeg was superior to Sita in improving glycemic control (A1C); (estimated treatment difference [ETD] IDeg-Sita: -0.43% points, [95% CI: -0.61, -0.24; p<0.0001] with observed mean reductions of 1.56% vs. 1.22% points, respectively). A1C <7% was achieved by 41% (IDeg) vs. 28% (Sita) of patients, estimated odds ratio IDeg/Sita: 1.60 [1.04, 2.47; p=0.034]. IDeg was superior to Sita in reducing FPG (ETD IDeg-Sita: -39.1 mg/dL [-46.8, -31.4; p<0.0001] with observed mean reductions of 58.0 vs. 25.1 mg/dL, respectively. Despite the lower FPG, there was no statistically significant difference in the rate of nocturnal confirmed hypoglycemia (PG <56 mg/dL or ADA defined severe episodes from 00:01 to 05:59) between IDeg and Sita (0.52 vs. 0.30 episodes/patient yr, estimated rate ratio (ERR): IDeg/Sita: 1.93 [0.90, 4.10; p=0.09]). Rates of overall confirmed hypoglycemia were higher with IDeg than with Sita (3.1 vs. 1.3 episodes/patient yr, ERR IDeg/Sita: 3.81 [2.40, 6.05; p<0.0001]); one severe episode was reported with IDeg. IDeg was associated with a larger weight gain than Sita: ETD IDeg-Sita: 2.75 kg [1.97, 3.54; p<0.0001]. The rate of adverse events was low for both groups. In conclusion, IDeg was superior to Sita in improving glycemic control; overall hypoglycemia was higher with IDeg, but there was no difference in severe or nocturnal hypoglycemia. IDeg is an effective and safe alternative to OADs.

1026-P

Better Glycemic Control and Weight Loss With the Novel Long-Acting Basal Insulin LY2605541 Compared With Insulin Glargine in Patients With Type 1 Diabetes

JULIO ROSENSTOCK, RICHARD M. BERGENSTAL, THOMAS BLEVINS, LINDA A. MORROW, MELVIN J. PRINCE, YONGMING QU, VIKRAM P. SINHA, D.C. HOWEY, SCOTT J. JACOBER, *Dallas, TX, Minneapolis, MN, Austin, TX, Chula Vista, CA, Indianapolis, IN*

The basal insulin analog LY2605541 (LY) is PEGylated insulin lispro designed to have a large hydrodynamic size which delays insulin absorption and reduces clearance, resulting in prolonged duration of action. Primary aim of this Phase 2, randomized, open-label, 2x2 crossover study was to determine if LY was noninferior (margin of 10.8 mg/dL) to glargine (GL) for daily mean blood glucose (BG) in treatment of T1D. Patients (N=137) received basal insulin (LY or GL) once daily, plus prandial insulin, for 8 weeks, followed by crossover treatment for 8 weeks. Daily mean BG was obtained from three 8-point self-monitored BG profiles (pre- and 2 hrs post-meal, at bedtime, and 3 AM) the week prior to each visit.After 8 weeks, LY was non-inferior but also superior to GL in daily mean BG (± SE: 144 ± 3 v 152 ± 3 mg/dL, LS mean difference = -10 mg/dL; 90% CI [-14.6, -5.2], p<.001). FBG variability (SD; 49 ± 2 v 57 ± 2 mg/dL, p<.001) and A1C (-0.59 v -0.43%, p<.001) were reduced with LY compared with GL. Prandial insulin dose was reduced during LY treatment (from 0.225 to 0.187 U/kg/d) and increased (to 0.242 U/kg/d) with GL (p<.001). LY was associated with weight loss and GL with weight gain (LS means -1.2 v +0.7 kg, p<.001).Total hypoglycemia rate was higher for LY (8.7 v 7.4 events/30d, p=.04), but nocturnal hypoglycemia rate was lower (0.9 v 1.1 events/30d, p=.01). Adverse events (including severe hypoglycemia) were similar, although more mild gastrointestinal-related events (dyspepsia, nausea, abdominal distension) occurred with LY (15 v 4%, p<.001). During LY treatment, mean changes were within normal range but were higher for ALT, AST, triglycerides, and LDL-cholesterol and lower for HDL-cholesterol compared to GL (all p<.02).In conclusion, LY provided greater improvements in glycemic control and reduced nocturnal hypoglycemia v GL in T1D. Notably, this was accompanied by reduced weight and lowering of prandial insulin doses.

Supported by: Eli Lilly and Company

1027-P

Comparison of 3 Algorithms for Initiation of Basal Insulin in Patients With Type 2 Diabetes Mellitus (T2DM)

GEORGE DAILEY, LISA AURAND, JOHN STEWART, BARBARA AMEER, RONG ZHOU, *La Jolla, CA, Bridgewater, NJ, Quebec, QC, Canada, New Brunswick, NJ, Cincinnati, OH*

To achieve target fasting plasma glucose (FPG) in patients with T2DM, many basal insulin titration algorithms have been studied and it may be difficult for health care providers to choose. This pooled analysis of patient-level data compared endpoints from studies using different algorithms for initiation and intensification of insulin glargine in insulin-naïve patients with T2DM.Data were pooled from 8 randomized controlled trials that added insulin glargine to oral antidiabetic drugs at 10U starting dose. Change from baseline endpoint variables was analyzed using a mixed model with algorithm as a factor and corresponding baseline measurement as covariate.Algorithm 1 (n=163; age 57; 66% men) required 1U daily when FPG above target; algorithm 2 (n=117; age 59; 62% men) 2U/3 days; and algorithm 3 (n=1100; age 57; 54% men) used treat-to-target, increasing 2-8U weekly based on 3 day mean FPG. At baseline, there were differences in FPG and A1C (Table). After adjusting for baseline measurements, algorithm 2 had significantly greater change in A1C than did 1 (Table). Algorithm 3 tended to more confirmed hypoglycemia (Table). Final insulin doses were 0.43U/kg, 0.60U/kg and 0.44U/kg for algorithms 1, 2 and 3; with significantly higher doses for algorithm 2 than 1 and 3.These data suggest that simpler titration algorithms (1 and 2) achieved similar glycemic control to more complex algorithms (3), with less hypoglycemia. This may assist the choice of algorithm for initiation and intensification of basal insulin in patients with T2DM. Due to limited numbers these data need validation with a randomized controlled trial.

Table. Baseline and Outcomes for 3 Titration Algorithms. P<0.05 a:1 vs 2, b:2 vs 3, c:1 vs 3

	Algorithm 1*	Algorithm 2*	Algorithm 3*
Baseline A1C, %Week 24 A1C, %	8.6[c]7.1	8.86.9	8.8[c]7.0
Achieving A1C <7.0%, %Change in A1C, %	53-1.54[a]	61-1.91[a]	52-1.81
Baseline FPG, mg/dL Week 24 FPG, mg/dL	192[a]120	223[a,b]126	198[b]121
Confirmed hypoglycemia < 56 mg/dL, n/N (%)	39/163 (23.9)	34/117 (29.1)	469/1100 (42.6)
Confirmed hypoglycemia < 70 mg/dL, n/N (%)	68/163 (41.7)	40/117 (34.2)	604/1100 (54.9)
Confirmed nocturnal hypoglycemia < 56 mg/dL, n/N (%)	12/163 (7.4)	11/117 (9.4)	253/1100 (23.0)

* In all groups, the incidence of severe hypoglycemia was low ranging from between 0 to 1.5%. Comparison between groups was limited due to small number of severe hypoglycemic events.

Supported by: sanofi-aventis

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

1028-P

Renal Glucose Handling: Impact of Chronic Kidney Disease (CKD) and SGLT2 Inhibition In Patients With Type 2 Diabetes

ELE FERRANNINI, STEPHAN A. VELTKAMP, JAN VAN DIJK, TAKESHI KADOKURA, RONALD SMULDERS, *Pisa, Italy, Leiderdorp, The Netherlands, Tokyo, Japan*

Ipragliflozin (ASP1941, Ipra), an SGLT2 inhibitor, increases urinary glucose excretion (UGE) and lowers glucose levels in type 2 diabetic (T2DM) patients. The pharmacodynamics of Ipra after a single oral dose were investigated in 57 T2DM patients (age=62±9 years, fasting glucose=133±39 mg/dl, mean±SD, 32 Caucasian and 25 Japanese) with renal function (as the estimated glomerular filtration rate, eGFR) in CKD class1 (eGFR≥90 mL·min^{-1}·1.73m^{-2}), class2 (60 ≤eGFR<90 mL·min^{-1}·1.73m^{-2}), class3 (30≤eGFR<60 mL·min^{-1}·1.73m^{-2}), or class4 (15≤eGFR <30 mL·min^{-1}·1.73m^{-2}). In CKD class1 (eGFR=109±16 mL·min^{-1}·1.73m^{-2}), Ipra increased UGE from 1.7 [5.6] (median [IQR]) to 52 [42] mg/min (p<0.001); in class2 (eGFR=73±9 mL·min^{-1}·1.73m^{-2}) from 0.6 [5.5] to 48 [34] mg/min (p<0.001); in class3 (eGFR=46±10 mL·min^{-1}·1.73m^{-2}), from 0.4 [1.5] to 22 [22] mg/min (p<0.001), and in class4 (eGFR=25±4 mL·min^{-1}·1.73m^{-2}) from 0.1 [2.1] to 8 [7] mg/min (p<0.01). In general, linear model analysis of the pooled data indicates that Ipra-induced glycosuria could be predicted by eGFR and fasting glucose as independent covariates, yielding a decrement in UGE for a decline in eGFR and an increment in UGE for increasing glucose concentrations. Ipra-induced fractional glucose excretion (excretion/filtration) in pts in CKD class1-3 averaged 42 [24]%, similar to that of 8 non-diabetic subjects (37 [17]%, eGFR 97±5 mL·min^{-1}·1.73m^{-2}), but dropped significantly in CKD class4 (to 30 [18]%, p=0.03 *vs* pooled class 1-3).In conclusion, in T2DM patients Ipra enhances UGE in direct, linear proportion to GFR and degree of hyperglycemia, such that the amount glycosuria can be reliably predicted in the individual patient.

Supported by: Astellas Pharma

1029-P

Plasma Fractalkine is Associated With Adipose Tissue Insulin Resistance and Low-Dose Pioglitazone Reduces Fractalkine Parallel With Reduced Adipose Tissue Insulin Resistance in Type 2 Diabetes

GIUSEPPE DANIELE, ZANDRA PEREZ-CADENA, ALBERTO CHAVEZ-VELAZQUEZ, SUBHASH KAMATH, PENGUO ZUO, ZHI CHANG, FRANCESCO ANDREOZZI, ANA M. PAEZ, PAOLO FANTI, AMALIA GASTALDELLI, RALPH DEFRONZO, DEVJIT TRIPATHY, FRANCO FOLLI, *San Antonio, TX, Pisa, Italy*

Pioglitazone (PIO) is an insulin sensitizer with mild anti-inflammatory effects, but its use may be limited by weight gain and fluid retention at higher doses (30-45 mg/day). Fractalkine (FRK), a novel chemokine, may be involved in adipose inflammation and insulin resistance (IR). We evaluated the effect of 6-month (m) low dose PIO (15 mg/day) vs placebo (PCB) on plasma FRK in 20 type 2 diabetes (T2D) patients (BMI: 33.5±1.3 Kg/m2, FPG: 145±8, A1c:7.5±0.3%) randomized to PIO (n=11) or PCB (n=9) group who participated in an OGTT, euglycemic-hyperinsulinemic clamp (M) with measurement of FFA, adipose tissue IR (AT-IR=FFA × insulin) and body fat (BF) at 0 and 6-m. All T2D subjects received dietary counseling and maintained their previous treatment (metformin/sulfonylurea). FRK was measured during OGTTs and insulin clamps and at 0, 1, 3, 5 and 6-m. PIO, but not PCB, significantly improved FPG (-14% vs -5%), A1c (-7% vs -3%), AT-IR (-47% vs +16%) and M value (+0.9 vs +1.1 mg/Kg min) (all p<0.02 vs baseline, p=ns vs PCB). At baseline fasting plasma FRK levels were 33[38] pg/ml (median [IQR range]), similar in PIO vs PCB (33[30] vs 29[42] pg/ml, p=ns). FRK did not change during OGTT. After 6-m, FRK decreased in PIO both during fasting state and clamp (13[24] and 19[36] p<0.01 vs 0 m) but not in PCB, whereas FRK tended to increase during clamp (40[34]; p=0.06 vs 0m, p<0.003 vs PIO), evident throughout the 6 m of observation since FRK significantly increased in PCB (51[69] pg/ml, mean of 6-m, p<0.007 vs 0 m) but not in PIO (40[32] pg/ml, p=ns vs 0 m, p<0.02 vs PCB). At 0 m FRK was associated with AT-IR after correcting for BF (r=0.75, p=0.002), and after 6 m the decrease in FRK was associated with decrease in AT-IR after correcting for changes in BF and improvement in glycemic control (r=0.62, p=0.05). In conclusion, plasma FRK is associated with AT-IR, and PIO mediated improvement in AT-IR could partly be due to decreased plasma FRK.

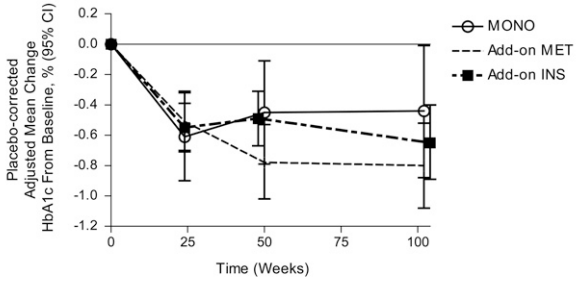
Supported by: Takeda Pharmaceuticals North America, Clinical Trial ID: NCT01223196

1030-P

Durability of Dapagliflozin Treatment Response in Patients With T2DM: 2-Year Results

AFSHIN SALSALI, KATJA ROHWEDDER, TRACI MANSFIELD, PAULA MARTIN, LI WEI, SHAMIK PARIKH, *Princeton, NJ, Wedel, Germany, Wilmington, DE*

Dapagliflozin (DAPA), an SGLT2 inhibitor, increases urinary glucose excretion and reduces hyperglycemia independently of insulin. Extended treatment results (wk 102-104) for 24-wk, randomized, double-blind, placebo (PBO)-controlled trials in patients with T2DM who received DAPA as monotherapy (MONO; NCT00528372), add-on to metformin (MET; NCT00528879), or add-on to insulin ± OAD (INS; NCT00673231) are reported. DAPA (10 mg/d) produced sustained reductions in HbA1c from baseline (BL) (Figure) and more patients achieved HbA1c <7% vs PBO (Table). Increases from BL in urinary glucose:creatinine (g/g) endured, eg, change (95% CI) at Wk 102 in the add-on to MET study was 31.8 (25.0, 38.5) for DAPA 10 mg vs -0.2 (-0.6, 0.2) for PBO. Reductions in body weight (BW) persisted (Table). Adverse events were generally balanced across groups and similar percentages of patients reported hypoglycemic events for DAPA 10 mg and PBO (MONO, 5.3% vs 4.3%; MET, 5.8% vs 5.2%; INS, 61.9% vs 60.7%). Events suggestive of genital and urinary tract infection were greater with DAPA vs PBO in all studies; infections were mostly mild to moderate in severity and occurred more often in the first 24 wks. HbA1c and BW reductions were sustained with long-term DAPA MONO or add-on therapy to MET or INS.



Sample Size per Time Point (excluding data after rescue)

PBO	71	55	46	18
DAPA 10 mg	63	55	45	21
PBO+MET	133	100	74	28
DAPA 10 mg+MET	132	117	102	57
PBO+INS	188	122	89	50
DAPA 10 mg+INS	192	158	139	100

Proportion of patients (%) achieving HbA1c <7% (95% CI)*†	PBO (N=72)	DAPA (N=65)	PBO+MET (N=134)	DAPA+MET (N=132)	PBO+INS (N=193)	DAPA+INS (N=194)
Wk 24	29.0 (19.1, 39.0)	42.2 (31.0, 53.5)	24.2 (17.4, 30.9)	38.2 (30.3, 46.1)	7.1 (3.5, 10.7)	18.6 (13.3, 23.8)
Wk 48/50	26.4 (16.9, 35.9)	43.9 (32.6, 55.1)	20.9 (14.4, 27.4)	39.7 (31.5, 47.8)	8.1 (4.2, 12.0)	16.0 (11.0, 21.0)
Wk 102/104	18.5 (9.7, 27.2)	27.9 (17.6, 38.1)	15.4 (9.5, 21.3)	31.5 (23.7, 39.3)	4.6 (1.6, 7.5)	6.9 (3.4, 10.4)
Adjusted Mean Change in Total Body Weight (kg) from Baseline (95% CI)‡						
Baseline ±SD	88.8±19.0 (n=75)	94.1±18.8 (n=69)	87.7±19.2 (n=136)	86.3±17.5 (n=133)	94.2±19.5 (n=188)	94.6±16.8 (n=192)
Wk 24	−2.9 (−3.2, −1.3) (n=56)	−3.3 (−4.3, −2.4) (n=56)	−0.9 (−1.4,−0.4) (n=99)	−2.9 (−3.4, −2.4 (n=116)	−0.0 (−0.4, 0.4) (n=123)	−1.7 (−2.1, −1.3) (n=161)
Wk 48/50	−2.1 (−3.3, −0.9) (n=46)	−2.9 (−4.2, −1.7) (n=45)	−0.7 (−1.3, −0.0) (n=74)	−2.9 (−3.5, −2.3) (n=102)	−0.2 (−0.8, 0.4) (n=89)	−1.8 (−2.3, −1.3) (n=141)
Wk 102/104	−1.3 (−2.8, 0.2) (n=19)	−3.9 (−5.4, −2.5) (n=22)	−0.7 (−1.7, 0.4) (n=28)	−2.8 (−3.6, −2.0) (n=57)	0.9 (−0.1, 1.9) (n=50)	−2.0 (−2.7, −1.3) (n=102)

*Target HbA1c <7% was adjusted for baseline HbA1c and assessed at the specified time point.
†Excluding data after rescue.

Supported by: Bristol-Myers Squibb and AstraZeneca

1031-P

Positive Impact of Revised FDA Guidance on Clinical Trial Design in Diabetes

M. ANGELYN BETHEL, HARALD SOURIJ, *Oxford, United Kingdom*

Positive Impact of Revised FDA guidance on Clinical Trial Design in DiabetesWe have investigated the impact of the 2008 revised US Food and Drug Administration (FDA) guidance, requiring robust assessment of cardiovascular safety for all new antidiabetic drugs, on the design and nature of clinical outcome studies. Clinicaltrials.gov was searched for interventional Phase 2

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

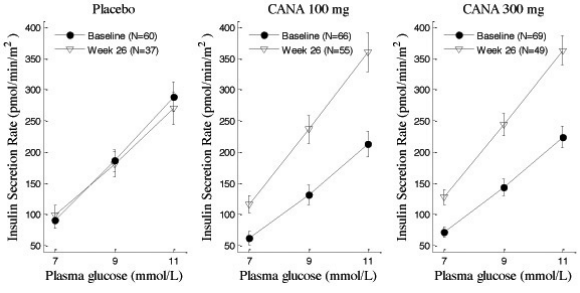
or higher glucose-lowering drug trials with primary cardiovascular (CV) outcomes and compared trial characteristics of those registered within 3 years before and after the guidance was issued.For the period March 2008_February 2011 versus March 2005_February 2008, the number of diabetes CV outcomes trials doubled (8 versus 16), and they were larger with median (IQR) 6000 (4082-9313) versus 1116 (300-4447) participants. Later trials had a wider international distribution of participants, with median 27 (6-35) countries recruiting in 501 (183-635) sites versus 17 (1-20) countries recruiting in 160 (3-332) sites. Nine of 16 trials registered after March 2008 recruited worldwide, with all having sites in North and South America, Europe, Australasia and Africa. None of the trials registered in the prior period recruited in all these regions. In the latter period CV composite endpoints contained fewer components, typically CV mortality, nonfatal myocardial infarction, nonfatal stroke, with or without CV hospitalization (13/16 trials), than earlier trials which included additional components, e.g. peripheral artery disease interventions, coronary angioplasty.Contrary to some expectations, the revised FDA guidance requiring more stringent CV outcomes assessment for diabetes medications did not diminish investment in diabetes outcomes research. The new generation of clinical trials are more globally representative and substantially larger, permitting more definitive estimates of potential benefits and risks that will more definitively inform the future management of diabetes.

1032-P

Treatment With Canagliflozin (CANA), a Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitor, for 26 Weeks Improves Indices of Beta-cell Function (BCF)

DAVID POLIDORI, YUE ZHAO, MARIA ALBA, ELE FERRANNINI, *San Diego, CA, Raritan, NJ, Pisa, Italy*

Loss of BCF is thought to underlie the progressive deterioration of glycemic control in type 2 diabetes (T2D). In hyperglycemic rodents, BCF can be restored when normoglycemia is achieved with SGLT2 inhibitor treatment. In previous clinical studies, indices of BCF were improved after 2-12 wks of CANA treatment. To assess the effects of longer-term treatment, indices of BCF were determined before and after 26 wks of treatment in a randomized (1:1:1 to placebo [PBO], CANA 100 mg, or CANA 300 mg), double-blind, Phase 3 study in T2D patients (pts) inadequately controlled with diet and exercise. 584 pts were randomized (mean age=55 yr, BMI=32 kg/m^2, A1c=8.0%) and dosed. A1c decreased by 0.91% with CANA 100 mg and 1.16% with CANA 300 mg (PBO-subtracted least squares mean changes, P<0.001 for both), with safety and tolerability consistent with previously reported studies. A subset of subjects was given a meal tolerance test with timed measurements of plasma glucose (G) and C-peptide (C) for 3 h. AUC C/AUC G was 162-165 pM/mM at baseline and increased by 41 (95% CI=19-63) and 51 (CI=28-73) with CANA 100 and 300 mg, respectively. Insulin secretion (from C deconvolution) at 9 mM G increased (from baseline of 139-160 pmol/min/m^2) by 107 (CI=65-150) and 119 (CI=76-161) with CANA 100 and 300 mg (Figure). Beta-cell glucose sensitivity (slope of the relation of insulin secretion to concomitant plasma G levels) increased (from baseline of 46 pmol/min/m^2/mM) by 22 (CI=11-33) and 22 (CI=10-33) with CANA 100 and 300 mg (Figure). In conclusion, 26 wks of CANA treatment improves BCF by ~50% in T2D pts.



Supported by: Janssen Research and Development, LLC

1033-P

Efficacy and Safety of Insulin Glargine vs. NPH Insulin in Subjects With Type 2 Diabetes Mellitus Uncontrolled on Oral Agents: A Pooled Analysis of RCT Data

GEREMIA B. BOLLI, FRANCESCA PORCELLATI, JAY LIN, EDWARD WANG, PAOLO LUCIDI, CARMINE G. FANELLI, *Perugia, Italy, Flemington, NJ, Bridgewater, NJ*

Insulin glargine has been shown in individual clinical trials to be as efficacious as Neutral Protamine Hagedorn (NPH) insulin with less hypoglycemia. The aim of this analysis was to provide multi-trial-based estimates of the comparative efficacy and safety of insulin glargine and NPH insulin in subjects with type 2 diabetes (T2DM) uncontrolled on oral agents. Intent-to-treat populations were pooled from 6 randomized clinical trials of subjects with T2DM begun on insulin for 24-36 weeks. Baseline and endpoint A1C, baseline body mass index (BMI), and demographic characteristics were measured. Subjects were required to have baseline and endpoint A1C measurements. Severe hypoglycemia and severe nocturnal hypoglycemia were defined as specified in each trial. There were 1385 subjects initiated on glargine and 1215 on NPH, with no significant difference in baseline characteristics between them (48% female; mean age, 57 y; BMI, 28.3 kg/m^2; duration of diabetes, 10.0 y). At endpoint, A1C levels fell from a mean (SD) of 9.0 (1.0) % at baseline in both groups to 7.6 (1.2) % in the glargine group and 7.7 (1.2) % in the NPH group. The change from baseline was not different between the groups (-1.3 [1.2] vs -1.3 [1.2]). The percentage of subjects achieving A1C < 7% at endpoint was not different between the groups (31% vs 29%). In contrast, fewer subjects on glargine than on NPH experienced severe hypoglycemia (2.0% vs 3.2%; P = 0.041) or severe nocturnal hypoglycemia (0.7% vs 2.1%; P = 0.002). These results confirm those of the individual trials that glargine is as efficacious as NPH but with less severe hypoglycemia, particularly nocturnal, in subjects whose T2DM is uncontrolled on oral agents.

Supported by: sanofi-aventis

1034-P

Pharmacological Inhibition of DGAT-1 Improves Insulin Sensitivity and Metabolic Profile

ADITI JATKAR, JUDITH COSGROVE, PHILLIP YATES, DAVID PERREGAUX, LI ZHANG, JILLENE WOCK, JAMES BAIN, MICHEAL MUEHLBAUER, JANICE D. WAGNER, CHRISTOPHER B. NEWGARD, CLAIRE M. STEPPAN, *Cambridge, MA, Groton, MA, Winston-Salem, NC, Durham, NC*

Excessive lipid accumulation is associated with insulin resistance. Acyl-CoA:diacylglycerol acyltransferase 1 (DGAT-1) is the predominant enzyme involved in the processing of exogenous fat, catalyzing the final and irreversible step in the formation of triacylglycerol in the intestine. Lack of functional DGAT-1 in mice causes reductions in TAG synthesis and post-prandial TAG excursion, improves insulin sensitivity and increases energy expenditure. We sought to determine if inhibition of DGAT-1 in obese, glucose intolerant cynomologous monkeys would confer insulin sensitivity. Following chronic administration of a potent, selective DGAT-1 inhibitor PF-04620110, monkeys demonstrated improvements in insulin sensitivity as assessed by IV-GTT and fasting lipid profile. Using a comprehensive mass spectrometric analysis approach we also demonstrate that chronic pharmacological DGAT-1 inhibition in cynomolgous monkeys causes distinctive alterations in the circulating levels of three classes of metabolites- amino acids, free fatty acids and acylcarnitines. Changes in the metabolome included reductions in metabolites that have been shown to be negative risk factors associated with human diabetes. An integrated view of the data suggests that DGAT-1 inhibition may have the potential to alter pathways of lipid oxidation and fuel utilization to cause a "lean metabolic profile" in obese, glucose intolerant monkeys.

1035-P

Linagliptin is an Effective Therapeutic for Non-alcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic Steatohepatitis (NASH)

THOMAS KLEIN, MICHAEL MARK, *Biberach, Germany*

Dipeptidyl peptidase (DPP)-4 inhibitors are an established treatment option for type 2 diabetes and have recently demonstrated insulin sensitizing, anti-inflammatory, and anti-oxidative effects. NASH is gaining importance as the hepatic manifestation of the metabolic syndrome and as a primary cause of cirrhosis and hepatocellular carcinoma. We investigated the effects of the DPP-4 inhibitor linagliptin in streptozotocin/high-fat diet (STZ/HFD) neonatal mice, a novel model for NASH. Two-day-old males were injected with STZ (200 µg/mouse, i.p.) and fed a HFD for 4 weeks. Treatment with linagliptin (1, 10, or 30 mg/kg/d) was either for 2 or 4 weeks. Histologic NAFLD scoring (fat deposition, lobular inflammation, hepatocellular ballooning), Sirius red collagen staining, and mRNA analysis for inflammation-related transcripts

and fibrosis markers were performed (all data are mean ± SEM). In the first study (treatment for 2 weeks), linagliptin significantly reduced NAFLD scores (1 mg/kg: 2.9±0.7, p<0.05; 10 mg/kg: 2.4±1.0, p<0.01) versus untreated controls (4.1±1.1). In addition, linagliptin significantly reduced hepatic tumor necrosis factor-α expression (1 mg/kg: 1.4±0.2, p<0.001; 10 mg/kg: 2.1±0.7, p<0.001) versus untreated controls (5.7±1.4). In the second study (treatment for 4 weeks), linagliptin also significantly reduced NAFLD scores (10 mg/kg: 3.7±0.4, p<0.05; 30 mg/kg: 3.6±0.3, p<0.01) versus untreated controls (4.6±0.6). Furthermore, linagliptin significantly reduced collagen formation (10 mg/kg: 0.64±0.02, p<0.05; 30 mg/kg: 0.59±0.05, p<0.01) versus untreated controls (0.96±0.09). In conclusion, the results of this study suggest that linagliptin may be a novel therapeutic approach for the treatment of NAFLD and NASH.

Supported by: Boehringer Ingelheim

1036-P

Sodium Nitrite Therapy Restores Blood Flow in Aged Type 2 Diabetes Experimental Critical Limb Ischemia

SHYAMAL BIR, CHRISTOPHER PATTILLO, XINGGUI SHEN, GOPI KRISNA KOLLURU, SIBILE PARDUE, CHRISTOPHER KEVIL, *Shreveport, LA*

Diabetes is a major risk factor for peripheral arterial disease that can progress to critical limb ischemia (CLI). The incidence of CLI is increasing and few effective therapies exist besides surgical intervention or amputation. Sodium nitrite is a prodrug of nitric oxide that can stimulate angiogenesis in ischemic tissue; however the effect and molecular mechanism of sodium nitrite in diabetic experimental critical limb ischemia is yet to be reported. Therefore, we have determined the effects and molecular mechanisms of sodium nitrite therapy on chronic critical limb ischemia in elderly Db/Db diabetic mice.Permanent hind limb ischemia was induced by ligation and excision of the left femoral artery in 42 week old Db/Db mice and assigned to four groups (n=8, each group); control (PBS), sodium nitrite (165 µg/kg), sodium nitrite + denatured VEGF aptamer (50mg/kg/day), sodium nitrite + VEGF aptamer (50mg/kg/day). Hind limb blood flow was determined by laser Doppler perfusion image system. Angiogenic and cellular proliferation index were measured histologically using anti-CD31/DAPI and anti--Ki67/DAPI staining, respectively. Tissue and plasma superoxide levels were measured by the hydroethidium/2-OH-E^+/HPLC method. VEGF level in ischemic tissue was measured by ELISA method.Sodium nitrite therapy did not alter glycemic status, body weight, or lipid profiles of diabetic mice. Ischemic tissue reperfusion, angiogenic index, cell proliferation index, and ischemic tissue VEGF concentration were significantly increased with sodium nitrite therapy; whereas, VEGF aptamer treatment blocked these effects. Sodium nitrite therapy also significantly decreased diabetic plasma and ischemic tissue superoxide levels compared to control.Delayed sodium nitrite therapy restored blood flow in aged type 2 diabetic critical limb ischemia by VEGF as well as anti-oxidant mediated pathway.

1037-P

Glycemic and Lipid Effects of the Short-Acting Glucagon Receptor Antagonist MK-3577 in Patients With Type 2 Diabetes

SAMUEL S. ENGEL, MARC L. REITMAN, LEI XU, PAULA J. ANDRYUK, MICHAEL J. DAVIES, KEITH D. KAUFMAN, BARRY J. GOLDSTEIN, *Whitehouse Station, NJ*

MK-0893, a glucagon receptor antagonist (GRA) with a long $t_{1/2}$ (60-100 hrs), improved glycemic control but increased LDL-cholesterol (LDL-C) in patients (pts) with type 2 diabetes. The present study evaluated the effects of MK-3577, a GRA with a shorter $t_{1/2}$ (~4 hrs), on glycemic and lipid profiles and the diurnal influence of glucagon receptor (GR) blockade. Based on PK-PD modeling, a twice-daily regimen was selected to provide sustained GR blockade (>80%) over 24 hrs, and 2 once-daily dosing regimens were selected to provide a reduced magnitude of GR blockade (<50%) during either daytime or nighttime. In a 5-period cross-over study, pts were randomized to MK-3577 10 mg QD AM, 6 mg QD PM, 25 mg BID, metformin 1000 mg BID, or placebo for 4 wks in each period. A planned interim analysis was performed after 118 pts completed ≥2 periods. The trial was stopped and results herein are for these pts (baseline mean age = 54 yrs; A1C = 7.6%). Relative to placebo, glycemic improvements were seen with all MK-3577 regimens and with metformin (Table). Increased LDL-C was also observed with the MK-3577 BID regimen. Numerically greater glycemic improvements and LDL-C increases were seen with PM dosing compared to AM dosing. In summary, near-complete GR blockade led to robust glycemic efficacy but increased LDL-C. Partial blockade of GR led to less effect on glycemia and LDL-C, with a trend towards greater effects with nocturnal GR blockade. There appears to be an association between glycemic efficacy and LDL-C increases with GR blockade. While GR blockade provides glycemic efficacy, lipid effects may limit clinical utility.

	Placebo	MK-357710 mg QD AM	MK-35776 mg QD PM	MK-0357725 mg BID	Metformin 1000 mg BID
Δ FPG, mg/dL	4.3 (-2.1, 10.6)	-7.2 (-13.0, -1.4)**	-17.5 (-23.3, -11.7)***	-31.7 (-37.5, -26.0)***	-14.4 (-24.7, -4.2)***
Δ 24-hr WMG, mg/dL	-1.6 (-8.5, 5.3)	-18.8 (-30.2, -7.4)*	-25.0 (-36.3, -13.7)***	n/a	-36.5 (-46.7, -26.3)***
%Δ LDL-C	2.3 (-1.6, 6.3)	1.5 (-2.0, 5.1)	6.8 (3.1, 10.6)	10.0 (6.3, 13.9)**	-1.7 (-7.7, 4.8)

Δ = LS mean or mean percent change from baseline (95% CI); n/a = not assessed with BID dosing; WMG = weighted mean glucose; ***p≤0.001, **p≤0.01, *p≤0.05 vs. placebo.

Supported by: Merck Sharp and Dohme

1038-P

Insulin Necessity is Better than Diabetes Duration in Predicting Liraglutide Treatment Response: The Association of British Clinical Diabetologists (ABCD) Nationwide Liraglutide Audit

KEN Y. THONG, CHRISTOPHER WALTON, ROBERT E. RYDER, ABCD NATIONWIDE LIRAGLUTIDE AUDIT CONTRIBUTORS, *Birmingham, United Kingdom, Hull, United Kingdom*

Liraglutide treatment may be more effective in earlier type 2 diabetes. Using data from a nationwide audit of liraglutide use in UK, we analysed A1c reduction at 3 months post-liraglutide 1.2 mg initiation stratified according to (1) extent of background diabetes therapy, or (2) diabetes duration. (1) Patients were divided into those receiving 1, 2, 3 OADs (oral anti-diabetes drugs) or insulin (±OAD), or (2) diabetes duration 0-5 years, 6-10 years, and >10 years. Effects on A1c changes were analysed using ANCOVA using baseline A1c as a covariate. Among 4129 patients, we excluded patients who lacked 3 month A1c data, switched from exenatide, used liraglutide 1.8 mg (too few to analyse), reduced >20% insulin dose or stopped an OAD at initiation. 638 patients (1 OAD *n*=119, 2 OADs *n*=209, 3 OADs *n*=67, insulin *n*=243) and 586 patients (duration 0-5 years *n*=181, 6-10 years *n*=195, >10 years *n*=210) were analysed. Non-adjusted mean (SE) A1c reduction according to OAD/insulin groups were: 1.4% (0.1), 1.8% (0.1), 1.9% (0.2) and 1.0% (0.1) (all p<0.01 compared with baseline). After adjustment, patients on 1, 2, and 3 OADs achieved greater A1c reduction compared with patients on insulin (difference of least square means and 95%CI): 0.8% [0.4,1.1%] (p<0.01), 0.8% [0.5,1.1%] (p<0.01) and 1.0% [0.6,1.5%] (p<0.01), respectively. No significant differences were found for A1c reduction between 1, 2 or 3 OADs. Mean A1c reduction among the three diabetes duration groups were: 1.6% (0.1), 1.5% (0.1) and 1.2% (0.1) (all p<0.01). Patients with diabetes duration 0-5 years achieved greater A1c reduction compared with patients with duration >10 years: 0.5% [0.2,0.8%] (p<0.01). When analysed together, the extent of diabetes treatment but not diabetes duration remained an independent predictor of A1c change. We conclude that the need for insulin and diabetes duration help predict treatment response to liraglutide.

Supported by: Novo Nordisk, Inc.

1039-P

Luseogliflozin (TS-071), a Selective SGLT2 Inhibitor, Improves Glycemic Control and Lowers Body Weight in Japanese Patients With Type 2 Diabetes Mellitus

YUTAKA SEINO, TAKASHI SASAKI, ATSUSHI FUKATSU, YOSHISHIGE SAMUKAWA, SOICHI SAKAI, TAKASHI WATANABE, *Osaka, Japan, Tokyo, Japan, Aichi, Japan*

SGLT2 inhibition is a new approach to the treatment of type 2 diabetes (T2DM). Luseogliflozin (LUSEO) is orally bioavailable and is a highly selective SGLT2 inhibitor. In a previous exploratory study, once daily administration of LUSEO demonstrated clinical amelioration in HbA1c and other glycemic parameters.The present study was designed to investigate the efficacy and safety of LUSEO in Japanese patients with T2DM. In this double-blind, placebo (PBO)-controlled, dose-finding study, 280 subjects were randomized to LUSEO 1, 2.5, 5, 10 mg once daily or PBO for 12 weeks. The primary endpoint was the change in HbA1c from baseline at the end of treatment.Mean baseline characteristics in each group were HbA1c 7.77-8.05%, fasting plasma glucose (FPG) 149.3-158.9 mg/dL, postprandial plasma glucose (PPG) at 2-hours after meal-test 245.2-257.7 mg/dL, and body weight 61.0-72.6 kg. HbA1c, FPG, PPG and body weight were decreased significantly (Table 1). There was a significant decrease in systolic blood pressure reductions without relevant change in pulse in all LUSEO groups. Frequency of adverse events was similar in all groups. No hypoglycemia (less than 70 mg/dL blood

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

glucose level) was observed. Eighteen pollakiuria or urine output increases were observed in all LUSEO groups, but all of these events were mild in severity.

Table 1. Change from baseline at end of trial (mean ± SE) *: P<0.001 vs. PBO

	Luseogliflozin (difference from PBO)			
	1 mg	2.5 mg	5 mg	10 mg
HbA1c (%)	-0.52 ± 0.08*	-0.65 ± 0.08*	-0.69 ± 0.08*	-0.66 ± 0.08*
FPG (mg/dL)	-19.6 ± 3.8*	-27.6 ± 3.8*	-30.1 ± 3.8*	-30.1 ± 3.7*
2-hour PPG (mg/dL)	-49.8 ± 7.5*	-60.0 ± 7.6*	-60.5 ± 7.6*	-48.6 ± 7.4*
Body weight (kg)	-0.96 ± 0.26*	-1.54 ± 0.26*	-2.12 ± 0.27*	-2.05 ± 0.26*

In conclusion, LUSEO ameliorated glycemic control and bodyweight. It was also confirmed that glycemic control of LUSEO at 2.5 mg or higher doses were similar, and that LUSEO showed favorable a safety profile as found in the previous exploratory study.

1040-P

The Effect of Alogliptin and Alogliptin Combined With Pioglitazone on β-cell Function in Type 2 Diabetic Patients: A Randomized Double-Blind Controlled Trial

DIANE L. MÖLLER-GOEDE, BJÖRN ELIASSON, DANIEL H. VAN RAALTE, ANDREA MARI, ANDREA TURA, KATARINA EEG-OLOFSSON, CRAIG WILSON, JAN CEDERHOLM, PENNY FLECK, MARJA R. TASKINEN, ULF SMITH, MICHAELA DIAMANT, *Amsterdam, The Netherlands, Gothenburg, Sweden, Padova, Italy, London, United Kingdom, Uppsala, Sweden, Helsinki, Finland*

In type 2 diabetes (T2DM) patients, thiazolidinediones may preserve β-cell function by direct effects on the β-cell and by improving insulin sensitivity. Dipeptidylpeptidase-4 inhibitors may improve β-cell function by enhancing incretin action.In this 16-week two-center, randomized, double-blind, placebo-controlled study we assessed the effects of alogliptin (ALO) and alogliptin combined with pioglitazone (ALO/PIO) as compared to placebo (PBO) on β-cell function in T2DM subjects by modeling analysis of glucose and C-peptide concentrations derived from standardized meal tests. Calculated parameters were glucose sensitivity (GS) describing the sensitivity of the β-cell to changes in plasma glucose levels, fasting secretory tone (FST) representing fasting insulin secretion rates, and oral glucose insulin sensitivity (OGIS), a marker of insulin sensitivity.Seventy-one patients (mean age 59.1±6.3 years), treated by diet and exercise, on a stable dose of metformin, sulfonylurea, or glinides for more than three months, with a mean A1C of 6.7±0.1%, were recruited. ALO and ALO/PIO decreased A1C from baseline by 0.4 and 0.9%, respectively (both P<0.001 vs PBO; P=0.006 ALO vs ALO/PIO). As compared to PBO, GS and FST significantly improved in patients randomized to ALO/PIO (51% and 36% from baseline, respectively; both P<0.001), whereas the ALO-related improvements of GS and FST (8% and 15%) were not significant. OGIS was significantly improved in patients randomized to ALO/PIO (27% from baseline) vs both ALO and PBO (P<0.001). ALO also significantly improved OGIS vs PBO (9% from baseline; P=0.013). The incidence of adverse events was 76, 59 and 63% for the ALO-, ALO/PIO- and PBO-group, respectively.Short-term treatment with ALO and ALO/PIO both reduced A1c and improved insulin sensitivity, while only the combined treatment with ALO/PIO improved meal-modeled GS and fasting insulin secretion rates.

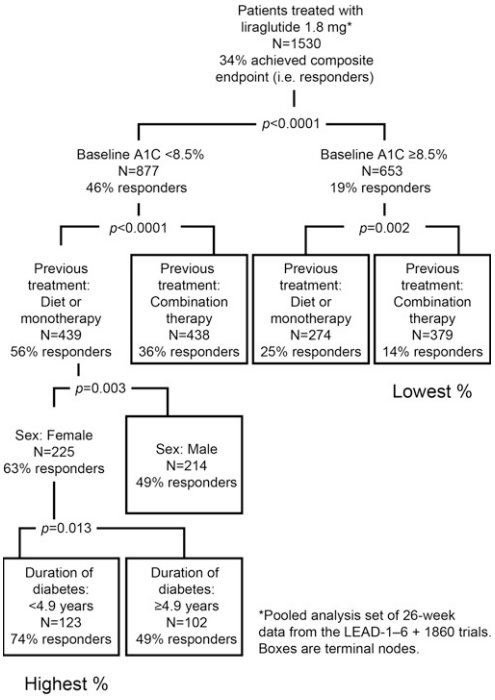
Supported by: Takeda Global Research and Development

1041-P

Identifying Predictors of Response to Liraglutide in Type 2 Diabetes using Recursive Partitioning Analysis

ROBERT E. RATNER, JASON BRETT, NAUM KHUTORYANSKY, VANITA ARODA, *Hyattsville, MD, Princeton, NJ*

Randomized clinical trials provide unbiased databases for comparative effectiveness analyses to see which patients respond best to available interventions. We evaluated patient-level data pooled from 7 phase 3 clinical trials with liraglutide to examine responder subgroups, as defined by those achieving a composite endpoint of A1C <7%, no weight gain and no hypoglycemia (episodes requiring assistance or self-treated with PG <56 mg/dL) over 26 weeks. Overall 34% of individuals on liraglutide 1.8 mg achieved the prespecified composite endpoint: the highest response rate among compared therapies. Candidate predictor variables included baseline age, sex, ethnicity, BMI, A1C, beta-cell function, FPG, insulin resistance, previous treatments, and diabetes duration. Using recursive partitioning to create classification trees, baseline A1C was the most significant predictor, with a probability of achieving the composite outcome of 46% with baseline A1C <8.5% as opposed to 19% if baseline A1C ≥8.5% (p<0.0001). Subsequent splits (with p-values <0.05) produced a subgroup within patients with a baseline A1C <8.5% that was identified by previous treatment with diet or monotherapy, female sex, and diabetes duration <4.9 years increasing probability of success to 74%. Six homogeneous subgroups were identified with different probabilities of achieving the composite outcome (Fig). In summary, recursive partitioning identified individual characteristics and subgroups of patients predicting the response to therapy. Such analyses may guide clinicians in individualizing treatment approaches.



1042-P

Long-Term Effectiveness of Dapagliflozin Over 104 Weeks in Patients With Type 2 Diabetes Poorly Controlled With Insulin

JOHN P. WILDING, VINCENT C. WOO, KATJA ROHWEDDER, JENNIFER E. SUGG, SHAMIK J. PARIKH, *Liverpool, United Kingdom, Winnipeg, MB, Canada, Wedel, Germany, Wilmington, DE*

Dapagliflozin (DAPA), an SGLT2 inhibitor, increases urinary glucose excretion and reduces hyperglycemia in type 2 diabetes (T2DM) independent of insulin (INS) secretion or action. We report results after 104 weeks (w) of patient and center blinded treatment in patients with T2DM poorly controlled on INS (n=808; mean baseline HbA1c 8.53%) randomized to placebo (PBO), 2.5, 5 or 10mg/d DAPA added to background INS (mean baseline INS 77 IU/d) ± oral glucose lowering drugs. Analyses at 24w (1° endpoint) and 48w were reported previously. At 48w, patients on DAPA 5mg were switched to 10mg (5/10 group) and 28 patients discontinued for lack of UK regulatory approval for continuation. INS was uptitrated if HbA1c was >7.5% from 52-65w or >7.0% from 78-104w. 63.6% of patients completed 104w. Analyses over 104w used observed cases and included data after INS uptitration. Mean HbA1c change from baseline at 104w was –0.43% in the PBO group and –0.64% to –0.82% in the DAPA groups. In the PBO group, mean INS dose increased by 18.3 IU/d and weight increased by 1.8kg at 104w, whereas in the DAPA groups, INS dose was stable and weight decreased by 0.9-1.4kg. Adverse events, including total hypoglycemia, were balanced across groups (Table). Proportions of patients with events suggestive of genital infection (GenInf) and of urinary tract infection (UTI) were higher with DAPA vs PBO (GenInf 7.4-14.3% vs 3.0%; UTI 8.4-13.8% vs 5.6%) but most occurred in the first 24w and most were single episodes. In summary, DAPA produced long-term reductions in HbA1c and weight with no escalation of INS dose over 104w in T2DM poorly controlled with INS.

Efficacy and Safety of DAPA over 104 weeks in Patients with T2DM Poorly Controlled on INS

	PBO + INS	DAPA 2.5mg+ INS	DAPA 5/10mg+ INS	DAPA 10mg+ INS
N	.	.	.	.
Randomized	197	203	212	196
Completing	108	134	129	142
Mean HbA1c,* %	.	.	.	.
Baseline	8.47	8.46	8.62	8.58
Change–from–baseline	–0.43	–0.64	–0.82	–0.79
(95%CI)	(–0.58,–0.28)	(–0.78,–0.50)	(–0.96,–0.68)	(–0.92,–0.65)
Difference vs PBO	.	–0.21	–0.39	–0.35
(95%CI)	.	(–0.41,–0.01)	(–0.59,–0.18)	(–0.56,–0.15)
INS uptitration or discontinuation due to lack of glycemic control,† %	.	.	.	.
Proportion	50.4	29.1	26.5	25.5
(95%CI)	(43.5,57.2)	(22.9,35.3)	(20.5,32.4)	(19.4,31.6)
Difference vs PBO	.	–21.3	–23.9	–24.9
(95%CI)	.	(–30.5,–12.0)	(–33.0,–14.8)	(–34.1,–15.6)
Mean INS dose,* IU/d	.	.	.	.
Baseline	74.0	79.9	77.1	78.0
Change–from–baseline	18.3	4.1	1.6	–0.8
(95%CI)	(13.7,22.9)	(–0.2,8.4)	(–2.7,5.9)	(–5.1,3.5)
Difference vs PBO	.	–14.3	–16.8	–19.2
(95%CI)	.	(–20.5,–8.0)	(–23.1,–10.5)	(–25.5,–12.9)
Mean weight,* kg	.	.	.	.
Baseline	94.5	93.0	93.4	94.6
Change–from–baseline	1.8	–0.9	–1.0	–1.4
(95%CI)	(1.0,2.6)	(–1.6,–0.2)	(–1.7,–0.2)	(–2.1,–0.7)
Difference vs PBO	.	–2.7	–2.7	–3.2
(95%CI)	.	(–3.8,–1.7)	(–3.8,–1.7)	(–4.2,–2.1)
Adverse Events, %	.	.	.	.
Total	78.2	80.2	78.3	80.1
Serious	19.8	19.3	15.1	18.4
Discontinuation	6.6	5.0	9.4	5.6
Deaths	0	0	0.9	0.5
Hypoglycemia, %	.	.	.	.
Total	61.9	69.3	61.3	60.7
Major	1.0	2.0	1.4	1.5

*Data are adjusted mean change from baseline derived from mixed models
†Data are adjusted proportions derived from logistic regression

Supported by: Bristol-Myers Squibb/AstraZeneca

1043-P

WITHDRAWN

1044-P

Linagliptin is More Effective than Glimepiride at Achieving a Composite Outcome of A1C Target With No Hypoglycemia and No Weight Gain Over 2 Years in Mildly Hyperglycemic T2D Pts on Metformin

BAPTIST GALLWITZ, JULIO ROSENSTOCK, ANGELA EMSER, MAXIMILIAN VON EYNATTEN, HANS-JUERGEN WOERLE, *Tübingen, Germany, Dallas, TX, Ingelheim, Germany*

A sulfonylurea (SU) is often added to metformin (MET) to achieve glycemic targets in type 2 diabetes (T2D) but is frequently associated with hypoglycemia and weight gain. We compared the long term clinical composite outcome of a DPP-4 inhibitor, linagliptin (LINA), with the commonly used SU glimepiride (GLIM). T2D patients (pts) on stable MET were randomized to LINA 5 mg/d or GLIM 1–4 mg/d over 2 years. Primary study results meeting non-inferiority on A1C changes were reported previously. The endpoint of this 104 week exploratory analysis was to assess the proportions achieving a glycemic target of A1C <7% without weight gain (defined as <1kg increase in body weight vs baseline) and without hypoglycemia (defined event per protocol). Analyses were based on a per-protocol population on treatment after 2 years without the use of rescue medication if FPG [mg/dL]: ≤270, wk1–4; ≤240, wk4–12; ≤220, wk12–16; ≤200, wk16–28; A1C: ≤8.0%, wk28–52; ≤7.5%, wk52–104.504 pts were evaluable (233 LINA; 271 GLIM). Baseline A1C levels were similar in the 2 groups (7.2% and 7.3%, respectively). After 104 weeks, LINA and GLIM each had mean A1C reduction from baseline of –0.6% and 76% of pts achieved A1C <7% in both groups. However, far fewer experienced hypoglycemia and weight gain with LINA than GLIM (6% vs 42%, and 22% vs 55%, respectively). Consequently, a significantly higher proportion in the LINA group than with GLIM achieved the composite endpoint (54% vs 23%, respectively). The odds ratio for achieving the composite endpoint was 4 times higher with LINA (3.9; 95% confidence interval, 2.6–5.7; p<.0001).In conclusion, LINA and GLIM added to MET provided similar improvements in long term glycemic control in T2D; however, a significantly greater proportion of the LINA group achieved an A1C target of <7.0% without hypoglycemia and without increase in body weight.

Supported by: Boehringer Ingelheim

1045-P

Fasting Plasma Glucose after Intensive Insulin Therapy Predicted Long-Term Glycemic Control in Newly Diagnosed Type 2 Diabetic Patients

JIANBIN LIU, JUAN LIU, YANBING LI, *Guangzhou, China*

To assecss the factors that areresponsible for long-term remission and/or hyperglycemia relapse afterintensive insulin therapy in patients with newly diagnosed type 2 diabetesOriginal data of 188 patients with newly diagnosed type 2 diabetes wasreanalyzed. All participants were treated with short term intensive insulintherapy with continuous subcuntanous insulin infusion and followed up for 12months. Patients who maintained glycemic control for 12 months with only lifestyle intervention were defined as remission group while those who did not asnonremission group. Relationships between metabolic control, β cell functionand insulin sensitivity with remission time and hyperglycemia relapse wereexplored.Totally 93 patients achieved 12-month euglycemic remission.Substantial ameliorations in blood glucose, parameters of β cell function andinsulin sensitivity were obtained both in remission and nonremission patients.Greater improvements in HOMA-β(P=0.024), DI (P=0.017)and AIR(P=0.010), otherthan HOMA-IR(P=0.600), were observed in remission group than in nonremissiongroup. Significant correlation was documented between the duration of remissionand FPG after CSII (*r*= -0.349, P=0.000). Multivariate logisticregression show that FPG after CSII was independent predictor of hyperglycemicrelapse (OR=1.585, P=0.001, 95%CI (1.210, 2.076)). All patients were stratifiedinto three groups according FPG level 15 hours after insulin cessation. As multivariateCox proportional hazards regression demonstrated, compared with the patientswith FPG<6.1mmol/L, risk for hyperglycemia relapse was increased 60% in thosewith 6.1 mmol/L≤FPG≤7.0 mmol/L (HR=1.60, P=0.049, 95%CI (1.13, 2.64)), and 1.69 folds inthose with FPG>7.0 mmol/L (HR=2.69, P=0.000, 95%CI (1.61, 4.50)).Fasting plasma glucose after intensive insulin therapyis a convenient and significant predictor for hyperglycemic relapse.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

1046-P

Ipragliflozin Reduces A1C and Body Weight in Type 2 Diabetes Patients Who Have Inadequate Glycemic Control on Metformin Alone: ILLUMINATE Study

KASHIA GOTO, ATSUNORI KASHIWAGI, KENICHI KAZUTA, SATOSHI YOSHIDA, EIJI UEYAMA, ATSUSHI UTSUNO, *Tokyo, Japan, Shiga, Japan*

Ipragliflozin (IPRA; ASP1941), a novel, selective SGLT 2 inhibitor, is currently in phase 3 clinical development for type 2 diabetes mellitus (T2DM) treatment.In this placebo-controlled, , double-blind, study we assessed efficacy, safety and tolerability of IPRA added to metformin in Japanese T2DM patients (pts), with inadequate glycemic control on metformin alone. From ≥ 12 weeks (wks) before randomization until (EOT), pts received a constant metformin dose (500-1500 mg).After screening (4 wks), followed by a 2-wk single-blind placebo run-in, pts were randomized (2:1 ratio) to IPRA 50 mg once daily (n=112) or placebo (n= 56) for 24 wks.At EOT, IPRA significantly reduced A1C (-1.29%) compared with placebo, as well as FPG (-39.4 mg/dL) and body weight (-1.69 kg). More IPRA-treated pts achieved A1C < 7.4% and < 6.9% (49.1% and 19.6%) compared with placebo (1.8% and 0%). Also, IPRA reduced systolic (-3.6 mmHg) and diastolic (-1.8 mmHg) blood pressure compared with placebo.Treatment emergent adverse event (TEAE) incidences were 71.4% in the IPRA arm and 80.4% in placebo. Drug-related TEAEs were reported by 29.5% (33/112) in the IPRA arm, and 21.4% (12/56) in placebo. No hypoglycemic events occurred during the treatment period. Urinary tract infections were reported by 1.8% (2/112) in the IPRA arm and 3.6% (2/56) in placebo. Genital infections only occurred in the IPRA arm (4.5%, 5/112).In conclusion, IPRA (50 mg) added to metformin for 24 wks was well tolerated and reduced A1C by 1.29% compared with placebo. Additional benefits were reductions in body weight and blood pressure.

Table. Efficacy parameters.

Parameter	Baseline values, mean ± standard deviation		Change from baseline to EOT, mean ± standard deviation		Adjusted mean change from baseline to EOT compared with placebo (95% CI)	*P* value
	Placebo (n = 56)	Ipragliflozin 50 mg (n = 112)	Placebo (n = 56)	Ipragliflozin 50 mg (n = 112)		
A1C*, %	8.38 ± 0.74	8.25 ± 0.71	0.38 ± 0.70	-0.87 ± 0.66	-1.29(-1.497 to -1.092)	*P* < 0.001
FPG, mg/dL	174.5 ± 24.84	161.6 ± 29.93	10.7 ± 27.46	-22.2 ± 26.72	-39.4(-46.96 to -31.85)	*P* < 0.001
Body weight, kg	67.51 ± 11.37	68.52 ± 13.86	-0.63 ± 1.68	-2.33 ± 1.80	-1.69(-2.256 to -1.117)	*P* < 0.001

CI, confidence interval; EOT, end of treatment period (24 weeks); FPG, fasting plasma glucose; FSI, fasting serum insulin; A1C, glycosylated hemoglobin. *, A1C levels were measured as defined by the Japan Diabetes Society (JDS) and estimated as National Glycohemoglobin Standardization Program (NGSP) equivalent value calculated by the formula A1C (%) = A1C (JDS (%)) + 0.4%.

1047-P

The Effect of Insulin Degludec on Glycemic Control and Nocturnal Hypoglycemia Compared With Insulin Glargine: A 1-Year Randomized Trial in Insulin-Naïve People With Type 2 Diabetes

BERNARD ZINMAN, ATHENA PHILIS-TSIMIKAS, YEHUDA HANDELSMAN, HELENA W. RODBARD, BERTRAND CARIOU, THUE JOHANSEN, LARS ENDAHL, CHANTAL MATHIEU, *Toronto, ON, Canada, La Jolla, CA, Tarzana, CA, Potomac, MD, Nantes, France, Bagsvaerd, Denmark, Leuven, Belgium*

Insulin degludec (IDeg) is a novel basal insulin with an ultra-long, flat action profile. This 52-wk randomized, open-label, noninferiority, treat-to-target trial compared efficacy and safety of IDeg to insulin glargine (IGlar) given sc once daily in insulin-naïve type 2 diabetes (T2DM) subjects inadequately controlled with OADs (metformin±DPP-4 inhibitor). 1030 adults (mean age 59.1 yrs; diabetes duration 9.2 yrs; baseline HbA1c 8.2%; fasting plasma glucose (FPG) 175 mg/dL) were randomized 3:1 to IDeg or IGlar. Both basal insulins were titrated to achieve self-measured blood glucose targets calibrated to PG of 70-89 mg/dL. Participant completion rates were 79% (IDeg) and 77% (IGlar). At 1 yr, IDeg reduced HbA1c (-1.06%) non-inferior to IGlar (-1.19%) (estimated treatment difference (ETD) IDeg-IGlar: 0.09% [95%CI: -0.04; 0.22]). FPG reductions were significantly larger with IDeg than IGlar (-67.7 vs -59.5 mg/dL; ETD: -7.7 mg/dL [95%CI: -13.3; -2.3]; *p*=.005). Overall confirmed hypoglycemia (PG<56 mg/dL and severe episodes requiring assistance) rates were similar for IDeg and IGlar (1.52 vs 1.85 episodes/patient-yr; estimated rate ratio (ERR) IDeg/IGlar: 0.82 [95%CI: 0.64; 1.04]; *p*=.11). Nocturnal confirmed hypoglycemia rates were significantly 36% lower with IDeg (0.25 vs 0.39 episodes/pt-yr; ERR: 0.64 [95%CI: 0.42; 0.98]; *p*=.04). Overall severe hypoglycemia was infrequent but significantly lower with IDeg (0.003 vs 0.023 episodes/pt-yr; ERR: 0.14 [95%CI: 0.03; 0.70]; *p*=.02). End-of-trial mean daily insulin doses were 0.59 (IDeg) and 0.60 (IGlar) U/kg. Mean weight gain was similar: 2.4 kg (IDeg); 2.1 kg (IGlar). Overall adverse event rates were low and similar between groups. In conclusion, in this treat-to-target trial with insulin-naïve T2DM participants, IDeg and IGlar provided similar long-term glycemic control, with significantly lower rates of nocturnal hypoglycemia with IDeg.

1048-P

Efficacy and Safety of Saxagliptin in Combination With Insulin in Elderly Patients With Type 2 Diabetes

BERNARD CHARBONNEL, ANTHONY H. BARNETT, JOHN MONYAK, GIANMARIA MINERVINI, NAYYAR IQBAL, *Nantes, France, Birmingham, United Kingdom, Wilmington, DE, Princeton, NJ*

To address the concerns of treating type 2 diabetes (T2D) in the elderly, especially those on insulin, a subanalysis of outcomes in patients aged ≥65 years (n=104) and <65 years (n=351) was performed from a placebo (PBO)-controlled trial in T2D patients with inadequate response to insulin alone or in combination with metformin, which had shown that adding saxagliptin (SAXA) 5 mg/d improved glycemic control, regardless of metformin use, and was generally well tolerated. At week 24, the overall incidence of adverse events (AEs) with SAXA and PBO was 54.9% vs 57.6%, respectively, in the elderly and 57.5% vs 60.2% in the nonelderly. No elderly patients discontinued the study owing to AEs; 1.7% and 2.5% of nonelderly patients discontinued in the SAXA and PBO groups, respectively. Glycemic improvement from baseline with SAXA add-on therapy was similar in the elderly and nonelderly groups (interaction of treatment by age *P*=0.942 for HbA_{1c}; *P*=0.184 for fasting plasma glucose; *P*=0.291 for 120-min postprandial glucose; Table). This subanalysis demonstrates that SAXA 5 mg/d added to insulin with or without metformin is well tolerated and effective in elderly patients with T2D.

	≥65 y		<65 y	
	SAXA + INS (n=71)	PBO + INS (n=33)	SAXA + INS (n=233)	PBO + INS (n=118)
HbA_{1c}, %				
Baseline mean (SE)	8.38 (0.08)	8.54 (0.14)	8.76 (0.06)	8.69 (0.08)
Adjusted mean (SE) change at 24 wk*	–0.73 (0.11)	–0.35 (0.16)	–0.73 (0.06)	–0.31 (0.08)
Difference vs PBO (95% CI)	–0.38 (–0.75, –0.01)		–0.42 (–0.62, –0.22)	
120-min PPG, mg/dL				
Baseline mean (SE)	273.2 (8.5)	275.0 (13.2)	244.7 (5.5)	249.6 (8.0)
Adjusted mean (SE) change at 24 wk*	–24.3 (8.8)	–6.4 (12.8)	–28.0 (4.9)	–3.6 (6.9)
Difference vs PBO (95% CI)	–17.94 (–48.31, 12.42)		–24.42 (–40.60, –8.25)	
FPG, mg/dL				
Baseline mean (SE)	171.0 (5.8)	178.1 (10.4)	174.2 (3.7)	171.7 (5.1)
Adjusted mean (SE) change at 24 wk*	–10.5 (5.6)	–15.8 (8.4)	–9.9 (3.3)	–3.3 (4.5)
Difference vs PBO (95% CI)	5.29 (–14.48, 25.06)		–6.56 (–17.11, 3.99)	
Response (HbA_{1c} <7% at wk 24),* % of patients	20.0	9.4	16.5	6.0
Difference vs PBO (95% CI)	10.6 (–3.2, 24.4)		10.5 (4.1, 17.0)	

FPG=fasting plasma glucose; INS=insulin alone or in combination with metformin; PBO=placebo; PPG=postprandial glucose; SAXA=saxagliptin 5 mg.*Last observation carried forward.

Supported by: Bristol-Myers Squibb/AstraZeneca

1049-P

ZYH1, a Novel PPAR Agonist that Shows Lipid-Lowering and Insulin-Sensitizing Effects With Good Safety Profile in Preclinical Models

MUKUL R. JAIN, SURESH GIRI, RAJESH SUNDAR, PRABODHA SWAIN, RAMCHANDRA RANVIR, *Ahmedabad, India*

PPAR-alpha agonists are known to show lipid-lowering activity, whereas PPAR-gamma agonists have insulin-sensitizing & anti-hyperglycemic effects. Most fibric acid derivatives are weak activators of PPAR-alpha and have negligible PPAR-gamma activity. ZYH1 is a novel non-fibric acid derivative that showed potent PPAR-alpha agonist effects with relatively weak PPAR-gamma activity. In cell-based transactivation assays, the EC50 values of ZYH1 for hPPAR-alpha and hPPAR-gamma was found to be 0.65 pM and 3 nM respectively. In db/db mice, 12-day repeated dose treatment with ZYH1 (0.01-3 mg/kg/day, p.o.) produced dose-dependent reduction in serum triglyceride (TG), free fatty acids and glucose. The ED50 for these effects was found to be 0.05, 0.19 and 0.19 mg/kg respectively with very significant (91%) reduction in serum insulin and improvement in glucose tolerance (59% reduction in AUC0-120) at 1mg/kg dose. Significant reduction in serum TG was also observed in Zucker fa/fa rats and ob/ob mice. Six-day treatment with

ZYH1 (0.01-10 mg/kg, p.o.) in Swiss albino mice showed up to 76 % reduction in serum TG. In this model, intravenous lipid tolerance test showed up to 68% reduction in AUC0-60 for serum TG. In high-cholesterol fed Sprague Dawley rats ZYH1 treatment (0.1-10 mg/kg, p.o.) caused up to 67 % reduction in LDL cholesterol in 4 days. Similarly, in high-cholesterol-high fat-fed Golden Syrian Hamsters, ZYH1 (0.03-10mg/kg, p.o.) caused up to 61% reduction in serum LDL-cholesterol and 89% reduction in serum TG after 14 days treatment. A comparative study in rats & marmosets confirmed efficacy potential of ZYH1, while ruling out PPAR-specific concerns for humans. Various molecular markers including mRNA for aP2, FATP, ACO, LPL ApoCIII etc. were evaluated in liver and/or adipose tissues; these markers showed expected species-specific changes. Based on efficacy & safety profile, ZYH1 shows good potential for treatment of dyslipidemia in diabetic patients.

1050-P

Effects of PF-04620110, a Novel Diacylglycerol Acyl-Transferase 1 (DGAT1) Inhibitor Administered for 14 days to Healthy-Obese Volunteers

ROBERTO A. CALLE, DANNY CHEN, VAISHALI SAHASRABUDHE, CLAIRE M. STEPPAN, JIE LI, STEPHANIE M. GUSTAVSON, *Cambridge, MA, Groton, CT*

Inhibition of DGAT1, the terminal enzyme in the synthesis of triglycerides (TG), has been proposed for the treatment of type 2 diabetes (T2DM). This study's aim was to examine the effect of a potent and selective DGAT1 inhibitor, PF-04620110, on vitamin A absorption (as a marker if DGAT1 activity), net TG, glucose, insulin and total amide glucagon-like peptide-1 (GLP-1) levels in response to a Vitamin A-Enriched Mixed-Meal Tolerance Test (MMTT) in Healthy-Obese volunteers (BMI 26.6-35.5 kg/m^2). In this randomized, placebo-controlled, ascending-dose, inpatient study, subjects received orally administered placebo (Pbo; n=15) or PF-04620110 (1, 3, 5, 10 mg QD; n=9/group) once daily for 14 days. PF-04620110 mean terminal $t_{½}$ values ranged from 7.8 - 11.3 hours. A MMTT was performed on days 0 and 14. The most common adverse events (AEs) were gastrointestinal (GI); diarrhea, nausea, vomiting. Of all subjects on active drug 61% experienced GI AEs vs. 20% on Pbo. Based on these GI AEs, 5 mg was considered the maximum tolerated dose. PF-04620110's pharmacodynamic effects (see table) were consistent with inhibition of intestinal DGAT1 activity (i.e., reduction of Vitamin A absorption and net TG, respectively), improved insulin sensitivity and enhanced GLP-1 incretin response. Thus, a study in subjects with T2DM is warranted to assess PF-04620110 potential as an anti-diabetic agent.

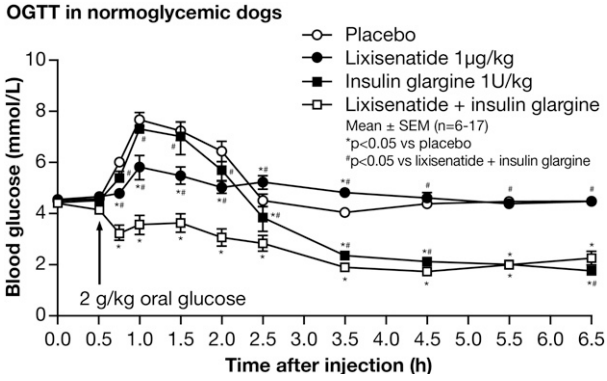
	Pbo (n=15)	1 mg (n=9)	3 mg (n=9)	5 mg (n=9)	10 mg (n=9)
Vitamin A $AUC_{(2-10)}$ (ng•hr/mL)					
Adjusted-geometric means (AGM)	3757.87	3322.40	3412.20	2889.71	2493.22
Ratio vs. Pbo (%)		88.41	90.80	76.90	66.35
90% CI (%)		65.72, 118.94	67.05, 122.97	55.17, 107.19	48.85, 90.12
Net triglycerides $AUC_{(2-10)}$ (mg•hr/dL)					
AGM	906.72	848.68	740.09	676.47	712.72
Ratio vs. Pbo (%)		93.60	81.62	74.61	78.60
90% CI (%)		81.16, 107.94	70.54, 94.45	63.61, 87.51	67.92, 90.97
Glucose $AUC_{(2-5)}$ (mg•hr/dL)					
AGM	289.24	293.93	283.88	302.49	294.62
Ratio vs. Pbo (%)		101.62	98.14	104.58	101.86
90% CI (%)		95.98, 107.60	92.50, 104.13	98.55, 110.98	96.16, 107.89
Insulin $AUC_{(2-5)}$ (mIU•hr/mL)					
AGM	142.65	163.88	77.64	62.26	71.82
Ratio vs. Pbo (%)		114.89	54.43	43.64	50.35
90% CI (%)		82.09, 160.79	38.89, 76.17	31.18, 61.09	35.76, 70.88
Total Amide GLP-1 $AUC_{(2-10)}$ (pM•hr)					
AGM	62.63	61.12	93.06	108.28	126.79
Test Reference	59.15	64.34	72.85	73.77	66.56
Ratio vs. Reference (%)	105.88	94.99	127.75	146.78	190.48
90% CI (%)	84.16, 133.21	73.6, 122.68	98.98, 164.98	110.07, 195.74	147.50, 245.99

1051-P

Combination of Lixisenatide and Insulin Glargine Demonstrates Complementary Pharmacological Activity on Glycemic Control in Animal Models of Diabetes

ULRICH WERNER, MANFRED GERLACH, MICHAEL HOFMANN, ANDREAS W. HERLING, *Frankfurt, Germany*

Glucose-lowering effects of lixisenatide combined with insulin glargine *vs* either drug alone were evaluated in overtly diabetic db/db mice and normoglycemic dogs. In db/db mice receiving either 10 µg/kg SC lixisenatide, 5 U/kg SC insulin glargine or a combination of lixisenatide+glargine, basal blood glucose was significantly decreased by all treatments, but the combination was significantly more effective than glargine alone, resulting in almost physiological glucose levels. In an oral glucose tolerance test (OGTT) in db/db mice, lixisenatide, insulin glargine and the combination all had a significant effect on glucose excursion (maximum excursion [all at 60 min]: 3.44, 7.47 and -2.77 mmol/L, respectively; all p<0.05 *vs* placebo [12.75 mmol/L]). Lixisenatide+glargine was significantly superior to either drug alone (p<0.05). Similarly in dogs, a single dose of 0.5 or 1.0 µg/kg SC lixisenatide alone significantly improved glucose excursion in an OGTT. In contrast, 1 U/kg SC glargine alone had no significant effect on glucose excursion during the absorptive phase of the OGTT, but significantly decreased glucose below control levels in the postabsorptive phase. For lixisenatide+glargine, glucose levels were decreased during both phases (Figure). Thus, the effects of lixisenatide and glargine appeared to be complementary: lixisenatide had a strong effect on postprandial glucose that added to the established effects of glargine on fasting glucose.



Supported by: sanofi-aventis

1052-P

Development of A New Rat Model of Non-Alcoholic Fatty Liver Disease With Insulin Resistance and Obesity

SHRIDHAR NARAYANAN, MALLIKARJUN S. JAJI, VIJAYARAJ DEVISINGH, NAGARAJ M. KULKARNI, NAVINRAJESH B., JEYAMURUGAN MOOKKAN, *Chennai, India*

Non-alcoholic fatty liver disease (NAFLD) is strongly associated with insulin resistance and obesity. Animal models are essential tool for screening of pharmaceutical agents. Thus, the aim of the current investigation was to develop an animal model, which simulates the natural history and metabolic characteristics of human NAFLD to screening of pharmaceutical agents. Day old male Wistar rat pups were treated either Streptozotocin 100 mg/kg i.p or vehicle. Twenty-one days post treatment, animals were weaned and neonatal Streptozotocin (nSTZ) treated group further divided into two groups. The animals were fed regular chow diet and normal drinking water or another group fed high fat diet (HFD - 60 Kcal %) with 40 % fructose in drinking water, for 20 weeks. After 20 weeks, oral glucose tolerance test was performed. Plasma glucose, hepatic triglyceride and insulin were determined. At the end of the study, animals were sacrificed organs obtained and weighed. Hepatic steatosis was assessed by histopathology.The nSTZ animals fed HFD with 40 % fructose showed significant increase in body weight (P<0.05), fat pad (P<0.01) and liver weight (P<0.01) as compared regular chow diet fed nSTZ animals. In addition these animals also showed significant increase in glucose intolerance (P<0.001 vs. nSTZ control; P<0.001 vs. normal control), HOMA- IR (Homeostasis Model Assessment of Insulin Resistance) (P<0.01 vs. nSTZ control; P<0.01 vs. normal control) and hepatic triglyceride content (P<0.01 vs. nSTZ control; P<0.01 vs. normal control). Liver histopathology assessment revealed the nSTZ animals fed HFD with 40 % fructose develop marked hepatic steatosis. In conclusions, these data demonstrate the nSTZ animals fed HFD with 40 % fructose develop NAFLD with insulin resistance and obesity that mimic the pattern of human NAFLD initiation and development. This model is also easy to develop and suitable for screening pharmaceutical agents for the treatment of NAFLD.

1053-P

Autacoid Protectin/Neuroprotectin D1 Promotes Pro-Healing and Neurotrophic Functions of Macrophages from Type-2 Diabetic Mice: Biosynthesis and Actions

SONG HONG, HAIBIN TIAN, YAN LU, STEPHANIE R. GROSS, JOSE A. GALINDO, QUANSHENG WANG, *New Orleans, LA*

Diabetes impairs the critical function of macrophages (Mfs) in healing wounds. This is the first study of pro-resolving protectin/neuroprotectin D1 (NPD1) biosynthesis in Mfs of type-2-diabetic *db/db* mice, and NPD1 action on Mf pro-healing functions in skin excisional-wounds of *db/db* mice.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

Lipidomics analysis via liquid chromatography - mass spectrometry shows that diabetic hyperglycermia or oxidative stress reduced NPD1 level but increased oxidative-stress marker isoprostanes. Mf depletion by clodrosome diminished the NPD1 formation, thus NPD1 is mainly produced by Mfs. NPD1 restored *db/db*-Mf pro-healing functions in promoting wound re-epithelialization (by reducing epithelial gap, 45 ± 5% vs 59 ± 3% of *db/db*-Mf alone), granulation tissue formation (327 ± 28% vs 180 ± 31% of *db/db*-Mf alone) (Fig. 1), and collagen deposition (35 ± 8% vs 21 ± 3% of *db/db*-Mf alone); Moreover NPD1-treated Mfs promoted nerve regeneration (nerve fiber density: 7.6 ± 0.9% vs 4.7 ± 0.8% of *db/db*-Mf alone) in diabetic wounds. In conclusion, NPD1 recovers Mf prohealing and neurotrophic functions impaired by diabetes; Mfs/monocytes treated with NPD1 could be used to restore diabetic wound healing.

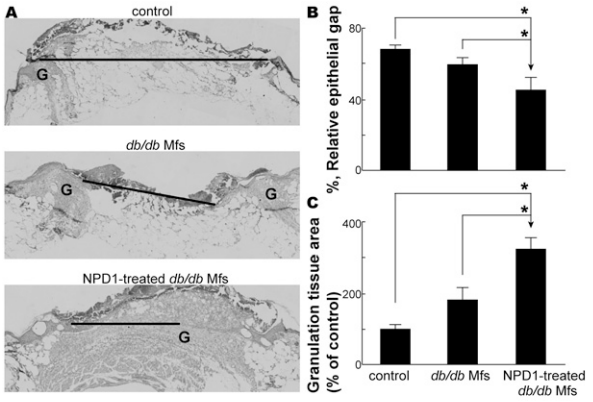


Fig. 1. NPD1 enhanced pro-healing functions of *db/db* Mfs in cutaneous wounds. At day 2 post-wounding (PW) of *db/db* mice, skin excisional-wounds were treated with *db/db* Mfs, NPD1(200 nM)-treated *db/db* Mfs (10^6 cells/wound), or PBS control. **A)** Representative micrographs of HE stained cryosections of wounds. Black bar: epithelial gap; G: granulation tissue. **B)** Relative epithelial gap and **C)** granulation tissue area (n = 8). Data are expressed as mean ± SEM. **P* < 0.05.

Supported by: NIH Grant 1-R01-DK087800 (S.H.)

1054-P

Glycemic Management in Heart Transplantation: Surgical Outcomes

CRISTINA GARCIA, AMISHA WALLIA, SURUCHI GUPTA, KATHLEEN SCHMIDT, SHILPA MALEKAR-RAIAR, DIANA JOHNSON, KATHLEEN GRADY, EDWIN MCGEE, WILLIAM COTTS, ADIN-CRISTIAN ANDREI, MARK E. MOLITCH, *Chicago, IL*

Our objective was to examine the efficacy & safety of intravenous (IV) and subcutaneous (SQ) insulin protocols with glucose (GLU) targets of 80 - 110 mg/dL implemented by a Glucose Management Service (GMS) for diabetic (DM) and non-diabetic (nonDM) patients (pts) undergoing heart transplant (HT).Charts of all 95 HT pts from 6/1/05 - 7/31/09 were analyzed for GLU levels and surgical outcomes for up to 30 days post HT using the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Values are given as mean ± SD and all GLU levels are in mg/dL. Two-sample t-tests, Mann-Whitney U tests and Fischer's exact tests were used as appropriate.All 95 pts were hyperglycemic postop; 3 were excluded from analysis (2 - combined kidney-HT, 1 death within 24h of HT). Of the remaining 92 pts, 26 (28%) had DM prior to HT. For the 92 pts mean GLU levels on IV protocol were 140±21 and on SQ protocol were 141±25. There were no significant differences between the DM and nonDM pts for the mean GLU levels prior to starting IV insulin (DM 248±91, nonDM 258±70), on the IV protocol (DM 146±24, nonDM 138±19) or on the SQ protocol (DM 141±22, nonDM 141±26). On the IV protocol there was no severe hypoglycemia (GLU <40) and 18 (20%) pts had moderate hypoglycemia (>40GLU<60) (7/26[27%] DM, 11/66 [17%] nonDM, p=NS). On the SQ insulin protocol 3 pts had severe & 24 pts had moderate hypoglycemia (7/26 [27%] DM, 17/66 [26%] nonDM, p=NS). There were no significant differences between DM vs nonDM for treated HT rejection episodes (8/26 [31%] vs 18/66 [27%]), reoperation (8/26 [31%] vs 12/66 [18%]), prolonged ventilation >24 hours (10/26 [38%] vs 21/66 [32%]), readmission within 30 days (5/26 [19%] vs 12/65 [18%]), number of ICU hrs (171±126 vs 166±148), hospitalization days after HT (18±11 vs 14±8) or infections (2/26 [8%] vs 4/66 [6%]. There was 1 death > 24 h postop but prior to discharge.IV and SQ protocols can be safely & effectively implemented by a GMS for even the most difficult to control pts, without significant differences in outcomes for those with and without a prior diagnosis of DM.

1055-P

Basal Plus Correction Versus Basal Bolus Insulin Regimen for the Management of Medical and Surgical Patients With Type 2 Diabetes: Basal Plus Trial

GUILLERMO UMPIERREZ, DAWN SMILEY, KATHIE HERMAYER, DARIN E. OLSON, AMNA KHAN, CHRISTOPHER NEWTON, VIVIAN FONSECA, SOL JACOBS, LIMIN PENG, INGRID PINZON, MARIA FEREIRA, ASHWINI GORE, VICKIE HUNT, DAVID REYES, MONICA RIZZO, *Atlanta, GA, Charleston, SC, New Orleans, LA*

This randomized multicenter trial compared the efficacy and safety of a daily dose of glargine plus corrective doses of glulisine (Basal Plus) to a basal bolus and to sliding scale regular insulin (SSI) regimen in general medical and surgical patients with T2DM. A total of 375 patients (age: 59±12 yr, admission BG: 204±83 mg/dl, A1C: 8.4±2.3%, ±SD) with a BG between 140-400 mg/dl and known T2DM were randomized to basal bolus (n=150), basal plus (n=148) and SSI (n=77). Patients in the basal bolus group were started at 0.5 U/kg, given half as glargine once daily and half as glulisine before meals. Basal Plus received 0.25 U/kg of glargine once daily plus correction doses of glulisine before meals for BG>140 mg/dl. SSI was given 4 times/day for BG>140 mg/dl. Basal plus regimen resulted in a similar glycemic control than the basal bolus group. Mean daily BG after day 1 was higher in SSI (172±41 mg/dl) than basal bolus (156±36 mg/dl) and basal plus (163±37 mg/dl), p=0.04. SSI resulted in more treatment failures (defined as >2 consecutive BG>240 mg/dl or a mean daily BG>240 mg/dl) compared to basal plus (19% vs 2%), p<0.001. There were no differences in length of stay or complications including wound infections, pneumonia, respiratory or renal failure and bacteremia between groups (p=NS). A BG <70 mg/dl occurred in 16 % of patients (1.7% of BG readings) in basal bolus, 13% (1.1% of BG readings) in basal plus, and 3% (0.4% of BG readings) in the SSI group, p:<0.02; but there was no difference in BG<40 mg/dl (1% of patients in basal bolus and basal plus and no patients in SSI, p=0.76).In summary, the basal plus regimen with glargine once daily plus correction doses of glulisine before meals resulted in similar glycemic control and frequency of hypoglycemia compared to basal bolus regimen. This randomized controlled trial indicates that basal plus is an alternative to basal bolus regimen in general medicine and surgery patients with T2DM.

Supported by: sanofi-aventis

1056-P

Dapagliflozin Treatment for Type 2 Diabetes Mellitus Patients With Comorbid Cardiovascular Disease and Hypertension

WILLIAM T. CEFALU, LAWRENCE A. LEITER, TJERK W. DEBRUIN, INGRID GAUSE-NILSSON, JENNIFER SUGG, SHAMIK J. PARIKH, *Baton Rouge, LA, Toronto, ON, Canada, Wilmington, DE, Moindal, Sweden*

To assess the benefit/risk of dapagliflozin (DAPA) in patients with type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), 2 trials were conducted. This double-blind study (NCT01031680) assessed DAPA, a selective SGLT2 inhibitor, in patients with HbA1c ≥ 7.0 - ≤ 10.0%, documented CVD and a history of hypertension (HTN). Randomized patients (N=922), aged ≥ 45/50 y (M/F), received 10 mg DAPA or placebo (PBO) for 24 wks added to usual care for T2DM and HTN (80-wk extension is ongoing). Patients receiving insulin (INS) had their randomization dose reduced by 25%. Rescue medication was allowed for glycemic and HTN need. Patients were stratified by age (< 65 or ≥ 65 y), INS use, and time from the most recent qualifying CV event. Mean age was 63±7 y; 42% were ≥ 65 y. Mean T2DM duration was 12 y. At baseline (BL), 40% of patients received 2 oral anti-diabetic agents. INS was used by 52% of patients: by 17% as the only treatment. The most common qualifying CV event was coronary heart disease (75%). Co-primary end points were change in HbA1c and patients (%) with a combined reduction of HbA1c ≥ 0.5%, body weight (BW) ≥ 3% and systolic blood pressure (SBP) ≥ 3 mm Hg. Greater reductions from BL occurred with DAPA vs PBO (P <0.01) in HbA1c (BL 8.1%; -0.4 vs 0.1%), BW (BL 93.1 kg; -2.6 vs -0.3 %) and SBP (BL 133.2 mm Hg; -3.0 vs -1.0 mm Hg). More patients met the 3-item end point for DAPA vs PBO (11.7 vs 0.9%, P <0.0001). The mean daily INS dose change for DAPA was 0.6 IU/d vs PBO 4.3 (10% increase) IU/day; nominal P <0.05. Age-stratified results were similar to overall results, except SBP reduction, which did not differ significantly among patients aged ≥ 65 y. Total AEs and CV events were balanced among groups. Events suggestive of genital infections were more often reported for DAPA vs PBO, and more often seen in women. DAPA, when added to standard of care in a 24-wk study of elderly T2DM patients with comorbid CVD and HTN, did not adversely impact CV safety while improving glycemic and BP control, and reducing body weight.

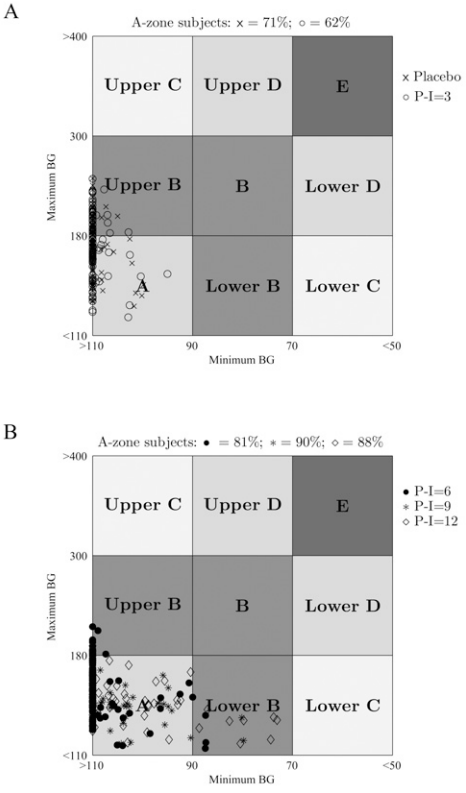
Supported by: AstraZeneca/Bristol-Myers Squibb

1057-P

In Silico Determination of a Pramlintide-Insulin Ratio for Co-Administration in Type 1 Diabetes (T1D)

FRANCESCO MICHELETTO, CHIARA DALLA MAN, BORIS KOVATCHEV, CLAUDIO COBELLI, *Padova, Italy, Charlottesville, VA*

This in silico study aims to determine a fixed pramlintide-insulin (P-I) ratio prior to use of a P-I mixture in clinical trials.A model of pramlintide action on gastric emptying was built using proprietary data for 15 T1D subjects studied twice with a standardized dual-tracer meal on placebo and on P-I mixture of 6µg of pramlintide per unit of insulin (P-I ratio of 6), and was then incorporated in our T1D simulator. Extensive experiments on 100 virtual subjects tested different P-I ratios for efficacy attenuating postprandial hyperglycemia and safety in terms of hypoglycemia. The meal was always 50g carbohydrate (CHO); insulin was given according to individual CHO ratios (CR = grams CHO/unit insulin).Experiment 1: Without adjusting subjects' individual CR for pramlintide use, P-I ratios of 6, 9 and 12 resulted in increased hypoglycemia, with 9%, 11%, and 15% of subjects experiencing glucose levels <50 mg/dl.Experiment 2: CR were individually adjusted for pramlintide to minimize hypoglycemia and the same P-I ratios were administered again. Figure 1A presents Control Variability-Grid Analysis (CVGA) showing that P-I ratio of 3 (o) was no more efficient than placebo (×), with 62% vs. 71% in A-zone. Figure 1B presents P-I ratios of 6 (·), 9 (*), and 12 (◊) resulting in significant improvement of postprandial glucose control: 81%, 90%, and 88% of subjects in CVGA A-zone, respectively, and no hypoglycemia.We conclude that in the clinic: (i) pramlintide dose should be adjusted in parallel with patients' carbohydrate ratio, and (ii) P-I ratio of 9 is likely to be most effective in terms of pramlintide efficacy and safety.

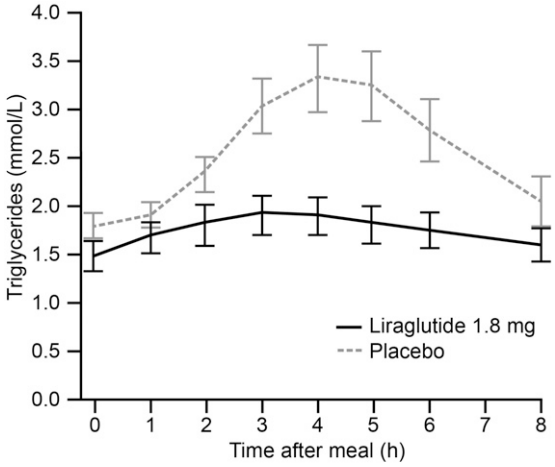


1058-P

Liraglutide Suppresses Postprandial Triglyceride (TG) and Apolipoprotein B48 (ApoB48) Responses to a Fat-Rich Meal in Subjects With Type 2 Diabetes

KJELD HERMANSEN, TINE A. BÆKDAL, MARIA DÜRING, ANNA PIETRASZEK, LENE S. MORTENSEN, KNUD E. KNUDSEN, ANNE FLINT, *Aarhus, Denmark, Bagsvaerd, Denmark, Tjele, Denmark, Søborg, Denmark*

This trial investigated the effect of steady-state 1.8 mg liraglutide compared to placebo on postprandial plasma lipid levels. In a crossover design, subjects with type 2 diabetes (T2DM) (n=20, 53-73 years, BMI 24-39 kg/m^2) were randomly treated for 3 weeks with once-daily liraglutide (weekly dose escalation from 0.6 to 1.8 mg) and placebo. After 3 weeks' treatment, a standardized fat-rich (63%E) meal was served and the effect of liraglutide on TG, free fatty acids (FFA), ApoB48, glycemic responses, and gastric emptying was assessed. After 3 weeks' liraglutide treatment, postprandial TG (Figure) and ApoB48 (incremental $AUC_{0\text{-}8h}$ -0.034, 95%CI [-0.051;-0.018], p=0.0003) decreased significantly compared to placebo. There was no significant difference in overall FFA response (incremental $AUC_{0\text{-}8h}$ (0.31, 95%CI [-0.38;0.99], p=0.3368). Neither method assessing postprandial rate of gastric emptying (paracetamol absorption technique and ^{13}C-octanoate breath test) displayed differences between treatments. Mean postprandial glucose and glucagon responses were significantly reduced and mean body weight was reduced (-1.77 kg [-2.54;-1.00], p<0.0001) after liraglutide treatment. Also, mean low-density lipoprotein and total cholesterol decreased significantly after treatment with liraglutide compared to placebo. Liraglutide was well tolerated. In conclusion, liraglutide treatment in subjects with T2DM significantly reduced postprandial excursions of TG and ApoB48 after a fat-rich meal. The effect was apparently independent of gastric emptying.



Data are mean ±SE.
$iAUC_{0\text{-}8\,h}$ (estimated difference –3.89, 95% CI [–5.83; –1.95], p=0.0008).

1059-P

Insulin Degludec Improves Glycemic Control in Insulin-Naïve Patients With Type 2 Diabetes: Results of a Randomized Pan-Asian Trial

YUKIKO ONISHI, SUNG WOO PARK, SOON JIB YOO, PER CLAUSON, SØREN C. TAMER, YASUHIKO IWAMOTO, *Tokyo, Japan, Seoul, Republic of Korea, Bagsvaerd, Denmark*

This 26-week, open-label, treat-to-target trial compared the efficacy and safety of insulin degludec (IDeg) to insulin glargine (IGlar), both administered once daily in an Asian population. In all, 435 insulin-naïve adults with type 2 diabetes (mean age: 59 yrs, diabetes duration: 11.6 yrs, A1C: 8.5%, FPG: 153.2 mg/dL) were randomized (2:1) to IDeg or IGlar as add-on therapy to stable treatment with ≥1 OAD(s) of which 89% and 93% completed the trial. IDeg was non-inferior to IGlar in improving glycemic control (estimated treatment difference IDeg-IGlar: 0.11% points, [95% CI: -0.03; 0.24]) with A1C reductions of 1.24% (IDeg) and 1.35% points (IGlar). A1C <7% was achieved by ~30% of subjects in both groups without confirmed hypoglycemia (PG <56 mg/dL or ADA defined severe episodes) during the last 12 weeks of treatment (NS). IDeg and IGlar reduced FPG to similar levels: 99.9 and 101.8 mg/dL, respectively (NS). The rate of overall confirmed hypoglycemia was 18% lower with IDeg than with IGlar (3.0 vs. 3.7 episodes/patient yr) during the full trial period (NS) and 37% lower during maintenance (after 16 weeks of treatment); (estimated rate ratio: 0.63 [95% CI: 0.42; 0.94]). The rate of nocturnal confirmed hypoglycemia (00:01-05:59) was 38% lower with IDeg than with IGlar during the full trial period, (0.8 vs. 1.2 episodes/patient yr) and 48% lower during maintenance (both NS). No episodes of severe hypoglycemia were reported with IDeg; one was reported with IGlar. Weight increased by 1.3 kg (IDeg) and 1.4 kg (IGlar) at mean daily doses of 0.28 and 0.35 U/kg, respectively. The overall rates of adverse events were low and similar with IDeg and IGlar, with no treatment-specific patterns. Insulin degludec effectively improves glycemic control in insulin-naïve Asians with type 2 diabetes with lower rates of confirmed hypoglycemic episodes during the maintenance period compared to insulin glargine. This supports findings from global trials including non-Asian patients.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

1060-P

Anti-Hypertensive Effect of Sitagliptin in Japanese Subjects With Type 2 Diabetes (T2DM) and Hypertension (HT)-A Continuous Blood Pressure (BP)-Lowing Effect During One Year

HIROYUKI MOTOSHIMA, MOTOYUKI IGATA, YUKI TAKAKI, TAKESHI MATSUMURA, TATSUYA KONDO, TAKAFUMI SENOKUCHI, SEIYA SHIMODA, TAKESHI NISHIKAWA, EIICHI ARAKI, *Kumamoto, Japan*

Sitagliptin (SITA), a DPP-4 inhibitor, is a tool to reduce blood glucose levels in pts with T2DM. Since GLP-1 has beneficial effects on renal and vascular function, DPP-4 inhibitors may alter blood pressure (BP). To study the effects of SITA on systolic and diastolic BP (SBP and DBP), 40 T2DM pts treated with SITA (50 mg daily) for at least 1 year were included in the present retrospective study (inclusion criteria; no change in anti-diabetic and anti-hypertensive agents for at least 3 month before addition of SITA, and exclusion; addition of any anti-diabetic and anti-hypertensive agents). SITA reduced HbA1c and SBP but not DBP (average of HbA1c, SBP and DBP before and after 3, 6, 12 month were 7.8→7.1→7.0→6.8 (%), 140→130→130→132, and 70→68→70→68 (mmHg), respectively). According to the summation of individual changes in SBP (S = ΔSBP3+ΔSBP6+ΔSBP12) after 3, 6 and 12 month from baseline, subjects were stratified into three groups: gA (S > 15), gB (15 > S > -15) and gC (S < -15). Each group included 18, 21 and 61 % of subjects. In gC, marked reductions in SBP (145→128→127→129 mmHg) and small in DBP were observed (71→65→67→65 mmHg). On the other hand, in gA, increases in SBP were observed after 3 and 12 month. Although no difference was observed in age, sex, BMI, HbA1c, DBP and duration of diabetes between 3 groups, pts in gC had higher SBP and more anti-hypertensive agents at baseline compared with those in gA. A cross-sectional analysis revealed that spot-urinary Na/Cr ratio was higher in pts with SITA compared with those without (2.1 ± 0.9 vs 1.1 ± 0.6, n = 24 each). Our study suggests that SITA reduces SBP and DBP in hypertensive T2DM pts with anti-hypertensive agents, and thus have additional beneficial effects to prevent diabetic complications and atherosclerosis. The mechanisms for SITA-induced BP-lowing effects may in part due to increased urinary Na excretion but should be determined in larger clinical prospective settings.

1061-P

Absence of Calcitonin Response in GLP-1R Knock-Out Mice After Treatment With Lixisenatide

THOMAS KISSNER, LUC ESSERMEANT, JEAN-FRANÇOIS GALLAS, GHISLAINE HADOUR, *Frankfurt, Germany, Montpellier, France*

Proliferative C-cell findings in rodent thyroid have been reported in long-term preclinical studies with GLP-1R agonists. Plasma calcitonin is increased in association with C-cell proliferation in rodents at very high doses and also in shorter-term studies without C-cell proliferation. Using GLP-1R knockout (KO) mice, we investigated the hypothesis that calcitonin release at high lixisenatide doses is mediated via GLP-1R activation. Male and female CD-1 (wild-type) mice and GLP-1R (-/-) KO mice based on CD-1 genetic background were given high SC doses of lixisenatide 1000 µg/kg BID or control vehicle for 14 days (n=8/group). Plasma calcitonin concentration was measured by immunoradiometric assay 2 h after last administration on Day 14. As 50% of calcitonin values were under the lower limit of quantification (10 pg/ml), an exact pairwise Wilcoxon's test was used to analyze between-group differences. In CD-1 mice, lixisenatide treatment resulted in statistically significant higher mean plasma calcitonin concentration *vs* control (Table; p<0.001 for pooled male/female animals). No lixisenatide-induced calcitonin release was noted in GLP-1R (-/-) KO mice (p=NS). In this group, the plasma calcitonin concentration remained low and similar to values observed in CD-1 and control KO mice. Moreover, at this dose level, no C-cell proliferation was seen in studies up to 3 months in wild-type mice. In summary, the absence of lixisenatide induced calcitonin release in GLP-1R (-/-) KO mice, in contrast to wild-type mice, suggests that the GLP-1R is involved in the rodent thyroid pathway of C-cell activation and calcitonin release.

Mean calcitonin levels in CD1 (wild-type)- and GLP-1R (-/-) KO mouse plasma on Day 14

Animal strain and treatment	Gender	Calcitonin concentration (pg/mL) on Day 14 (Mean ± SD)
CD-1 (wild-type), control vehicle	Female (n=6) Male (n=2)	13.3 ± NA 7.5 ± NA
CD-1 (wild-type), lixisenatide 1000 µg/kg BID	Female (n=5) Male (n=3)	99.8 ± 50.9 86.6 ± 29.8
GLP-1R (-/-) KO, control vehicle	Female (n=6) Male (n=2)	10.7 ± NA 16.3 ± N A
GLP-1R (-/-) KO, lixisenatide 1000 µg/kg BID	Female (n=5) Male (n=3)	6.1 ± NA 14.9 ± 8.7

For values below the lower limit of quantification (LLOQ), a value of half LLOQ was used to calculate the mean.
NA - Not applicable as either all values or more than 50% of value were below the LLOQ; SD - standard deviation

Supported by: sanofi-aventis

1062-P

The Effect of Luseogliflozin (TS-071), a Selective SGLT2 Inhibitor, on Pharmacodynamics and Pharmacokinetics in Japanese Type 2 Diabetic Subjects With Renal Impairment

MASAKAZU HANEDA, YUTAKA SEINO, TAKASHI SASAKI, ATSUSHI FUKATSU, YOSHISHIGE SAMUKAWA, SOICHI SAKAI, YURI SATO, TAKASHI WATANABE, *Hokkaido, Japan, Osaka, Japan, Tokyo, Japan, Aichi, Japan*

SGLT2 inhibition is known as a new approach for the treatment of type 2 diabetes mellitus (T2DM). Luseogliflozin (LUSEO) is a highly selective inhibitor of SGLT2. This study was conducted to evaluate the effect of LUSEO on urinary glucose excretion and plasma glucose levels, the pharmacokinetics, and safety in Japanese T2DM subjects with renal impairment.Japanese T2DM subjects with normal renal function (NRF [eGFR (mL/min/1.73m^2)] 90-), and mild (G2 [eGFR 60-89]), moderate (G3 [eGFR 30-59]), and severe (G4 [eGFR 15-29]) renal impairment received a single oral dose of LUSEO (5 mg) before breakfast (n = 57). Pharmacodynamic parameters were measured for comparing the values before and after administration of LUSEO, and pharmacokinetic parameters were measured between administration groups. Mean 24-hour urinary glucose excretion (UGE) was significantly increased from baseline levels in all groups (ΔUGE (g, mean ± SD): NRF: 88.3 ± 36.9, G2: 69.7 ± 19.1, G3: 45.3 ± 16.8, G4: 21.8 ± 7.1). The values of postprandial plasma glucose (PPG: 2 hours after breakfast) were significantly decreased from baseline levels in all groups, except G4 (ΔPPG (mg/dL): NRF: -49.3 ± 33.6, G2: -33.6 ± 27.1, G3: -24.4 ± 34.7, G4: -3.3 ± 32.1). Moreover, the values of fasting plasma glucose (FPG) 24 hours after administration of LUSEO were also significantly decreased from baseline levels in all groups, except G4 (ΔFPG (mg/dL): NRF: -28.7 ± 22.0, G2: -16.2 ± 18.3, G3: -7.7 ± 13.4, G4: 10.3 ± 12.1). Systemic exposure (AUCinf of plasma LUSEO concentration) was comparable among all groups. No serious adverse event or renal/urinary tract adverse event was observed during the study period.In conclusion, LUSEO may be effective and may not require dose adjustment in the treatment of T2DM subjects even with mild to moderate renal impairment. A long-term clinical trial to assess the efficacy of LUSEO in T2DM subjects with moderate renal impairment is in progress.

1063-P

Single-Dose Pharmacokinetics (PK) and Glucodynamics (GD) of the Novel, Long-Acting Basal Insulin LY2605541 in Healthy Subjects

VIKRAM P. SINHA, DANIEL C. HOWEY, DANNY KWANG WEI SOON, SIAK LENG CHOI, KENNETH F. MACE, KWEE POO YEO, SHUFEN T.H. LIM, *Indianapolis, IN*

Basal insulin LY2605541 (LY) is PEGylated insulin lispro designed to have a large hydrodynamic size which delays insulin absorption and reduces clearance, resulting in prolonged duration of action.Two Phase 1 open-label studies have characterized the PK, GD, safety, and tolerability of LY in healthy subjects during the euglycemic glucose clamp. In Study 1 (a single ascending-dose crossover design), 33 subjects (29 M/4 F; mean [SD] age, 34.3 [10.5] yrs) received subcutaneous (SC) doses of LY (0.1-20 nmol/kg) and insulin glargine (GL; 0.5 and 0.8 U/kg) followed by a clamp for up to 24 or 36 h. In Study 2, the absolute bioavailability of LY was assessed in 8 male subjects (mean [SD] age, 37.1[12.5] yrs) who received an i.v. dose (0.5 nmol/kg) and SC dose (6 nmol/kg) of LY followed by a clamp for up to 24 h.The LY C_{max} and AUC increased in a greater than dose proportional manner. The medians for t_{max} and geometric means for $t_{1/2}$ and apparent clearance (CL/F), respectively, ranged from 18.0-42.0 h, 24.4-45.5 h, and 1.8-2.8 L/h for SC LY and from 10.0-12.0 h, 12.2-14.9 h, and 51.4-65.2 L/h for SC GL. The LY duration of action based on glucose infusion rate (GIR) mirrored the PK profile; the GIR profiles were sustained for at least 36 h. In contrast, the GL PK and GIR profiles waned at 24 h and suggested a peak effect at 12-14 h that increased with dose. After i.v. administration the geometric mean $t_{1/2}$ of LY was 2.3 h, and absolute bioavailability was 73% (90% CI, 60-88%). The LY intrasubject variability (CV%) was <18% for PK and <32% for GD.There were no clinically significant changes in laboratory tests, vital signs, ECGs, or anti-LY antibodies. The most common adverse events (AEs) were related to study procedures, and all AEs were mild to moderate in severity.LY has low intrasubject variability and a basal profile that is amenable to once daily dosing. Through both delayed absorption and reduced clearance, the LY serum concentration-time profile and duration of action are prolonged compared to GL.

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

1064-P

Low-Dose (15 mg/day) Pioglitazone Treatment Improves Glycemic and Sub-Inflammatory State in Obese Type 2 Diabetic Subjects in 24 Week Intervention Study

GIUSEPPE DANIELE, ZANDRA PEREZ-CADENA, ALBERTO CHAVEZ-VELASQUEZ, SUBHASH KAMATH, PENGUO ZUO, ZHI CHANG, FRANCESCO ANDREOZZI, ANA M. PAEZ, MARCEL FOURCAUDOT, DEIDRE WINNIER, RUTH ARYA, ANDREA HANSIS-DIARTE, CHRISTOPHER JENKINSON, PAOLO FANTI, AMALIA GASTALDELLI, RALPH DEFRONZO, DEVJIT TRIPATHY, FRANCO FOLLI, *San Antonio, TX, Pisa, Italy, Catanzaro, Italy*

Obesity and type 2 diabetes (T2D) are characterized by systemic inflammation. Pioglitazone (PIO) is an insulin sensitizer but its use may be limited by weight gain and fluid retention at higher doses (30-45mg/day). We tested the hypothesis that low dose PIO (15 mg/day) vs placebo (PCB) for 6 months (-m), improves glycemic and inflammatory state without known side effects. We studied 20 patients with T2D (BMI: 33.5±1.3 Kg/m^2, FPG: 145±8 mg/dl, A1c:7.5±0.3%) randomized to PIO (n=11) or PCB (n=9). All T2D subjects received dietary counseling during the study and did not stop their previous treatment (metformin/sulfonylurea). An OGTT and euglycemic-hyperinsulinemic clamp were performed both at baseline and 6 months after treatment. Inflammatory markers (TNF-α, MCP-1, IL-6) were measured during the OGTTs and clamps, and at 1, 3, 5 and 6 months. A group of 18 non diabetic subjects (BMI: 32.2±1.4 Kg/m^2, FPG: 100±2 mg/dl, A1c: 5.6±0.1%) was used as controls (CT). PIO treatment, but not PCB, significantly improved FPG (-14% vs -5%), A1c (-7% vs -3%) and insulin sensitivity (+0.9 vs +1.1 mg/kg min); all p<0.02 vs baseline, p=ns vs PCB. At baseline, cytokine levels of PIO were comparable to PCB (TNF-α: 16.5±2 vs 16.1±2, MCP-1: 478±38 vs 403±58, IL-6: 3.8±0.5 vs 3.6±0.9 pg/ml, p=ns) but higher than in CT (TNF-α: 9.0±0.7, MCP-1: 224±23, IL-6: 2.9±0.1 pg/ml; all p<0.05 vs T2D). During the 6-m treatment, low dose PIO prevented the increase in both MCP-1 (1-m: 379±63 vs 544.1±63; 3-m: 355±45 vs 525±48, p:002, at 5-m: 395.2±48 vs 499.4±36, all p<0.02; 6-m: 360.4±48 vs 429.1±52 pg/ml, p=ns) and in IL-6 (1-m: 4.0±0.9 vs 10.3±3.0, 3-m: 3.6±0.9 vs 12.9±4.1, 5-m: 6.2±1.4 vs 9.0±2.9, all p<0.01, 6-m: 3.6±0.8 vs 4.3±0.7 pg/ml, p:ns) compared to PCB. TNF-α did not change. In conclusion, low dose PIO improves glucose profile and prevents deterioration of inflammatory state in obese T2D.

Supported by: Takeda Pharmaceuticals North America, Inc. Clinical Trial: NCT01223196

1065-P

Lixisenatide Does Not Induce Thyroid C-Cell Proliferation in Mice after 3-Month SC Bolus or Continuous Infusion

THOMAS KISSNER, MANUELA STOLTE, MARTINA DORAU, FELIX CHEVALIER, *Frankfurt/Main, Germany*

In preclinical safety studies, some glucagon-like peptide-1 receptor (GLP-1R) agonists have been shown to induce proliferation of rodent thyroid C-cells. Whether this is a class effect in rodents or a ligand-specific phenomenon has not been elucidated. In subchronic studies, the response is quantitatively different between specific compounds, which may relate to different drug kinetics. Liraglutide once daily SC bolus for 9 wk induces focal C-cell hyperplasia (FCCH) in mice, whereas exenatide twice daily SC bolus for 12 wk does not induce FCCH, but does when given as a continuous infusion. The effect of the GLP-1R agonist lixisenatide on FCCH was investigated in CD-1 mice in 2 studies: 1) 1000 µg/kg BID SC bolus for 13 wk, and 2) 2000 µg/kg/day continuous infusion via osmotic mini-pump for 12 wk; control animals received vehicle. At the end of treatment, thyroid glands (n=10 per sex) were examined for FCCH using hematoxylin and eosin staining and immunohistology of Ki-67 (cell proliferation marker). Also, total RNA was isolated from thyroid tissue to determine gene expression of proliferation markers Ccnd1, Ccnd2, Ccnd3, C-myc, Bcl-xL, p21 and p27. In both studies, no lixisenatide-related macroscopic or microscopic findings in the thyroid glands were observed and no proliferation of C-cells was detected by immunohistochemistry. Gene expression analysis for proliferation markers showed no lixisenatide-related changes in either study (Table). Thus, lixisenatide does not appear to be associated with proliferative thyroidal effects after SC bolus or continuous infusion over 3 months in mice.

Summary of thyroid C-cell proliferation findings in mice

	Lixisenatide SC bolus injection 1000 µg/kg BID 13 weeks	Lixisenatide SC continuous infusion 2000 µg/kg/day 12 weeks
Thyroid microscopy (H&E staining)	No proliferation	No proliferation
Thyroid Immunohistology (Ki-67)*	No proliferation	No proliferation
Proliferation marker gene expression (mean fold-change *vs* control)†	No relevant changes:	No relevant changes:
Ccnd1	+1.32 (M), -1.27 (F)	+1.53 (M), -1.15 (F)
Ccnd2	-1.01 (M), -1.33 (F)	+1.14 (M), -1.05 (F)
Ccnd3	-1.19 (M), +1.02 (F)	+1.03 (M), -1.02 (F)
C-myc	-1.18 (M), -1.10 (F)	+1.17 (M), +1.07 (F)
Bcl-xL	-1.09 (M), -1.01 (F)	+1.23 (M), +1.04 (F)
p21	+1.08 (M), -1.15 (F)	-1.11 (M), +1.15 (F)
p27	-1.10 (M), -1.19 (F)	+1.26 (M), -1.10 (F)

*With calcitonin double-staining; †Control value = 1-fold (ie, +/- 1 is not different from control);
F=female mice; M=male mice; H&E= hematoxylin and eosin
Ccnd1= Cyclin D1; Ccnd2=Cyclin D2; Ccnd3=Cyclin D3; C-myc=myelocytomatosis oncogene;
Bcl-xL=Bcl2-like protein 1, B-cell lymphoma extra large; p21=cyclin-dependent kinase inhibitor 1A, Cip1;
p27=cyclin-dependent kinase inhibitor 1B, Kip1

Supported by: sanofi-aventis

1066-P

GLP-1 Analog Improved BNP through Improvement in Myocardial Diastolic Dysfunction

YUUKI MATSUMOTO, KUNIMASA YAGI, JUNJI KOBAYASHI, AZUSA OHBATAKE, SATOKO OKAZAKI, NAOKO ITO, KAORU NAKANO, YOSHIYUU TAKEDA, MASAKAZU YAMAGISHI, *Kanazawa, Japan*

Myocardial diastolic dysfunction is known to occur in an early stage of diabetes, resulting in chronic heart failure.Some basic researches have shown that GLP-1 analog (GLP-1a) enhances the vascular smooth muscle cell relaxation through improving the endothelial dysfunctional especially deteriorated NO production.Recently, several clinical studies have shown that GLP-1a treatment suppressed cardiovascular events including heart failure more effectively than insulin treatment in diabetics. This prompted us to speculate that GLP-1a improves myocardial diastolic dysfunction, and thus we performed this study.Study subjects were 36 type 2 diabetics introduced liraglutide (Lir). Clinical features of the whole subjects were as below; M/F 22/14, age 64.9±13.0 yrs, duration of diabetes 18.6±13.2 yrs, BMI 25.5±5.4 kg/m^2, sBP 124±17 mmHg, dBP 69±11 mmHg. We evaluated HbA1c and BNP before and after Lir introduction. In 9 subjects (M/F 5/4), we also evaluated UCG parameters for diastolic dysfunction including E/A, DcT, E/E', and EF in UCG before and after Lir introduction.HbA1c was improved from 7.28±1.16% to 6.81±0.74% (p<0.01). BNP was also improved from 46.2±63.3 pg/ml to 32.5±45.9 pg/ml (p= 0.017). No significant changes were observed in blood pressures. In subjects who received UCG examination, E/E', which is the most reliable parameter for myocardial diastolic dysfunction, was improved significantly from 14.4±3.0 to 11.1±3.3 (p< 0.01). Other UCG indices did not show significant changes including EF.Based on the above findings, we suggest that GLP-1a improved BNP possibly through improvement in diastolic dysfunction without changing systolic function.

1067-P

The Effect of Hepatic Impairment on the Pharmacokinetics, Safety and Tolerability of Empagliflozin, a Potent Sodium Glucose Cotransporter-2 Inhibitor

SREERAJ MACHA, PETER ROSE, MICHAELA MATTHEUS, RODICA M. CINCA, SABINE PINNETTI, ULI C. BROEDL, HAN J. WOERLE, *Ridgefield, CT, Biberach, Germany, Ingelheim, Germany, Timisoara, Romania*

Empagliflozin is a potent and selective sodium glucose cotransporter-2 inhibitor in development for the treatment of type 2 diabetes mellitus. This open-label, parallel-group study investigated the effect of various degrees of hepatic impairment on the pharmacokinetics, safety, and tolerability of empagliflozin. Thirty-six subjects (8 each with mild, moderate or severe hepatic impairment according to Child-Pugh classification, and 12 matched controls with normal hepatic function) received a single 50 mg dose of empagliflozin. Mean (range) age was 53.9 (33-71) years and 17 subjects were male. Empagliflozin was rapidly absorbed and, after reaching peak levels, plasma drug concentrations declined in a biphasic fashion. Compared with subjects with normal hepatic function, geometric mean ratios (90% CI) of $AUC_{0-\infty}$ and C_{max} were 123.15% (98.89-153.36) and 103.81% (82.29-130.95), respectively, in patients with mild hepatic impairment, 146.97% (118.02-183.02) and 123.31% (97.74-155.55), respectively, in patients with moderate hepatic impairment, and 174.70% (140.29-217.55) and 148.41% (117.65-187.23), respectively, in patients with severe hepatic impairment. Adverse events (AEs) were reported in 0, 3 and 2 subjects with mild, moderate and severe hepatic impairment, respectively, and 6 subjects with normal hepatic function. All AEs were mild or moderate in intensity. In conclusion, empagli-

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

flozin was well tolerated in subjects with hepatic impairment. The increase in empagliflozin exposure was less than 2-fold in patients with impaired liver function, therefore no dose adjustment of empagliflozin is required in these patients.

Supported by: Boehringer Ingelheim

1068-P

Comparison of Efficacy and Safety of Coadministration of Sitagliptin and Low-Dose Pioglitazone With High-Dose Pioglitazone Monotherapy

VIVIAN FONSECA, HELMUT STEINBERG, ROBERT R. HENRY, BART STAELS, MARGARET Z. CHOU, RUJUN TENG, GREGORY T. GOLM, RONALD B. LANGDON, KEITH D. KAUFMAN, BARRY J. GOLDSTEIN, *New Orleans, LA, Whitehouse Station, NJ, San Diego, CA, Lille Cedex, France*

Pioglitazone (Pio), an insulin sensitizing agent, is associated with adverse effects (AEs) such as edema and congestive heart failure that are potentially dose-dependent. The incidence of bladder cancer has also been reported in epidemiologic studies to be potentially dependent on Pio dose and cumulative exposure. Use of lower doses of Pio with a second agent may minimize incidence of these AEs while providing comparable glycemic control. We compared the efficacy and safety of Pio 15 mg/day + sitagliptin (Sita) 100 mg/day (Pio/Sita 15/100) *vs* monotherapy with Pio 30 mg, Pio/Sita 15/100 *vs* Pio 45 mg, and Pio/Sita 30/100 *vs* Pio 45 mg, using data from a study that also included groups receiving Sita 100 mg, Pio 15 mg, and Pio/Sita 45/100 mg. The key efficacy endpoints were change from baseline in A1C (ΔA1C), fasting plasma glucose (ΔFPG), and 2-hour post-meal glucose (ΔPMG) after 24 weeks of treatment. Change in body weight (ΔBW), as well as incidences of adverse events of edema and symptomatic hypoglycemia, were prespecified safety parameters of special interest. Comparison of ΔA1C between Pio/Sita 30/100 mg and Pio 45 mg was prespecified; all other comparisons were *post hoc*. Combinations of low-dose Pio with Sita generally produced greater glycemic improvements than higher doses of Pio (Table). Incidences of AEs of edema and symptomatic hypoglycemia, as well as ΔBW, were generally similar in these comparisons. In conclusion, the combination of Sita with lower-dose Pio provides equal or better glycemic control than higher-dose Pio and is generally well tolerated.

	A1C (%)		FPG (mg/dL)		2-h PMG (mg/dL)	
Treatment group [mg/day] (n)	baseline mean	ΔA1C	baseline mean	ΔFPG	baseline mean	ΔPMG
Pio 30 (158–181)	8.9	−1.2	181	−30	259	−53
Pio 45 (136–171)	8.7	−1.2	181	−37	250	−67
Pio/Sita 15/100 (149–179)	8.8	−1.5	184	−41	249	−69
Pio/Sita 30/100 (143–173)	8.7	−1.6	180	−47	251	−85
Comparison	Df in LS-means	p-value	Df in LS-means	p-value	Df in LS-means	p-value
Pio/Sita 15/100 vs Pio 30	−0.3	0.008	−11.1	0.018	−16.7	0.029
Pio/Sita 15/100 vs Pio 45	−0.3	0.007	−3.6	0.444	−2.6	0.743
Pio/Sita 30/100 vs Pio 45	−0.4	<0.001	−9.5	0.045	−18.9	0.019

Df = difference; negative between-group differences favor superiority of combinations. LS = least squares

1069-P

Effects of Gender and Age on the Pharmacokinetics and Pharmacodynamics of Luseogliflozin (TS-071), a Selective SGLT2 Inhibitor

TAKASHI SASAKI, YUTAKA SEINO, YOSHISHIGE SAMUKAWA, SOICHI SAKAI, TAKASHI WATANABE, *Tokyo, Japan, Osaka, Japan*

Luseogliflozin (LUSEO) is a selective SGLT2 inhibitor. Studies to evaluate the possible effects of gender and age on the pharmacokinetics (PK) and pharmacodynamics (PD) of LUSEO were undertaken.An open label single dose study was conducted in healthy elderly male and female Japanese subjects (65-88 years). Subjects received a single 5 mg dose of LUSEO before breakfast and the PK (blood and urine sampling) of LUSEO and PD (urinary glucose excretion (UGE)) were characterized for 24 hours under hospitalization. Safety assessments included recording of adverse events, vital signs, ECG and clinical laboratory tests. Age-related effects were assessed by comparison to results of single and multiple dose (5 mg) studies previously conducted in healthy adult Japanese males (21-38 years).No AEs, laboratory abnormalities, or abnormal changes in vital signs or ECGs were observed. PK profiles of LUSEO (including its metabolites) and UGE were comparable between elderly males and females (Table 1). In healthy elderly and adult male subjects, systemic exposure of LUSEO was comparable as measured by Cmax and AUC_{0-24}. However, the amount of glucose excreted in the urine in elderly male subjects was approximately 26% lower than in adult male subjects. The reduction in UGE observed in elderly subjects correlates well with the decrease in estimated glomerular filtration rate (eGFR).

Table 1. Demographic, PK and PD Parameters (mean ± SD)

	Elderly Female	Elderly Male	Adult Male
N	12	12	16
Age (years)	71.4 ± 4.9	71.2 ± 6.3	27.9 ± 5.2
eGFR (mL/min/1.73m^2)	77.6 ± 11.9	69.9 ± 9.3	101.7 ± 12.9
Cmax (ng/mL)	265 ± 72.0	248 ± 55.9	209 ± 51.2
AUC_{0-24} (ng·hr/mL)	1790 ± 196	1670 ± 225	1530 ± 231
UGE_{0-24} (g)	37.4 ± 6.3	42.0 ± 7.9	57.0 ± 8.5

In conclusion, while dose adjustment of LUSEO is not necessary for age, gender or renal function from the standpoint of PK parameters, effects on UGE of LUSEO may decrease with reduction in renal function (eGFR).

1070-P

Insulin Treatment of Hyperglycemia in Hospitalized Patients Receiving Total Parenteral Nutrition (TPN)

DAVID BALDWIN, KELLY KINNARE, BORIS DRAZNIN, STACEY A. SEGGELKE, JAMES KRINSLEY, SHRUTI GANDHI, VIRAJ BHALANI, SUSAN BRAITHWAITE, CHITRA SRINIVASAN, KATIE HEINTZ, KATHLEEN DUNGAN, JENNIFER BERNARD, ADRIENNE EDGREN, JOSEFINA DIAZ, MEGAN ARONSON, ADRIENNE BARNOSKY, MARYANN EMANUELE, *Chicago, IL, Denver, CO, Stamford, CT, Evanston, IL, Columbus, OH, Maywood, IL*

The ideal strategy for using insulin (I) to achieve blood glucose (BG) control in hospitalized patients receiving TPN is uncertain. We collected data from 111 patients in 8 medical centers who required I to treat TPN associated hyperglycemia for ≥3 days. 39% had a previous history of DM; 77% had surgery during the hospital stay, and 48% received care in an ICU. All BG values, I doses, TPN dextrose doses, and episodes of hospital-acquired infection were collected. Daily insulin ordering was managed in 20% of patients by a TPN team, 19% by an endocrinology team, and 61% by primary teams. A mean of 6.7 days of data was collected per patient. A mean of 8.4% of patients received an IV I infusion with mBG 146±49 mg/dl. A mean of 65% of patients had I added to the TPN solution and 68% of these also received extra doses of subcutaneous (SQ) I. Their mBG was 162±59 mg/dl. 40% of patients only received SQ rapid acting I on day 1, and this decreased to a mean of 10% by day 5. Their mBG was 178±61 mg/dl. A mean of 9% of patients received only SQ long-acting I, and their mBG was 187±78 mg/dl. BG control was significantly better using IV I or I added to TPN as compared with the SQ insulin groups P<. 001. A mean of 1 unit I was given per 14 g of TPN dextrose on day 1, but increased to 1 unit per 10 g by day 7. 19 patients had 40 episodes of BG < 70 mg/dl. 43% of IV I, 11% of I added to TPN, 10% of SQ short-acting I, and 50% of SQ long-acting I experienced a BG < 70 mg/dl. 31% of patients developed a new infection during the hospital stay. Their mBG was 162±57 mg/dl as compared with a mBG 168±63 mg/dl in the patients who did not develop infection p=.02In summary IV I infusion achieved the lowest mBG level. I added to TPN with or without supplemental SQ I yielded the best combination of BG control and a low risk of hypoglycemia. The sole use of short or long-acting SQ I was significantly less effective. Future study is needed to see if further lowering of mBG can safely be achieved and if that intervention could reduce the rate of developing infections in TPN treated patients.

1071-P

Dapagliflozin as Add-On Therapy to Sitagliptin With or Without Metformin: A Randomized, Double-Blind, Placebo-Controlled Study

SERGE JABBOUR, ELISE HARDY, JENNIFER SUGG, SHAMIK PARIKH, *Philadelphia, PA, Wilmington, DE*

Dapagliflozin (DAPA) is a selective sodium glucose co-transporter 2 (SGLT2) inhibitor in development for the treatment of type 2 diabetes. DAPA reduces hyperglycemia through an increase in urinary glucose excretion. In this 24-week, randomized, double-blind, placebo (PBO) controlled study (NCT00984867) with a 24-week blinded extension period, 452 patients with inadequate glycemic control on a stable DPP-4 inhibitor± metformin (MET) received DAPA 10 mg QD or PBO plus sitagliptin (SITA; 100mg QD) ± MET (≥ 1500 mg QD). At week 24 glycemic measures (HbA1c, fasting plasma glucose - FPG) and body weight (BW) were improved with DAPA and statistically significant versus PBO (LOCF, P<0.0001). Adverse events were balanced between groups and discontinuation rates were low. At week 24, events of genital and urinary tract infection were more frequent with DAPA (9.3% and 5.8%) than with PBO (0.4% and 3.5%).Over 48 weeks 31.8% of subjects receiving DAPA were discontinued or rescued for failing to achieve glycemic targets compared with 56.6% with PBO. Whether the data after rescue were excluded (Table) or included, glycemic and weight benefits observed at

week 24 were maintained through week 48 (Table) and similar results were observed when the data were stratified by background therapy.

		PBO corrected change with DAPA 10mg/day (Excluding data after rescue)[a]		
Background therapy		DAPA overall	Stratum: SITA monotherapy	Stratum: SITA + MET
		PBO N=224 DAPA N=223	PBO N=111 DAPA N=110	PBO N=113 DAPA N=113
HbA1c % (SE)	24 weeks	-0.46 (0.09)	-0.55 (0.15)	-0.39 (0.10)
	48 weeks	-0.68 (0.10)	-0.85 (0.20)	-0.59 (0.11)
FPG mg/dL (SE)	24 weeks	-23.3 (3.1)	-24.0 (4.2)	-22.9 (4.5)
	48 weeks	-33.1 (4.3)	-39.9 (8.1)	-30.0 (4.7)
BW kg (SE)	24 weeks	-2.03 (0.29)	-1.86 (0.39)	-2.04 (0.43)
	48 weeks	-2.22 (0.39)	-2.23 (0.54)	-2.07 (0.57)

[a]Longitudinal repeated measures analysis.

Supported by: AstraZeneca/Bristol-Myers Squibb

Clinical Diabetes/ Therapeutics **POSTERS**

1072-P

Long-Term Combination Treatment With Linagliptin and Telmisartan in Hypertensive Rats: Effect on Blood Pressure and Oxidative Stress

MARKUS L. ALTER, KAROLINE VON WEBSKY, LYUBOV CHAYKOVSKA, MARGARETE HOHMANN, OLEG TSUPRYKOV, BARBARA KUTIL, ROBIN KRAFT, THOMAS KLEIN, BERTHOLD HOCHER, *Berlin, Germany, Potsdam, Germany, Zurich, Switzerland, Biberach, Germany*

Many patients with type 2 diabetes concomitantly suffer from hypertension and may be treated with angiotensin receptor blockers (ARB). Dipeptidyl peptidase (DPP)-4 inhibitors are reported to interact with ARB and alter systolic blood pressure (SBP). We tested the effects of the DPP-4 inhibitor linagliptin on SBP and heart morphology, alone and in combination with the ARB telmisartan, in the 2-kidney, 1-clip (2K1C) hypertensive rat model. Male Wistar rats (n=57) were randomized into 4 groups after unilateral renal artery stenosis was set by surgery (2K1C): telmisartan (10 mg/kg/d in drinking water), linagliptin (89 ppm in chow), linagliptin+telmisartan, and vehicle. A total of 15 rats underwent sham surgery. SBP was assessed 6 times during the 16-week study. 2K1C caused a significant increase in SBP compared with sham rats, as measured by $AUC_{(0\text{-}112d)}$ (17126±1975 mmHg*d vs. 12616±659 mmHg*d; p<0.001). Telmisartan alone normalized SBP (13526±2675 mmHg*d), while the combination of linagliptin+telmisartan further reduced SBP (11970±1542 mmHg*d; p<0.001 vs. vehicle). Heart weight and myocyte diameter were significantly higher in 2K1C versus sham rats, an effect which was abolished by telmisartan with or without linagliptin. Of note, plasma levels of oxidized low-density lipoprotein, a marker of oxidative stress, were significantly higher in 2K1C than in sham rats ($AUC_{(0\text{-}112d)}$: 2187±902 ng/ml*d vs. 1479±455 ng/ml*d; p<0.05). This increase was prevented by linagliptin alone (1528±667 ng/ml*d) and in combination with telmisartan (1599±553 ng/ml*d; both p<0.05 vs. 2K1C), but not by telmisartan alone (1836±483 ng/ml*d; n.s. vs. 2K1C). In conclusion, DPP-4 inhibition with linagliptin does not abolish the SBP-lowering effects of telmisartan in this model. Moreover, linagliptin may have additional positive effects on oxidative stress independent of blood pressure control.

Supported by: Boehringer Ingelheim

1073-P

GLP-1 Receptor Agonist (GLP1ra) and Insulin Efficacy in Primary Health Care

GILLIAN C. HALL, ALEX D. MCMAHON, MARIE-PAULE DAIN, EDWARD WANG, PHILIP D. HOME, *London, United Kingdom, Glasgow, United Kingdom, Paris, France, Bridgewater, NJ, Newcastle, United Kingdom*

Clinical trials have shown greater weight reduction in GLP1ra versus insulin use. We investigated HbA_{1c} and weight change in usual UK care.People using 2-3 oral glucose lowering drugs (OGLDs) were grouped by first ever GLP1ra (exenatide, liraglutide) or insulin (glargine, detemir, NPH). Mean change in HbA_{1c} and weight were compared between groups adjusting for baseline (BL) weight, BMI, HbA_{1c}, age, diabetes duration, gender, prior and BL OGLD number, eGFR, and severe gastrointestinal and microvascular disease. Data were from the THIN observational database (2007-2011).BL characteristics of the GLP1ra (1123) versus insulin (1842) groups were HbA_{1c} 78 vs 84 mmol/mol (9.3 vs 9.8 %), weight 112 vs 89 kg, BMI 38 vs 31 kg/m^2; 17% vs 55% began therapy pre-2009. The GLP1ra group was younger, had shorter diabetes duration, less microvascular disease or heart failure, higher eGFR, and more prior and BL OGLD use. HbA_{1c} reduction was less on GLP1ra (6.5 vs 13.4 mmol/mol (0.6 vs 1.2 %) at 1 year (n =366 vs 892); after adjustment the mean difference was not statistically significantly (unadjusted -6.9 (95%CI -9.3, -4.5), adjusted (AMD) -1.7 (-4.1, 0.8) mmol/mol) except in the highest BL HbA_{1c} fifth (>96 mmol/mol (10.9 %): AMD -16.7 (-26.2, -7.2) mmol/mol). The GLP1ra group lost weight (-4.5 vs +1.5 kg: AMD 4.4 (3.5, 5.4)) at 1 year (n= 335 vs 634). In both groups higher BL HbA_{1c} gave poorer weight and better HbA_{1c} reduction (all p<0.01); higher BL BMI improved weight change (GLP1ra p<0.05, insulin p<0.01). A UK 6 month target reduction for GLP1ra of 10.9 mmol/mol (1.0 %) HbA_{1c} and 3% weight was reached by 22%, with mean loss of 4.2 kg at 6 months and 4.5 kg at 1 year.Compared to starting basal insulin, a different group starts a GLP1ra, including having higher weight and better glycemic control, and has weight loss but no difference in HbA_{1c} reduction after adjustment unless BL HbA_{1c} is very high. Heavier people lose more weight but benefit less in glycemic control, which improves most with high BL HbA_{1c}. The UK 6 month GLP1ra target was often not reached.

Supported by: sanofi-aventis

1074-P

Experience of Three-Times-Daily Biphasic Insulin Aspart in Clinical Practice: Results from the A_1chieve Study

MOHAMMAD E. KHAMSEH, MOHAMMAD I. HASAN, ZANARIAH HUSSEIN, PRADANA SOEWONDO, JIAN-WEN CHEN, WENYING YANG, *Tehran, Islamic Republic of Iran, Lahore, Pakistan, Putrajaya, Malaysia, Jakarta, Indonesia, Zurich, Switzerland, Beijing, China*

A_1chieve was a non-interventional study evaluating the safety and clinical effectiveness of insulin analogs in people with type 2 diabetes (n=66 726) in routine clinical care in 28 countries across four continents. This A_1chieve subgroup analysis included 1033 patients who received twice-daily (BID) biphasic insulin aspart 30 (premix 30) and were then intensified to three-times-daily (TID) premix 30 during the 24-week study period.Mean age of the group was 56.4 (SD 12.2) years and diabetes duration 9.1 (6.6) years. At baseline, 833 (80.6%) of this subgroup were receiving oral glucose-lowering drugs. Glycemic control was not to target at baseline (mean [SD] A1C and fasting plasma glucose [FPG] were 9.8 [1.9] % and 204.5 [67.9] mg/dl respectively). Both improved significantly following increased insulin dose/frequency, with significant reductions in post-breakfast plasma glucose level across the global regions being indicative of the mealtime effect of premix 30 (Table). Overall, a reduction in incidence of hypoglycemia from 4.28 to 3.76 events/person-year was observed by 24 weeks. However, hypoglycemia varied considerably by region. There was a small overall increase in nocturnal events associated with TID dosing. Change in body weight from baseline varied by region but was generally minimal, with an overall gain of 0.4 kg. In summary, this analysis confirms the efficacy and tolerability of an increase in premix 30 dosing frequency from BID to TID where required.

Glycemic control and body weight by region

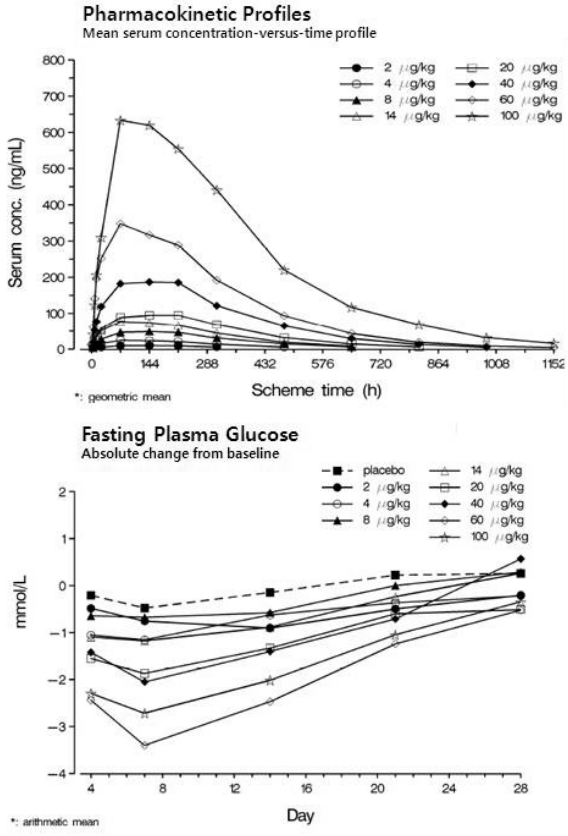
	All regions	China	South Asia	East Asia	North Africa	Middle East/Gulf	Latin America	Russia
n	1033	263	89	74	49	307	12	239
A1C (%)								
Baseline	9.8 (1.9)	9.0 (2.0)	9.7 (1.4)	10.0 (2.5)	9.8 (1.9)	10.1 (1.9)	10.9 (2.1)	9.9 (1.7)
Change from baseline	-2.2 (1.8)*	-2.2 (1.8)*	-2.3 (1.5)*	-2.3 (2.5)*	-1.3 (2.1)*	-2.1 (1.7)*	-2.8 (1.6)	-2.4 (1.6)*
							(*p*=0.018)	
FPG (mg/dl)								
Baseline	204.5 (67.9)	187.5 (63.4)	211.6 (63.9)	203.8 (78.3)	204.8 (63.5)	235.2 (75.4)	152.5 (31.4)	191.7 (53.6)
Change from baseline	-76.3 (67.8)*	-68.5 (60.8)*	-83.0 (69.7)*	-69.5 (83.1)*	-52.2 (82.4)*	-95.2 (77.0)*	-41.0 (37.7)	-70.5 (54.2)*
							(*p*=0.045)	
PPPG (mg/dl)								
Baseline	261.6 (83.2)	249.5 (82.8)	292.0 (81.8)	263.1 (88.9)	298.7 (90.6)	308.3 (87.2)	195.0 (NA)†	228.4 (58.6)
Change from baseline	-96.4 (79.8)*	-89.8 (78.9)*	-109.9 (85.5)*	-89.1 (107.0)*	-97.5 (104.3)*	-119.1 (93.2)*	-33.0 (NA)*††	-84.0 (57.2)*

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

Hypoglycemia (events/person-year [% of individuals with event])								
All events								
Baseline	4.28 (9.6)	1.68 (5.7)	1.75 (5.6)	4.92 (12.2)	4.51 (12.2)	6.65 (11.7)	0.0 (0.0)	5.00 (11.7)
Week 24	3.76 (13.0)	1.90 (7.5)†	6.73 (18.8)	1.91 (7.4)†	6.64 (19.1)†	3.90 (15.7)†	2.17 (8.3)†	4.51 (14.2)†
	(p=0.014)		(p=0.01)					
Nocturnal								
Baseline	0.76 (3.1)	0.2 (1.1)	0.73 (4.5)	2.99 (9.5)	2.65 (6.1)	0.25 (1.3)	0.0 (0.0)	0.98 (4.6)
Week 24	0.82 (4.0)†	0.46 (2.4)†	1.07 (7.1)†	0.38 (1.5)†	4.15 (10.6)†	0.67 (4.1)	0.0 (0.0)	0.82 (4.2)†
						(p=0.042)		
Body weight (kg)								
Baseline	77.9 (16.5)	69.4 (11.6)	73.7 (11.6)	67.9 (14.6)	76.9 (14.1)	80.2 (16.9)	76.8 (18.1)	87.8 (16.2)
Change from baseline	0.4 (3.9)*	0.5 (3.8)†	1.6 (2.9)*	1.0 (3.7)	2.2 (4.6)	0.6 (4.3)	1.9 (3.7)†	-0.6 (3.6)
				(p=0.037)	(p=0.003)	(p=0.029)		(p=0.017)
Insulin dose (U/kg/day)								
Pre-study insulin‡	0.58 (0.31)	0.49 (0.21)	0.57 (0.28)	0.69 (0.45)	0.56 (0.28)	0.70 (0.32)	0.54 (0.22)	0.44 (0.23)
Premix dose, baseline	0.47 (0.23)	0.38 (0.18)	0.48 (0.20)	0.62 (0.30)	0.53 (0.20)	0.57 (0.26)	0.48 (0.16)	0.38 (0.15)
Premix dose, week 24	0.74 (0.30)	0.61 (0.24)	0.84 (0.29)	0.90 (0.39)	0.73 (0.23)	0.91 (0.31)	0.70 (0.18)	0.64 (0.21)

Mean (SD) or as stated; *p<0.001; †p=NS; ††Only one patient provided PPPG values at baseline and week 24 and thus SD is unavailable; ‡Pre-study dose=dose of insulin before starting premix 30 in insulin-experienced individuals. FPG, fasting plasma glucose; NA, not applicable; NS, not significant; PPPG, postprandial plasma glucose; SD, standard deviation



Supported by: Hanmi Pharm. Co., Ltd.

1075-P

Pharmacokinetics and Pharmacodynamic Effects of a Single Dose of the Long-Acting GLP-1R Agonist LAPS-Exendin-4 in Subjects With Type 2 Diabetes Mellitus

YUNG I. KIM, SEI-EUN KIM, IN YOUNG CHOI, SUNGMIN BAE, KYU HWANG LEE, KYUNG-MI PARK, JAHOON KANG, SE CHANG KWON, JEEWOONG SON, *Seoul, Republic of Korea, Hwaseong-si, Republic of Korea*

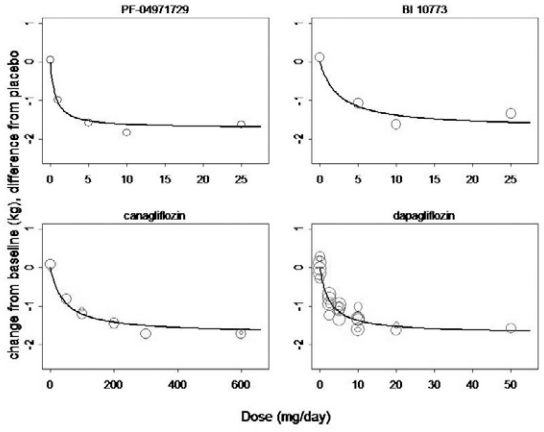
LAPS-Exendin-4 was developed by conjugating CA Exendin-4 (Exendin-4 analog) and the constant region of human immunoglobulin via non peptidyl linker. To assess the safety, tolerability and efficacy, 48 patients with T2DM were dosed 2 ~ 100 μg/kg LAPS-Exendin-4. Most frequently reported TEAEs were gastrointestinal disorders with mild intensity consisting of diarrhea (29% vs 25% placebo) and flatulence (21% vs 13% placebo). Mild nausea was reported at low frequency (17%) as well as eructation (13%). All TEAEs were mild to moderate and resolved without sequelae. All serum samples were negative for anti-LAPS-Exendin-4 antibodies. No signs of arrhythmia, electrocardiographic changes due to QTc prolongation or conduction disorders were found. LAPS-Exendin-4 showed delayed absorbance, and the half-life of LAPS-Exendin-4 ranged between 135 ~ 180 hours. Fasting blood glucose levels were lower for more than weeks compared to baseline at dose levels from 4 to 100 ug/kg in patients receiving LAPS-Exendin-4. The post-prandial glucose levels were lower following LAPS-Exendin-4 doses of 20 to 100 μg/kg compared to placebo and compared to the pre-dose. For the dose levels of 40 to 100 μg/kg LAPS-Exendin-4, the fructosamine levels showed a decrease on Day 21 with the largest decrease seen for the 100 μg/kg dose level. Based on these findings, a single injection of LAPS-Exendin-4 was well tolerated in T2DM patients, improved glycemic parameters in a dose dependent manner and showed the possiblity of exploring the weekly or even less frequent dosing regimens.

1076-P

Model-Based Meta-Analysis of the Effect on Body Weight of PF-04971729, a Sodium Glucose Co-Transporter-2 Inhibitor (SGLT2i), in Comparison to other SGLT2i and Anti-Diabetic Agents (ADA)

JAAP MANDEMA, KEVIN SWEENEY, STEVEN TERRA, VAISHALI SAHASRABUDHE, *Menlo Park, CA, Groton, CT, Cambridge, MA*

PF-04971729 is a potent, selective SGLT2i in development for treatment of type 2 diabetes mellitus (T2DM). Since there is growing recognition of the need for comparative effectiveness of various ADA, a model was developed to quantify the time course of dose vs body weight change for PF-04971729 relative to other ADA including SGLT2i, DPP4 inhibitors (DPP4i), GLP-1 agonists (GLP1), sulfonylureas (SU), thiazolidinediones (TZD), and metformin. A systematic literature review yielded 120 randomized controlled trials representing >52000 T2DM patients and 21 drugs. Data for PF-04971729 were obtained from a 12-week, randomized, placebo-controlled study in T2DM patients on metformin background. A dose response was observed for weight effect of SGLT2i, TZD, DPP4i and GLP-1 whereas a dose-independent treatment effect was estimated for metformin and SU. The treatment effect was significantly dependent on baseline weight. The model predicted a statistically significant weight loss for SGLT2i (1.5 to 2 kg), GLP1 (0.7 to 1.5 kg) and metformin (0.4 kg), and a statistically significant weight gain for DPP4i (0.5 to 1.1 kg), TZD (3.1 to 3.3 kg) and SU (2.8 to 4.3 kg) at 24 weeks. The figure illustrates model-estimated and observed dose response for various SGLT2i. Estimated differences in weight loss between PF-04971729-25 mg and top doses of other SGLT2i were small (-0.1 to -0.3 kg). This analysis offers a quantitative framework to leverage external data and thus enables an indirect comparison of novel drugs with existing treatments.



Each arm in each trial is shown; symbol size is proportional to 1/standard error; response shown is at 12 weeks on metformin background and baseline body weight of 90 kg

1077-P

Sitagliptin Provides Similar Glycemic Improvement With Less Hypoglycemia in the Elderly With Type 2 Diabetes Mellitus Compared to Sulfonylurea

RAVI SHANKAR, SAMUEL S. ENGEL, LEI XU, GREGORY T. GOLM, MICHAEL J. DAVIES, KEITH D. KAUFMAN, BARRY J. GOLDSTEIN, *Whitehouse Station, NJ*

In the US, 45% of patients with type 2 diabetes mellitus (T2DM) are elderly (≥65 years old), a group that presents unique therapeutic challenges due to comorbidities. Sulfonylurea (SU) use is associated with greater risk for hypoglycemia (HYPO) in the elderly and its use increases with age. HYPO and its consequences may be more pronounced in the elderly. Sitagliptin (SITA), a DPP-4 inhibitor, improves glycemic control, with a low risk of HYPO when used alone or with metformin. This *post hoc* analysis pooled data of patients ≥65 years from 3 double-blind studies to compare effects of SITA (100 mg/day) or SU (in titrated doses) on change from baseline in A1C, fasting plasma glucose (FPG), body weight (BW) and incidence of symptomatic HYPO. Patients on diet alone or metformin were randomized to SITA or glipizide for 104 weeks (study 1-2) or glimepiride for 30 weeks (study 3); hence, the analysis included 373 elderly patients who completed trials through 30 weeks. Both A1C and FPG decreased with SITA and SU, with no statistical difference between treatments (Table). Significantly lower incidence of HYPO was observed with SITA. BW decreased significantly with SITA. Significantly more patients on SITA than SU achieved the composite endpoint of >0.5% A1C reduction with no HYPO or BW gain at 30 weeks. In conclusion, SITA provided similar glycemic efficacy, with less HYPO and with BW loss compared to SU in elderly patients, suggesting that SITA is an effective and well-tolerated treatment option for patients ≥65 years with T2DM.

	Sitagliptin N = 178	Sulfonylureas N = 195
Baseline A1C, %	7.5 ± 0.7	7.5 ± 0.8
Δ A1C, %	-0.73 (-0.84, -0.61)	-0.78 (-0.89, -0.67)
A1C <6.5%, n (%)	63 (35.4)	73 (37.4)
Baseline FPG, mg/dL	150.9 ± 32.8	157.4 ± 38.4
Δ FPG, mg/dL	-21.3 (-26.5, -16.1)	-23.4 (-28.4, -18.3)
Patients with HYPO AE, n (%)	11 (6.2)	55 (28.2)*
Baseline BW, kg	84.6 ± 14.6	83.6 ± 15.1
Δ BW, kg	-1.7 (-2.3, -1.2)	0.4 (-0.1, 1.0)*
Composite†, n (%)	78 (44.1)	31 (15.9)*

Data are mean ± SD, LS mean change (Δ) from baseline (95% CI), or counts (proportion of patients).*p<0.001 for difference between SITA and SU†Composite = patient experienced an A1C decrease >0.5% with no HYPO and no BW gain

1078-P

Pharmacokinetics, Safety, and Tolerability of a Long-Acting C-Peptide (Ersatta™) in Patients With Type 1 Diabetes

HOWARD FOYT, JOHN WAHREN, MARK DANIELS, MARK MILAD, JAMES CALLAWAY, *La Jolla, CA, Plymouth, MI*

C-peptide is co-secreted in equimolar amounts with insulin in response to elevations in blood glucose. Accumulating data suggest that lack of C-peptide in type 1 diabetes patients is an important contributing factor in the onset and progression of long-term complications. Previous efforts to replace circulating levels of C-peptide have been stymied by its short half-life (~1 h). A long-acting product (Ersatta) has been developed for subcutaneous delivery following PEGylation of the peptide's N-terminus, distal from the biologically active C-terminus. A randomized, blinded, placebo-controlled, serial-cohort, multiple ascending dose study with Ersatta has been conducted. Thirty type 1 diabetes patients (10 subjects per cohort; 8 active/2 placebo) were dosed at one of three dose levels: 0.3 mg, 1.0 mg (estimated C-peptide "replacement" dose level), and 3.3 mg. Assessments of the safety, tolerability, and the single and multiple dose pharmacokinetics (PK) of plasma Ersatta were conducted. Peak concentrations (Cmax) generally occurred 2-4 days after subcutaneous administration of single or multiple (4-5 total) dose(s). Cmax and AUC increased in proportion to increasing dose. Single dose PK was predictive of multiple dose PK. Following multiple doses of 0.3, 1, and 3.3 mg Q7days, the corresponding geometric mean Cmax values were 0.688, 2.28, and 10.8 nM; AUCtau values were 4.21, 14.2, 64.5 nM·day; and Cmin values were 0.455, 1.60 and 6.54 nM. The mean plasma half-life of Ersatta was 6-7 days. The study drug was safe and well tolerated with no reportable SAEs. Pharmacodynamic data were collected at baseline and 12 weeks in the form of electrophysiological measurements, including sural sensory nerve conduction velocities (SCNV). It is concluded that Ersatta is a potentially attractive therapeutic agent that warrants additional testing in larger clinical trials.

1079-P

Implementation of a Carbohydrate Counting Protocol in Hospitalized Patients With Cystic Fibrosis Related Diabetes

NADIA KHOURY, MICHAEL ELLIOTT, STEPHEN SCHAFERS, NICHOLAS HAMPTON, AMY SCHRADER, GARY S. TOBIN, JULIE M. SILVERSTEIN, *St. Louis, MO*

Inpatient management of cystic fibrosis related diabetes (CFRD) is challenging because of the use of high carbohydrate and high protein diets as part of medical nutrition therapy. Traditional hospital protocols, which use rapid acting insulin based on a fixed meal dose, often do not adequately control blood sugars in CFRD patients. To address this issue, we designed an inpatient carbohydrate counting protocol for CFRD patients hospitalized at our institution. All patients were prescribed their home dose of long acting insulin and a sliding scale. Meal time rapid acting insulin was prescribed based on an individualized carbohydrate ratio (CR). At each meal or snack, patients counted their carbohydrates and received insulin based on the prescribed CR. We prospectively compared glucose control using our protocol in CFRD patients over a 10 month period (PRO, n=21) to a retrospective review of blood glucose data in CFRD patients hospitalized over a 10 month period during the previous year (RET, n=37). We also assessed patient satisfaction with an 11 question survey. There was no significant difference in the mean average blood glucose (193 mg/dl vs 191mg/dl, p=0.9) between the PRO and RET groups respectively. There was also no difference in the percent of patients who experienced at least one episode of severe hypo- (BS < 40 mg/dl, n=4 (19%) vs n=2 (5.4%), p=0.176), moderate hypo- (BS < 70 mg/dl, n=11 (52.4%) vs n=21 (56.8%), p=0.747) or hyper- (BS > 200 mg/dl, n=21 (100%) vs n=36 (97.3%), p=1.0) glycemia in the PRO and RET groups respectively. Over 50% of patients felt their glucose control, insulin administration timing, and hospital experience improved as compared to previous hospitalizations. Most patients also reported increased comfort with carbohydrate counting and thought they could better manage their diabetes at home. This small pilot study shows that implementation of carbohydrate counting in the hospital is safe and may improve patient well-being and satisfaction.

1080-P

Myostatin Inhibition Improves Insulin Signaling in Muscles of Mice With High Fat-Diet-Induced Diabetes

YANJUN DONG, HQ HAN, YANLAN DONG, WILLIAM E. MITCH, LIPING ZHANG, *Houston, TX, Thousand Oaks, CA*

Myostatin is principally produced in skeletal muscle and can inhibit its growth. Animals lacking myostatin are literally "muscle bound" and the large muscles are associated with reduced adiposity and lower blood glucose even mice supply with a high-fat diet. We investigated whether myostatin inhibition would improve the metabolic profile of insulin-resistant mice. C56/BL6 mice were fed with a high fat diet (HFD; 58% calories from fat) for 10 months and for the last 3 weeks, myostatin was blocked by injections of a myostatin peptibody. Results were compared to those HFD-induced-diabetic mice injected with PBS. Body weight, lean mass and adipose tissue were quantified using an X-ray Imager (PIXImus Body Composition, Lunar Corp); oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured using an animal monitoring system. Compared to responses in PBS-

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

injected mice, myostatin inhibition (MI) decreased blood glucose (158 in MI vs 254 mg/dl in PBS, mean±SE), serum insulin (1.64±0.16 in MI vs 2.47±0.2 ng/ml in PBS) and increased glucose disposal in response to insulin. There also was increase in energy expenditure (11.42±0.54 in MI vs 9.13±0.69 cal/h in PBS), associated with a decrease in the % body fat (9.16±1.36% in MI vs 3.03±0.78% in PBS) plus a decrease in serum fatty acids (1.11±0.079 in MI vs. 1.36±0.067 mg/dl in PBS). All differences were statistically significant ($p<0.05$). Myostatin inhibition also increased p-Akt in both muscle and white adipose tissue (WAT), responses linked to increased expression of fatty acid oxidation genes in muscle and WAT, plus an increase in AMPK activation plus expression of PPAR-α, β and γ isoforms in both skeletal muscle and WAT. We propose that myostatin, by suppressing both the AMPK and PPAR axes in skeletal muscle and adipose tissue interferes with insulin signaling and reduces fatty acid oxidation. Blocking myostatin corrects these defects, improving insulin signaling and reducing lipid accumulation.

Supported by: Satellite Health, Harold Selzman and NIH (R37DK37175)

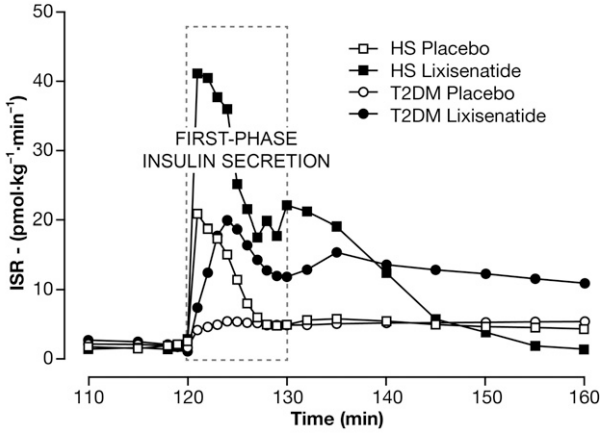
1081-P

Restitution of Glucose Disposition With Lixisenatide in T2DM Subjects

REINHARD H. BECKER, CHRISTOPH KAPITZA, JENS STECHL, PETER RUUS, JEROME MSIHID, *Frankfurt, Germany, Neuss, Germany, Chilly-Mazarin, France*

Restitution of glucose disposition (GD) is a therapeutic goal in T2DM. We compared insulin secretion (IS) and GD with lixisenatide (LIXI) in early-stage T2DM and non-diabetic healthy subjects (HS). In 2 parallel, 2-period, 2-treatment, 2-sequence, single-center, single-dose, crossover studies, HS (14M/6F, mean age 36 yr, BMI 25 kg/m^2) and T2DM subjects (13M/9F, mean age 55 yr, BMI 30 kg/m^2) received LIXI 20 µg SC or placebo (PBO) 2 h prior to an iv glucose challenge (IVG; 0.3 g/kg over 30 s). Integration of IS rate (ISR) by C-peptide (CPEP) deconvolution was used to determine 1st- (ISR-AUC$_{0\text{-}10min}$) and 2nd- (ISR-AUC$_{10\text{-}120min}$) phase IS. Insulin (INS), CPEP and glucagon (GC) concentration-time curves and GD rate (K_{glu}) were determined for 2 h. LIXI enhanced 1st-phase IS in T2DM to HS PBO levels, while 2nd-phase IS was greater and elevated for >2 h in T2DM, both on PBO and LIXI (Table, Figure). INS and CPEP were correspondingly greater. K_{glu} was accelerated 2-fold by LIXI, but did not fully recover to HS values. When INS changed, GC followed inversely and glucose was brought to normal levels. A single dose of LIXI 20 µg quantitatively restored 1st-phase insulin release to IVG in T2DM, enlarged 2nd-phase and enhanced GD towards normal values, without impairing counter-regulation by GC.

	Subject	Placebo	Lixisenatide	Ratio
ISR-AUC$_{0\text{-}10}$ pmol.kg^{-1}	T2DM	48	110	2.8
	HS	112	267	2.4
ISR-AUC$_{10\text{-}120}$ pmol.kg^{-1}	T2DM	530	925	1.6
	HS	370	341	0.8
INS-AUC$_{0\text{-}10}$ pmol.min.L^{-1}	T2DM	503	2835	6.6
	HS	2620	8269	3.2
INS-AUC$_{10\text{-}120}$ pmol.min.L^{-1}	T2DM	10200	31000	3.0
	HS	6371	21885	2.4
Kglu min^{-1}	T2DM	0.56	0.98	1.8
	HS	1.58	3.84	2.3



Supported by: sanofi-aventis

1082-P

Luseogliflozin (TS-071), a Novel, Potent and Selective SGLT2 Inhibitor, Prevents Diabetic Retinopathy in Rats

TEISUKE TAKAHASHI, MICHIHITO ONISHI, HARUHIRO YAMASHITA, EMI GUNJI, TAKUYA TAKEDA, HIDEKI TOMOIKE, SAEKO UCHIDA, KENZO TAKAHASHI, *Saitama, Japan*

The risk of diabetic retinopathy is directly related to the degree and duration of hyperglycemia. In this study, we examined the effects of luseogliflozin (LUSEO), a novel SGLT2 inhibitor, on diabetic retinopathy in streptozotocin (STZ)-induced diabetic rats. STZ rats were treated with LUSEO as admixture to diet for 9 weeks. Control STZ rats (DC) and normal SD rats (NC) were fed a drug-free diet. LUSEO causes sustained improvement in glycemic control over the course of treatment [GHb(%) at 8 weeks: NC 3.9±0.1, DC 11.6±0.2, LUSEO 0.001% 9.4±0.5**, LUSEO 0.003% 7.6±0.5***, LUSEO 0.01% 6.1±0.5***, **$p < 0.01$, ***$p < 0.001$ vs. DC]. Electroretinography (ERG) is a used technique to evaluate retinal functions and provides an early warning of retinal abnormalities in diabetes. In STZ rats, the peak latencies of oscillatory potential (OP) in the ERG were prolonged as compared to NC (OP1 and OP2: $p<0.001$; OP3: $p<0.01$). After 8-week treatment, LUSEO (0.01%) completely prevented the prolongation of peak latencies for OPs (OP1: NC 25.0±0.2, DC 27.1±0.3, LUSEO 25.0±0.3***; OP2: NC 32.0±0.3, DC 34.9±0.5, LUSEO 31.7±0.4***; OP3: NC 41.5±0.5, DC 44.0±0.7, LUSEO 40.8±0.5**, **$p < 0.01$, ***$p<0.001$ vs. DC). At the end of the study, histopathological analyses of the retina were conducted. LUSEO prevented the reductions in the thickness of the inner plexiform layer (IPL) and suppressed the Müller cell expression of glial fibrillary acidic protein (GFAP) as a cellular marker for retinal damage [IPL (µm): NC 41.5±0.9, DC 36.4±1.0, LUSEO 0.003% = 40.6±0.8*, LUSEO 0.01% 41.5±1.3**; GFAP-positive area (µm^2): NC 1050±182, DC 5676±1346, LUSEO 0.003% 2299±554, LUSEO 0.01% 1304±97*, *$p < 0.05$, **$p<0.01$ vs. DC]. Furthermore, LUSEO reduced the development of lens opacity as diabetic cataract (Incidence rate: NC 0/12, DC 5/12, LUSEO 0.001% 2/12, LUSEO 0.003% 0/12, LUSEO 0.01% 0/12). In summary, these results indicate that LUSEO protects against diabetes-induced retinal dysfunction and organ damage in rats.

1083-P

Potential Mechanisms Underlying Diacylglycerol Acyltransferase 1 Inhibition in Mediating GLP-1 Release and Glucose Homeostasis

JINQI LIU, DAVID MCLAREN, DUNLU CHEN, HAIYING LIU, GAIL FORREST, YANQING KAN, STEVEN STOUT, ZHU SHEN, THOMAS RODDY, THOMAS GUSTAFSON, ROBERT DEVITA, SHIRLY PINTO, *Rahway, NJ*

Acyl coenzyme A:diacylglycerol acyltransferase 1 (DGAT1) is a key enzyme catalyzing the final committed step of triglyceride (TG) synthesis. Through genetic knockout and pharmacological modulation, DGAT1 has been implicated as a crucial mediator in dietary fat absorption and insulin sensitivity. Blockade of DGAT1 results in beneficial metabolic phenotypes. Most notably, DGAT1 inhibition leads to reduction of post-prandial plasma triglyceride levels, prolongation of GLP-1 release and improved glucose homeostasis. To investigate the underlying mechanism of DGAT1 inhibition in mediating GLP-1 release, a stable isotope tracing approach using [^{13}C]oleic acid was employed to monitor newly synthesized lipid species and study postprandial lipid homeostasis in plasma and different segments of intestinal tissue over time. We demonstrated that DGAT1 inhibition led to spatial and temporal alterations of fat absorption along the gut, which may yield a prolonged increase in GLP-1 release. Furthermore, significant reduction of liver TG in diet-induced obesity mice was observed in imaging studies following chronic treatment with a small molecule inhibitor of DGAT1, indicating an improvement in liver steatosis via inactivation of DGAT1. Enhancements in Akt phosphorylation and glucose uptake were also demonstrated in mouse myotubes in the presence of DGAT1 inhibitors, suggesting a beneficial effect of DGAT1 inhibition on glucose disposal. Taken together, these data provide insights into the underlying mechanisms of DGAT1 inhibition and provide further support for DGAT1 as a key player in metabolic pathways.

1084-P

Novel Effects on Lipids of GSK1292263, a GPR119 Agonist, in Type 2 Diabetics

DEREK J. NUNEZ, MARK A. BUSH, DAVID A. COLLINS, SUSAN L. MCMULLEN, GLEN APSELOFF, GEORGE ATIEE, LEONOR COSINO, LINDA MORROW, PAUL L. FELDMAN, *Research Triangle Park, NC, Columbus, OH, San Antonio, TX, Durham, NC, Chula Vista, CA*

GPR119 receptor agonists improve glucose control in animal models of type 2 diabetes (T2D). GSK1292263, a selective and potent GPR119 agonist, was investigated in two randomized, placebo-controlled studies with T2D patients either washed off prior anti-diabetic medications (NCT01119846)

or on metformin monotherapy (NCT01128621). Previously, we described the safety, tolerability and PK of GSK1292263 and reported that 100-600mg/day for 14 days (n≈12 per arm) did not reduce $AUC_{glucose}$ (0-24h) as monotherapy or dosed with metformin or sitagliptin, but it increased circulating gut hormone levels, especially postprandial PYY. We now present novel plasma lipid effects of GSK1292263 observed in these studies with the highest doses, 300mg BID and 600mg QD.

For GSK1292263 monotherapy.

Parameter (* = fasting)	**% Change from Baseline: Comparison to Placebo**	**Least Squares Mean**	**Lower 95% CI**	**Upper 95% CI**
HDL-C*	300mg BID	+26.9	+15.8	+37.9
HDL-C*	600mg QD	+20.6	+9.6	+31.6
LDL-C*	300mg BID	-23.5	-40.1	-6.9
LDL-C*	600mg QD	-22.4	-39.0	-5.8
Triglycerides*	300mg BID	-24.7	-47.6	-1.9
Triglycerides*	600mg QD	-32.5	-55.4	-9.6
Triglycerides AUC (0-24h)	300mg BID	-68.5	-129.5	-7.6
Triglycerides AUC (0-24h)	600mg QD	-73.3	-135.7	-10.8

For GSK1292263 co-dosed with metformin.

Parameter (* = fasting)	**% Change from Baseline: Comparison to Placebo**	**Least Squares Mean**	**Lower 95% CI**	**Upper 95% CI**
HDL-C*	300mg BID	+29.0	+18.6	+39.5
HDL-C*	600mg QD	+10.5	+0.5	+20.5
LDL-C*	300mg BID	-35.5	-49.0	-22.0
LDL-C*	600mg QD	-25.2	-38.2	-12.3
Triglycerides*	300mg BID	-63.0	-88.5	-37.5
Triglycerides*	600mg QD	-53.2	-77.8	-28.7
Triglycerides AUC (0-24h)	300mg BID	-82.1	-124.2	-40.0
Triglycerides AUC (0-24h)	600mg QD	-72.0	-114.1	-29.9

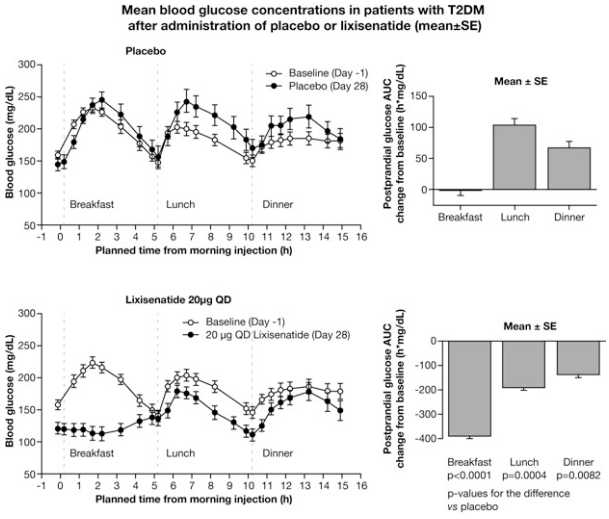
In both studies, GSK1292263 also reduced significantly apoB(B100), with trends for a reduction of apoE and an elevation of apoA1. Sitagliptin 100mg had no significant lipid effects.These data suggest that GPR119 agonism with GSK1292263 can provide clinically meaningful lipid improvements in T2D patients.

1085-P

Effects of Lixisenatide Once Daily on Gastric Emptying and Relationship to Postprandial Glycemia in Type 2 Diabetes Mellitus

MARTIN LORENZ, CLAUDIA PFEIFFER, AXEL STEINSTRÄßER, PETER RUUS, *Frankfurt, Germany*

The effects of lixisenatide once daily (QD; n=19) were compared with placebo (PBO, n=22) on postprandial blood glucose (area under the curve, PPG-AUC) in relation to gastric emptying rate in patients with T2DM. Data were obtained from a randomized, double-blind, PBO-controlled, parallel-group study with a treatment duration of 28 days in patients on up to 2 OADs. Lixisenatide was injected subcutaneously using an ascending dose range from 5-20 µg, increased in 4-day intervals in increments of 2.5 µg. For 20 µg lixisenatide QD, the change in PPG-AUC from baseline on Day 28 after 4 weeks of treatment demonstrated a significant reduction compared with PBO after a standardized breakfast (p<0.0001, Figure) and after lunch (p=0.0004) and dinner (p=0.0082). Thus, 20 µg lixisenatide administered in the morning demonstrated a pharmacodynamic effect on blood glucose throughout the day. As assessed by ^{13}C-octanoic acid breath test, mean gastric emptying half-life ($T_{½}$) showed a significant increase for 20 µg lixisenatide compared with PBO (p=0.0031): mean (± SD) changes from baseline for $T_{½}$ were -24.1 ± 133.1 min for PBO (n=17) and 211.5 ± 278.5 min for lixisenatide (n=17). There was an inverse relationship between PPG and gastric emptying rate for 20 µg lixisenatide based on the regression line of PPG $AUC_{0.14\text{-}4.55h}$ *vs* $T_{½}$ (n=17, r^2=0.4889, p=0.0018). In conclusion, lixisenatide significantly slowed gastric emptying accompanied by a significant PPG reduction, which is considered as an important mechanism for beneficial effects of lixisenatide on glycemic control.



Supported by: sanofi-aventis

1086-P

Clinical Significance of Serum Androgen Levels in Young and Middle-Aged Men With Type 2 Diabetes Mellitus Accompanied by Erectile Dysfunction

FANG-PING LI, *Guangzhou, China*

Objective: To study on the relationship between erectile dysfunction (ED) and serum androgen levels in young and middle-aged men with type 2 diabetes mellitus (T2DM). Methods: 53 male patients withT2DM under 50 years old were collected, of which 28 patients with ED as case group (ED group), 25 cases of non-ED as control group (NED group) and serum Serum concentrations of total testosterone (TT), free testosterone (FT), sex hormone-binding globulin(SHBG), dehydroepiandrosterone sulfate(DHEA-S), androstenedione (A2) and other indicators were detected, and free testosterone index (FTI) and calculated free testosterone (cFT) were calculated through TT, SHBG. The difference for each indicator was compared in the two groups. Results: Age, duration of diabetes, body fat, serum lipids, blood pressure and serum luteilizing hormone (LH), follicle-stimulating (FSH), prolactin (PRL) levels in the two groups were matched, and there were no significant differences on serum TT, FT, cFT, FTI, SHBG, DHEA-S, A2 levels and other indicators in the two groups (P> 0.05). Conclusion: The occurrence of diabetic ED may have little to do with the gonadal and adrenal androgens in young and middle-aged men with T2DM. So testosterone or DHEA-S supplement therapy for diabetic ED still should be careful in young and middle-aged men with T2DM.

1087-P

A Multi-Center, Open, Randomized, Parallel-Group, 2 Arm Study to Compare the Efficacy and Safety of Insulin Add-On to Glimepiride/ Metformin 1/500mg b.i.d vs. to Glimepiride 4mg qd in Type 2 DM Patients With Inadequate Glycemic Control

JAE MIN LEE, KANG SEO PARK, SOON HYUN PARK, DONG MEE LIM, JONG MIN LEE, KEUN YONG PARK, SANG JIN KIM, *Dae Jeon, Republic of Korea, Cheonan, Republic of Korea*

The aim of this study was to compare the HbA1c changes of between two groups of poorly controlled type 2 diabetic patients treated with oral antidiabetic drugs when added to insulin glargine.: one group with insulin glargine add-on to a fixed-dose combination of glimepiride 1mg and metformin 500mg twice daily, and the other group with insulin glargine add-on to glimepiride 4mg once daily. An open-label, parallel, 16-week trial was conducted in 4 study centers. 127 patients were screened, 97 patients were randomized into two groups.The primary efficacy end point was HbA1c change and the secondary efficacy end point were insulin resistance, changes of FPG and PPG2hr and hypoglycemic incidence. After 16 weeks of treatment, adjusted mean HbA1c changes from baseline were -0.97% and -0.22% in glimepiride/metformin and glimepiride groups respectively. Adjusted mean fasting plasma glucose level changes were -51.2mg/dl and -39.8mg/dl from baseline. 2 hr postprandial glucose levels changed by average -69.7 mg/dl for glimepiride/metformin group and -37.8 mg/dl for glimepiride group.The glimperide/metformin group required less insulin than the glimepirde group. Hypoglycemic events were experienced in 19 patients (39.6%) in glimepiride/metformin group and 20 patients (41.7%) in glimepiride group, and night

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

time hypoglycemic events were experienced in 9 patients (18.8%) in both groups, but there was no any serious hypoglycemic adverse events. Insulin add-on to glimepiride/metformin was more effective than insulin add-on to glimepiride in glycemic control and this group required lesser insulin without increasing hypoglycemic incidence.

1088-P

Safety, Tolerability, and Pharmacodynamic Effects of the Novel PPAR-delta/gamma Agonist DB959Na in a Phase 1 Escalating Multiple Dose Study

MARY K. DELMEDICO, WILLIAM A. WARGIN, RALPH A. SCHUTZ, GEOFFREY C. BANKS, JEFFERY E. COBB, MICHAEL J. DALTON, NANCY W. OGLESBY, SUSAN E. SPRUILL, STEVEN H. GROSSMAN, *Raleigh, NC, Chapel Hill, NC, Overland Park, KS, Durham, NC, Spruce Pine, NC*

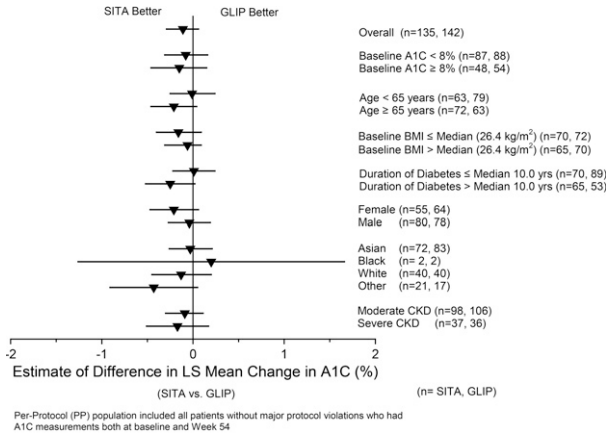
DB959, a non-TZD dual PPAR-δ/γ agonist, has shown efficacy in animal models of diabetes and dyslipidemia. Study DB959-102 enrolled 32 healthy female and male volunteers in 4 cohorts (6 active + 2 placebo / cohort) with escalating doses of 5, 20, 100, or 200 mg QD for 7 days. Safety was assessed by hematology, blood chemistry, urinalysis, physical examination (PE), vital signs (VS), ECGs, and adverse events (AEs). Pharmacokinetic (PK) parameters were calculated using non-compartmental analysis. Pharmacodynamic (PD) effect was assessed with the PPAR-γ biomarker adiponectin.No clinically significant laboratory, PE, VS, or ECG changes were observed that were judged to be DB959Na related. All AEs were mild or moderate in severity, and AE incidence was similar between groups of subjects who received either placebo or DB959Na at all dose levels.Mean DB959 concentration-time profiles were similar and median Tmax values of 3-4 hours were consistent between doses on Days 1 and 7. Trough concentrations increased slightly on Days 2-6. At steady state, Cmax and AUCτ were linear and dose proportional and CLss/F was independent of dose, suggesting linear PK. Comparison of AUC at steady state with Day 1 revealed accumulation ratios of 1.82 - 3.31, suggesting modest accumulation. Estimates of mean half-life on Day 7 were dose independent and ranged from 20.9 - 46.1 hours.Mean plasma levels of adiponectin increased dose dependently over the course of the study (3.2-fold maximum change). Evaluation of AUCτ vs. adiponectin change from Day 1 to 11 revealed a sigmoidal PK-PD relationship.The administration of multiple, oral doses of up to 200 mg DB959Na was safe and well tolerated; the half-life of DB959 indicated that once daily dosing is optimal; and the increases in adiponectin provided evidence for the pharmacological activity of DB959 in a dose range with a good safety profile. These results provide a compelling rationale for continued clinical development of DB959Na.

1089-P

Consistency of the A1C-Lowering Effects of Sitagliptin Versus Glipizide in Patients With Type 2 Diabetes and Chronic Renal Insufficiency Across a Variety of Baseline Characteristics

JUAN CAMILO ARJONA FERREIRA, SAMUEL S. ENGEL, HUA GUO, GREGORY T. GOLM, AMY O. JOHNSON-LEVONAS, KEITH D. KAUFMAN, BARRY J. GOLDSTEIN, *Rahway, NJ*

In a 54-wk, randomized, double-blind study conducted in patients (pts) with type 2 diabetes (T2DM; n=423) with moderate (mod) to severe (sev) chronic kidney disease (CKD) (eGFR 30-<50 or <30 mL/min/1.73 m^2, respectively) sitagliptin (SITA) was previously shown to be non-inferior to glipizide (GLIP) in lowering A1C in the prespecified per protocol (PP) population (n=277). The present analysis further assessed the consistency of the A1C-lowering effects of SITA vs GLIP across subgroups of the PP population (see graph). Eligible pts were ≥30 yrs with T2DM and mod to sev CKD not on dialysis with A1C ≥7.0 and ≤9.0% on diet/exercise alone. Pts were randomized (1:1) to SITA or GLIP and stratified by renal status (mod/sev). Doses of SITA for pts with mod and sev CKD were 50 mg/d and 25 mg/d respectively; the dose was adjusted downward (from 50 to 25 mg/d) if renal status changed from mod to sev during the study. The initial GLIP dose was 2.5 mg/d and could be titrated up to 10 mg BID as needed for glycemic control; the dose could also be reduced or interrupted to prevent hypoglycemia. For the PP population, LS mean changes from baseline in A1C were -0.76% (SITA) and -0.64% (GLIP), with a between-group difference [95% CI] of -0.11% [-0.29, 0.06]. The between-group differences were generally consistent across the prespecified subgroups. In pts with T2DM and CKD, treatment with SITA produced A1C reductions similar to those with GLIP, irrespective of baseline A1C, age, BMI, diabetes duration, gender, race or severity of CKD.



Per-Protocol (PP) population included all patients without major protocol violations who had A1C measurements both at baseline and Week 54

1090-P

Low-Dose (15 mg/day) Pioglitazone Treatment Improves Glycemic Control, and Whole-Body and Adipocyte Insulin Resistance With Minimal Weight Gain in Type 2 Diabetic Subjects

ZANDRA PEREZ-CADENA, GIUSEPPE DANIELE, ALBERTO CHAVEZ, SUBHASH KAMATH, PENGOU ZUO, ZHI CHANG, FRANCESCO ANDREOZZI, ANA PAEZ, DEIDRE WINNIER, RUTH ARYA, ANDREA HANSIS-DIARTE, LAUREN CORTEZ, CHRISTOPHER JENKINSON, PAOLO FANTI, AMALIA GASTALDELLI, RALPH DEFRONZO, DEVJIT TRIPATHY, FRANCO FOLLI, *San Antonio, TX, Pisa, Italy*

Pioglitazone (PIO) is a potent insulin-sensitizer but its use is limited by weight gain and fluid retention at higher doses (30-45mg/day). We examined the effects of low-dose PIO (15mg/day) on metabolic parameters and body composition in 20 T2DM subjects (age 56 ±1 yr, BMI 33.5 ±1.3 kg/m^2, FPG =145 ±8.3mg/dl, HbA_{1c} 7.5%) randomized to PIO (n=11, M/F 7/4, 15mg/day) or PLAC (n=9, M/F 7/2) who participated in an OGTT with insulin and C-peptide measured every 30 min, euglycemic-hyperinsulinemic clamp (80mU/m^2-min) with measurement of body fat (BF) at 0 and 24 wks. Insulin secretion was measured by deconvolution analysis from C-peptide (insulin secretory rate) during OGTT. At baseline, subjects in both groups had similar age, BMI, % BF, HbA_{1c} and fasting and 2-h plasma glucose. PIO led to a greater reduction in fasting PG (140 ±11 to 118 ±9.5 vs 150 ±13 to 140 ±12 mg/dL, p=0.004), 2-h PG (265 ±16 to 243 ±15 vs 285 ±12 to 293 ±10 mg/dL, p=0.02), HbA1c (7.0 ±0.2 to 6.5 ±0.2 vs 8.0 ±0.5 to 7.7 ±0.5%, p=0.02), and triglyceride levels (190 ±16 to 135 ±17 vs 207 ±49 to 180 ±44 mg/dL, (p=0.005). PIO improved whole-body insulin sensitivity (IS) (3.2 ± 0.5 to 4.1 ± 0.5 vs 3.4 ±0.5 to 4.5 ±0.5 mg/kg/min, p=0.005). Improved IS was primarily due to improvement in non-oxidative glucose metabolism (1.6 ±0.5 to 3.7 ±0.5 mg/kg/min, p=0.05). The insulin secretion IS index (ISR x M-value) improved with PIO (13.8 ±4.2 to17.0 ±3.9, p=0.05) but not with PLAC. Body weight and % BF increased by 1.8 ±0.5kg and 2%, respectively (p<0.05), vs PLAC in patients treated with PIO, which was considerably lower than that reported with higher doses of PIO. Despite similar insulin levels, a greater suppression of plasma FFA concentrations was noted during insulin clamp following therapy with PIO (0.066 ±0.008 vs 0.082 ±0.007mM, p=0.04). In conclusion, low-dose PIO therapy improves glycemic control, lipid profile and whole-body and adipose insulin resistance with minimal weight gain.

Supported by: Takeda Pharmaceuticals North America, Clinical Trial ID: NCT01223196

1091-P

Intensive Versus Conventional Glucose Control in Type 2 Diabetic Patients on a General Medicine Ward: A Pilot Study

JOHN W. RICHARD, STEVE FORDAN, BEVERLEY ADAMS-HUET, RUBEN AMARASINGHAM, CHANHAENG RHEE, *Dallas, TX*

To determine how glycemic control on a general medicine ward using a basal-bolus regimen affects length of hospital stay.We identified known type 2 diabetic patients admitted within 24 hours to a general medicine ward at Parkland Memorial Hospital and classified them according to the Charlson Co-morbidity Index. Patients were then randomized to a conventional (pre-prandial capillary blood glucose [CBG] <180mg/dl) or intensive (pre-prandial CBG <110 mg/dl) arm using a basal-bolus regimen. Once the primary team determined the patients to be safe for discharge, length of stay (LOS) was calculated. The study included 100 patients, 49 assigned to conventional treatment and 51 assigned to intensive treatment. The median [range] LOS

was 4.0 [1.8-22] days in the conventional arm and 3.8 [1.5-20.2] days in the intensive arm and there was no statistically significant difference in LOS between the two study arms (p=0.71). There also was no statisticaldifference in length of stay (4.2 days [1-109], n=4650, p= 0.55) when comparing each individual study arm (conventional and intensive) to the entire diabetic population admitted to Parkland Memorial Hospital during the enrollment period.Additional measures were also evaluated including: hypoglycemic events (<80 mg/dl) and hospitalization and medication costs by length of stay. There was a 54% reduction in hypoglycemic events per person day in the intensive versus conventional arm with a relative risk of 0.46 (0.37-0.58). This was a statistically significant difference (p<0.0001). The median [range] cost per day for hospitalization (including medications) showed no statistical difference (p=0.45) between the intensive ($5125.90) and conventional ($5708.70) arms.The present study shows no statistical difference in our primary endpoint,however, we did observe a significant difference in hypoglycemic events in the intensive versus conventional arm. However, further larger studies are needed to confirm these findings.

1092-P

No Evidence of Pancreatitis Following 13 Weeks' Treatment With Liraglutide in Diabetic Male and Female ZDF Rats

LOTTE SIMONSEN, NIELS VRANG, JACOB JELSING, ANDRES E. JENSEN, INGER THORUP, HENRIK SØEBORG, LOTTE BJERRE KNUDSEN, *Maaloev, Denmark, Hoersholm, Denmark*

Male and female diabetic ZDF rats were used to investigate the effects of continuous administration of liraglutide on pancreatitis. Liraglutide (0.4 mg/kg/day or 1.0 mg/kg/day, s.c. once daily) was administered for 13 weeks to male and female ZDF rats (n=12/group). Both diabetic and non-diabetic rats were used as controls, as well as a separate group of diabetic animals at baseline. The numbers reported below are from the highest dose of liraglutide. Liraglutide lowered HbA1c levels in both male and female ZDF rats (8.1±0.3, 6.9±0.4% for males, vehicle and liraglutide, respectively and 7.4±0.8, 4.1±0.3% for females, p<0.0001). Whereas no change in plasma lipase levels were observed, small increases in P-amylase levels were seen in animals treated with liraglutide (1969±178, 2272±244 U/L for males, vehicle and liraglutide, respectively and 1630±366, 2127±206 U/L for females, p<0.001). However, concurrent or permanent increases in lipase and P-amylase levels were never observed. Triglycerides were lowered or unchanged (9.1±2.4, 5.0±1.0 mmol/L, p<0.0001 for males, vehicle and liraglutide, respectively and 8.7±3.7, 10.0±2.1 mmol/L for females, NS). The qualitative histopathological findings did not reveal adverse effects of liraglutide. Acinar cell atrophy and metaplasia, ductal proliferation and inflammatory cell infiltration was found, but not in a higher frequency for liraglutide than for the control groups. The findings seen were mainly minimal in severity and focal in distribution. Similarly, the quantitative stereological analyses revealed no effects of liraglutide on overall pancreas weight (1.3±0.2, 1.2±0.2 g, NS for males, vehicle and liraglutide, respectively and 1.2±0.1, 1.1±0.1 g for females, NS) or on exocrine and duct cell mass or proliferation. These data do not confirm that liraglutide can cause pancreatitis although an association in human subjects cannot be excluded.

1093-P

DPP-4 Inhibitors Versus Sulfonylureas on Top of Metformin in a Real World Setting—Results of 1 Year Follow-up of the Prospective DiaRegis Registry

DIETHELM TSCHÖPE, PETER BRAMLAGE, CHRISTIANE BINZ, MICHAEL KREKLER, KRISTIAN LÖBNER, EVELIN DEEG, ANSELM K. GITT, *Bad Oeynhausen, Germany, Mahlow, Germany, München, Germany, Wedel, Germany, Ludwigshafen, Germany*

DPP-4 inhibitors have been shown to provide non-inferior glycaemic control compared to the sulfonylureas with reduced body weight and a significantly lower risk of hypoglycaemia when given on top of metformin in patients with type-2 diabetes. We aimed to validate these results in a large sample of patients participating in the prospective DiaRegis registry in Germany. Among 3810 participants 780 received a DPP-4 inhibitor (20.5%) and 324 any sulfonylurea (8.5%) on top of prior metformin monotherapy. Patient characteristics of those receiving DPP-4 inhibitors were virtually identical to those receiving sulfonylureas except for a slightly lower age (64.1 vs. 67.5 years; p<0.05). There were no differences in glycaemic control at baseline: HbA1c (7.3 vs. 7.3%; p=0.73), fasting (137 vs. 139 mg/dl; p=0.87) and postprandial glucose (175 vs. 178 mg/dl; p=0.12). Based on treatment decisions at baseline there was a significantly lower fasting (Met/DPP-4 119 vs. Met/SU 123 mg/dl; p<0.05) and postprandial glucose (147 vs. 166 mg/dl; p<0.05) but not HbA1c (6.7% in both groups) at the 12 months follow-up. Patients receiving DPP4 inhibitors had more weight loss (-1.1±6.1 vs. -0.1±4.7 kg; p<0.01) and a reduced risk for hypoglycaemia of any severity (6.1 vs. 14.5%; OR 0.38; 95%CI 0.24-0.60). There were no differences in the rate of micro- and macrovascular events during the 12 months follow-up. The present results in primary diabetes care confirm those of randomized controlled trials: the DPP-4-inhibitor/metformin combination therapy provided an HbA1c reduction over 12 months which was comparable to SU plus metformin, with reduced body weight and a significantly lower risk of hypoglycaemia. The results suggest that multiple variables may be affected by antidiabetic treatment, which should be considered when making clinical decision.

Supported by: Bristol-Myers Squibb/AstraZeneca

1094-P

Saxagliptin (SAXA) Effectively Reduces HbA_{1c} and Is Well Tolerated When Added to a Combination of Metformin (MET) and Sulfonylurea (SU)

ROBERT G. MOSES, SANJAY KALRA, DEBBIE BROOK, JIM SOCKLER, JAYANTI VISVANATHAN, SIMON A. FISHER, *Wollongong, Australia, Karnal, India, North Ryde, Australia, Drummoyne, Australia, Singapore, Singapore*

Combination therapy with MET and SU is common in patients with type 2 diabetes (T2D), and many will require triple oral therapy (TOT). This 24-wk, multicenter, double-blind, phase 3b study evaluated the efficacy and safety of the DPP-4 inhibitor SAXA vs placebo (PBO) as add-on therapy in 257 adults with T2D who had inadequate glycemic control (HbA_{1c} 7%-10%) after at least 8 wk on dual therapy with MET and SU at stable, maximum tolerated doses. The primary endpoint was change from baseline HbA_{1c} at wk 24. Most baseline characteristics were similar in the SAXA and PBO groups: mean age, 57.2 vs 56.8 y; mean BMI, 29.4 vs 29.1 kg/m^2; white 45.7% vs 44.5%; Asian 54.3% vs 55.5%; baseline HbA_{1c} was slightly higher in the SAXA group (Table). A total of 87.6% of patients in the SAXA group and 88.3% in the PBO group completed the study. At wk 24, reductions in HbA_{1c} were greater with SAXA than with PBO added to MET and SU (Table). TOT including SAXA was well tolerated; 59.7% vs 69.5% of patients receiving SAXA vs PBO, respectively, had ≥1 adverse event (AE). AEs occurring in ≥5% of patients receiving either SAXA or PBO were nasopharyngitis (6.2% vs 9.4%, respectively), diarrhea (5.4% vs 3.9%), hypertension (5.4% vs 1.6%), dyslipidemia (3.9% vs 5.5%), and urinary tract infection (3.1% vs 6.3%). Incidences of all reported hypoglycemia were 10.2% with SAXA and 6.3% with PBO; confirmed hypoglycemia (symptoms + glucose <50 mg/dL) were 0.8% with SAXA and 0 with PBO. SAXA used in triple oral therapy in patients whose T2D is inadequately controlled on MET and SU effectively improves glycemic control and is well tolerated.

	SAXA +MET + SU (n=129)	PBO +MET + SU (n=128)	Difference vs PBO (95% CI)
Mean (SD) baseline HbA_{1c}, %	8.37 (0.848)	8.19 (0.832)	–
Adjusted mean change from baseline HbA_{1c} at week 24,* %	–0.74	–0.08	–0.66 (–0.86, –0.47) P<0.0001

*Last observations carried forward.

Supported by: Bristol-Myers Squibb/AstraZeneca

1095-P

AdipoRs Activation Reduced Ectopic Fat Accumulation and Inflammation, Leading to Improved Glucose/Lipid Metabolism

TOSHIMASA YAMAUCHI, MIKI OKADA-IWABU, MASATO IWABU, TAKASHI KADOWAKI, *Tokyo, Japan*

Adiponectin (Ad) has been reported to produce a metabolic profile desirable for treating obesity-related disorders such as type2 diabetes and extend lifespan.In muscle, by using muscle-specific AdipoR1 knockout (KO) mice, we showed that calcium signaling as well as AMPK and PGC-1a areprincipal mediators activated by Ad/AdipoR1, which increase mitochondria, and ameliorate insulin resistance, like exercise.With regard to liver, we show that hepatocyte-specific disruption of AdipoR1 results in increased molecules involved in gluconeogenesis, whilehepatocyte-specific disruption of AdipoR2 results in decreased PPARapathways such as decreased molecules involved in fatty-acid combustion such as ACO, both of which are associated with insulin resistance. We next try to identify and characterize orally active small molecules thatcould be AdipoRs activators. One of these compounds, AdipoR activator (ARA) could activate AMPK, increase PGC-1a in myocytes. On a high-fat diet, orally administered ARA ameliorates insulin resistance and glucose intolerance in control, but not in AdipoR1/R2 KO mice. ARA activates AMPK and increases molecules involved in mitochondrial biogenesis such as PGC-1a, ERRa and Nrf1, molecules involved in fatty-acid combustion such as MCAD and oxida-

For author disclosure information, see page 797.

tive stress-detoxifying enzymes such as catalase in muscle, and at the same time increases exercise endurance. In liver, ARA also activates AMPK and suppresses molecules involvedin gluconeogenesis as well as increases PPARa target genes involved infatty-acid combustion such as ACO. In white adipose tissues, ARA suppresses pro-inflammatory cytokines. These effects result in reduced ectopic fat accumulation and inflammation in insulin target organ. Importantly, in AdipoR1/R2 KO mice, all these effectsare almost completely abolished.In conclusion, activation of both AdipoR1/R2 are promising novel therapeutic approach for treating obesity-related disorders such as T2D.

1096-P

Identification of a Mitochondrial Target of Thiazolidinediones (mTOT)

WILLIAM G. MCDONALD, GREGORY S. CAVEY, SERENA L. COLE, DANIELLE D. HOLEWA, ANGELA S. BRIGHTWELL-CONRAD, ROLF F. KLETZIEN, JERRY R. COLCA, *Kalamazoo, MI*

Thiazolidinediones (TZDs) are insulin sensitizing compounds with proven clinical efficacy but with an incompletely understood pleiotropic pharmacology and significant side effects that have limited their clinical utility. Here, we use a selective, photo-catalyzable affinity probe and mass spectrometry-based proteomics to identify a previously unrecognized mitochondrial target of insulin sensitizing agents. This newly identified mitochondrial target (mitochondrial Target of TZDs, mTOT) is part of a phylogenetically conserved complex in the mitochondrial membrane, which is responsible for binding of these agents to mitochondrial membranes. To determine the degree to which this complex is involved in the actions of insulin sensitizers, we have studied the ability of various analogs, including PPARγ-independent TZDs MSDC-0160 and MSDC-0602, to enhance differentiation of brown adipose tissue (BAT) progenitor cells from genetically modified mice. Ablation of the gene encoding mTOT results in embryonic lethality in mice and loss of drug-enhanced differentiation of BAT cells *in vitro*. Conversely, a targeted mutation that deletes the first 16 amino acids from the amino terminal sequence results in marked enhancement of differentiation in response to the active compounds. Insulin sensitizers of other chemical classes including MRL-24, also signal through this complex. The active compounds elicit a metabolic signal resulting in post-translational changes including activation of GSK3β associated with mitochondria. This process is necessary for differentiation of BAT cells since enforcement of Wnt signaling with LiCl or a specific inhibitor of GSK-3β (Chi-99021) completely blocked drug action. Elucidation of the mitochondrial TZD target and signaling mechanism provides an alternative approach to discovery of novel anti-diabetic agents that may avoid the side effects associated with direct activators of nuclear transcription factors.

1097-P

Acid-Base Analysis in Diabetic Ketoacidosis by Physicochemical Approach

TSUNENORI ASAKAWA, TAKESHIGE KUNIEDA, HIROMICHI TANAHASHI, MAKOTO HAYASHI, NORIYOSHI YAMAKITA, KEIGO YASUDA, *Gifu, Japan*

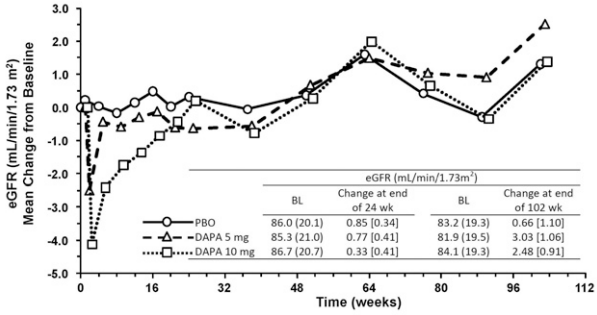
It is hard to make clear the pathophysiological changes in acid-base derangements in diabetic ketoacidosis (DKA) with conventional approach. We analyzed acid-base disturbances in DKA with Stewart's physicochemical approach modified by Fencl and Figge. Nineteen patients with DKA were involved. They were also divided into 2 groups due to serum lactic acid (LA) under 2.2 mmol/L (group 1; n = 10, mean LA; 1.6 mmol/L) and over 2.3 mmol/L (group 2; n = 9, mean LA 3.4 mmol/L). For comparison with the institutional normal values (INV), Student's t-test was used.Of 19 patients with DKA, 16 (84%) had mixed acid-base disorders with conventional analysis. Mean laboratory data of 19 patients were as follows: plasma glucose 760 mg/dl, HbA1c 10.5%, arterial pH 7.250, PaCO2 26.2 mmHg, HCO3 14.7 mEq/L, BE -11.3 mEq/L, serum Na 130.7 mEq/L, and Cl 88.3 mEq/L. These data were significantly increased or decreased compared with INV (P = 0.01 - 0.000). Mean Na corrected (Nacorr) strong ion difference (SID) and Nacorr strong ion gap (SIG) were 50.0 mEq/L (not significant vs. INV) and 25.7 mEq/L (P = 0.001 vs. 9.1 mEq/L in INV), respectively. There was no significant difference in mean total week acids. And also there were no differences in these parameters between groups 1 and 2. Serum Na/Cl ratio (mean value 1.47) was significantly lower than INV (1.35) (P = 0.000), and serum Cl was negatively correlated with SIG (r = -0.61, P = 0.02).In conclusion, the present study indicated that a chain of acid-base derangements, acidosis due to increased SIG but not associated with lowered SID, and alkalosis with both hypochloremia and hypocapnia, finally led to acidosis in DKA, and that the decreased serum Cl played an important role in the compensation of DKA. Furthermore, moderate hyperlactatemia observed in DKA plays few roles for acid-base pathophysiology. Physicochemical approach is a clinically useful tool for analysis of DKA, in particular, with mixed acid-base disorders.

1098-P

Effect of Dapagliflozin on Renal Function

AGATA PTASZYNSKA, ALEXANDROS-GEORGIOS CHALAMANDARIS, JENNIFER SUGG, KRISTINA JOHNSSON, SHAMIK PARIKH, JAMES F. LIST, *Princeton, NJ, Braine-l'Alleud, Belgium, Wilmington, DE*

Dapagliflozin (DAPA), an SGLT2 inhibitor, lowers blood glucose by inhibiting renal glucose reabsorption and is in development for patients with T2DM. Due to its renal site of action, DAPA's effect on renal function was thoroughly assessed. Data were collected from 12 placebo (PBO)-controlled randomized studies involving T2DM patients. Adverse events (AEs) and lab tests were analyzed up to 24 wk (>4000 patients) for all 12 studies and up to 102 wk (>2500 patients) in 5 of these 12 studies. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation. With DAPA, eGFR decreased by Wk 1, returned to baseline (BL) by Wk 24, and was maintained to Wk 102 (Figure). Mean serum creatinine (Cr) changed minimally (±0.01 mg/dL) from BL to Wk 24 in all groups. DAPA had no adverse effect on albuminuria, assessed as urinary albumin:Cr ratio or shift in normal, micro-, or macro- albuminuria category through 102 wk. DAPA renal AEs were similar to PBO through 24 wk but were reported slightly more frequently for DAPA through 102 wk (Table). No change from BL was noted in serum Na, K, HCO_3, Cl or Ca with DAPA or PBO; slight increases were seen in Mg and P with DAPA. DAPA treatment is not associated with increased risk of acute renal toxicity or deterioration of renal function.



*Data are mean (standard deviation) at BL or mean change [standard error] from BL at the end of the period including data after rescue

Adverse Events (AEs): Data are n (%) including data after rescue

	Up to 24 weeks			Up to 102 weeks		
	PBO N= 1393	DAPA 5mg N=1145	DAPA 10mg N=1193	PBO N=694	DAPA 5mg N=767	DAPA 10mg N=768
Serious AE of renal impairment	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (0.1)	0 (0)
AE of renal impairment leading to discontinuation	3 (0.2)	3 (0.3)	5 (0.4)	1 (0.1)	7 (0.9)	8 (1.0)
AE related to renal function	12 (0.9)	15 (1.3)	11 (0.9)	11 (1.6)	14 (1.8)	15 (2.0)
Blood creatinine increase	7 (0.5)	6 (0.5)	9 (0.8)	4 (0.6)	6 (0.8)	9 (1.2)
GFR decrease	0 (0)	3 (0.3)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Hypotension/Dehydration/ Hypovolemia	5 (0.4)	7 (0.6)	8 (0.7)	6 (0.9)	8 (1.0)	12 (1.6)

Supported by: Bristol-Myers Squibb, AstraZeneca

1099-P

Pharmacokinetics and Pharmacodynamics of a New Exenatide Formulation, Exenatide Suspension

LEIGH MACCONELL, STEPHEN FLORE, BRENDA CIRINCIONE, MATT ZIERHUT, CHRISTOPHER BIWALD, WENYING HUANG, TAMMY BOOKER PORTER, LISA PORTER, *San Diego, CA*

Exenatide, a GLP-1 receptor agonist, has been shown to improve glycemic control and body weight with twice daily or once weekly subcutaneous (SC) injections in patients with T2DM. Exenatide suspension uses the same extended-release microspheres as exenatide once weekly (EQW) but is reformulated with a medium chain triglyceride (MCT) vehicle with a history of safe use in humans. This formulation was developed to 1) yield a presuspended product not requiring reconstitution of microspheres just prior to injection as with EQW, 2) be compatible with an easier-to-use pen device, and 3) further reduce the initial exenatide release that appears to affect gastrointestinal tolerability. Using an in vitro method to compare release profiles, exenatide suspension demonstrated a blunted initial release compared to EQW but similar overall release profile. A single 10-mg dose in

30 healthy volunteers confirmed the in vitro profile; exenatide concentrations increased gradually over time, peaked at wk 6-7 and approached lower level of detection after ~wk 10. Nonparametric superpositioning simulations of single-dose data predicted steady state concentrations (Css) with 2 mg weekly exenatide suspension similar to EQW.35 patients with T2DM (31% F, 52±11 y, WT 105±22 kg, A1C 8.0±0.9%, FPG 167±34 mg/dL, mean±SD) treated with diet/exercise, metformin (MET), pioglitazone (PIO), or MET+PIO were randomized to exenatide once weekly suspension (EQWS 2 mg SC, N=23) or MCT control (SC, N=12). EQWS achieved mean Css by ~wk 8 that were in the range of Css previously seen with EQW. At wk 12, LS mean [SE] change from baseline was significantly greater with EQWS than MCT for A1C (-0.9 [0.2] vs +0.1 [0.2]%; *P*=0.0013) and FPG (-32 [10] vs +8 [12] mg/dL, *P*=0.0035) and was associated with weight loss (-1.4 kg). No unique safety findings were observed with EQWS relative to EQW. EQWS was well tolerated, with improvements in glycemic control and weight loss in patients with T2DM comparable to EQW, supporting further development of EQWS.

1100-P

Long Term Follow Up of Patients With Type 1 Diabetes on Liraglutide and the Effect of Liraglutide as Additional Treatment in Obese Patients With Type 1 Diabetes

NITESH D. KUHADIYA, RITU MALIK, NATALIE BELLINI, JANE LYONS-PATTERSON, ANDREA TRAINA, ANTOINE MAKDISSI, PARESH DANDONA, *Buffalo, NY, Rochester, NY*

We have recently shown that the addition of Liraglutide to insulin in the treatment of well controlled, non-obese patients with type 1 diabetes leads to a significant further rapid reduction in glycemia, glycemic excursions, HbA1c, insulin requirements and body weight within days. We now present data of 8 patients with type 1 diabetes (mean age: 43±8 yrs; mean duration of diabetes: 29±11 yrs) on Liraglutide treatment (mean dose: 1.72±0.67mg) for 1.24± 0.21 yrs. Percent time spent in hyperglycemia calculated by using 3 glycemic thresholds (>150,200 and 250 mg/dl) fell by 45.35%(p = 0.01), 45.19%(p = 0.03) & 61.92%(p =0.001) respectively. There was a reduction in the bolus, basal and total daily doses of insulin by 26%(p = 0.009), 19%(p = 0.01) and 20%(p = 0.008) respectively. The body weight fell from 85.3± 12.6 to 78.7±15.9 Kg (p = 0.01) and the BMI from 30.3 ± 3.9 to 27.8 ±4.9Kg/m^2 (p = 0.01). Fasting C-peptide concentrations were non-detectable at the outset and at the end of the study. We have now also investigated the effect of the addition of 1.8 mg of Liraglutide in 15 obese patients with type 1 diabetes (10 females, 5 males, 14 Caucasian, 1 African American; mean age: 47 ±13.81 yrs; mean duration of diabetes: 20.06 ± 10.18 yrs) who were not well controlled (mean HbA1c: 7.8±0.82). Over a period of 6 months, HbA1c fell to 7.39± 0.77%(p = 0.05); the bolus dose of insulin decreased significantly from 35.92 ± 19.69 to 29.52 ± 17.10 units (p = 0.03) while the basal dose did not change; the body weight fell from 100.63 ± 18.31 Kg to 95.96±19.22 kg (p = 0.008) and the BMI from 34.06±7.36 to 32.33±6.85 Kg/m^2 (p = 0.01). The systolic BP decreased from 137.53± 18.86 to 121.86±13.53(p = 0.003). We conclude that Liraglutide treatment in patients with type 1 diabetes has a rapid, sustained and durable effect on glycemia, body weight, insulin dose and systolic blood pressure. In addition, poorly controlled, obese patients with type 1 diabetes also benefit from this treatment.

1101-P

Comparative Pleiotropic Gene Profiling of Simvastatin and Vytorin in Hypercholesterolemic Subjects

ZOHARA STERNBERG, TREVOR CHICHELLI, ALISON DRAKE, FREDERICK MUNSCHAUER, *Buffalo, NY*

Background: Accumulated data indicates that similar to statins, Ezetimibe possesses pleiotropic effects beyond its lipid lowering effects.Objectives: This randomized crossover clinical trial tested the hypothesis that combination treatment with Simvastatin/ Ezetimibe (Vytorin) leads to broader changes in immunomodulatory genes, when compared to Simvastatin monotherapyMethods: Illumina's GenomeStudio gene expression module was used to compare the immunomodulatory gene profiles of Vytorin and Simvastatin in 20 hypercholesterolemic subjects.Results: The expression levels of twice as many immunomodulatory genes were altered post-Vytorin combination therapy compared to Simvastatin monotherapy.Vytorin mostly altered the expression levels of genes related to inflammation/oxidative stress; it downregulated the NF-KappaB and upregulated the expression of anti-inflammatory cytokine, IL-10, and anti-oxidant enzymes, GPX1 and SOD2.Nevertheless, Vytorin also upregulated the expression of genes involved in cellular activation, including platelet activation, adhesion, and genes involved in the activation of the coagulation cascade, including VWF, F7, PF4, PF4V1, SELP and ITGB3.Simvastatin mostly altered the expression levels of genes related to cellular apoptosis/cell proliferation. It upregulated the expression level of apoptosis-related genes such as APAF1, BAX, IER3 and CSF1R and downregulated the expression levels of genes related to cellular proliferation including PTN and CD69.Conclusion: The nature of the pleiotropic effects may play a role in Vytorin's and Simvastatin's clinical efficacy. The upregulation of genes involved in platelet activation/adhesion and the activation of the coagulation cascade may reduce Vytorin's potential to combat vascular disease. The combination treatment with agents which reduce platelet activation and/or reduce the pro-thrombotic state may improve Vytorin's clinical efficacy profile.

Supported by: Merck

1102-P

Efficacy and Safety of a Basal-Bolus Regimen of Basal Insulin Plus Insulin Glulisine in Patients With Type 2 Diabetes: A Pooled Analysis of 5 Clinical Trials

GEORGE DAILEY, JAY LIN, EDWARD WANG, *La Jolla, CA, Flemington, NJ, Bridgewater, NJ*

The "basal-bolus" regimen is the ultimate step in insulin therapy intensification. Data from 5 randomized, multicenter studies were pooled to evaluate the efficacy and safety of adding bolus doses of insulin glulisine (t.i.d.) to basal insulin for up to 6 months in type 2 diabetes mellitus (T2DM) patients.Participants were previously on insulin therapy for ≥ 3 months. Basal insulin and glulisine doses were titrated to protocol-defined fasting (FBG) or postprandial glucose (PPG) targets. A1C, FBG, PPG, insulin doses, and demographics were measured at baseline and endpoint.1413 subjects were included in the analysis (49.5% female, 86.6% White, mean age 58.0 y, mean duration of diabetes 13.7 y). In 3 studies, glargine (41.0% of pooled cohort) was the basal insulin used, while in 2 studies, patients received Neutral Protamine Hagedorn (NPH) (58.5%). Basal-bolus regimen resulted in significant decreases in A1C and FBG, and highly significant decreases in PPG (Table). Basal insulin and glulisine doses significantly increased, as did body weight (Δ weight, mean [SD]: 2.6 [4.4] kg) and body mass index (Δ BMI: 0.9 [1.5] kg/m^2). Subjects with A1C < 7% increased from 17.6% at baseline to 49.8% at endpoint. The prevalence of severe hypoglycemia (defined the same in each protocol) was 6.9%.Results of this pooled analysis suggest that a basal-bolus treatment of basal insulin + glulisine improves glycemic control with a low prevalence of severe hypoglycemia and moderate weight gain in previous, relatively well controlled (mean A1C < 8%) T2DM patients.

	Baseline	Endpoint	*P* Value
A1C, SD	7.9 (1.0)	7.1 (1.0)	< 0.001
FBG, mg/dL	153 (49)	132 (44)	< 0.001
PPG, mg/dL	183 (49)	152 (38)	< 0.001
Weight, kg	97.2 (21.2)	99.9 (22.1)	< 0.001
BMI, kg/m^2	34.1 (6.8)	35.0 (7.2)	< 0.001
Basal insulin dose, U	34.7 (26.2)	50.6 (45.4)	< 0.001
Glulisine dose, U	26.8 (26.3)	45.8 (60.8)	< 0.001

Values are mean (SD). BMI, body mass index.

Supported by: sanofi-aventis

1103-P

Starting Insulin Detemir in Older Versus Younger Adults With Type 2 Diabetes (T2DM): Results from the A$_1$chieve Study

PHILIP HOME, SIDDHARTH N. SHAH, GUILLERMO GONZÁLEZ-GÁLVEZ, NABIL K. EL NAGGAR, PRAFUL N. CHAKKARWAR, LEÓN E. LITWAK, *Newcastle upon Tyne, United Kingdom, Mumbai, India, Guadalajara, Mexico, Jeddah, Saudi Arabia, Dubai, United Arab Emirates, Ciudad de Buenos Aires, Argentina*

A$_1$chieve was a 24-week, non-interventional study evaluating the safety and effectiveness of starting an insulin analog in people with T2DM (n=66 726) in routine clinical care in 28 countries across four continents. The present subgroup analysis investigated the effectiveness of starting insulin detemir (detemir) in older (>65 yr; n=1967) and younger (≤65 yr; n=9890) insulin-naïve adults with T2DM.Baseline characteristics are shown in the table. The majority of people in both subgroups were using two oral glucose-lowering drugs at baseline (56% ≤65 yr, 55% >65 yr). A1C was poor for both age groups (9.5%) but the addition of detemir resulted in significant improvement to 7.6 (SD 1.2) and 7.4 (1.1) % (p<0.001) in older and younger participants, respectively. Starting insulin treatment with detemir was also associated with significant improvements in fasting plasma glucose (PG) and postprandial PG in both subgroups (p<0.001) at 24 weeks (Table). The overall incidence of hypoglycemia increased but remained low, while the incidence of major

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

hypoglycemia decreased from 0.07 (≤65 yr) and 0.09 (>65 yr) to 0.00 events/person-year (p<0.001 and p=0.003 respectively). Quality of life and health, as assessed by the EQ-5D 100-point visual analog scale, reported significant improvement at 24 weeks in both age groups (p<0.001) (Table).Thus, starting treatment with insulin detemir in both older and younger insulin-naïve adults with poorly controlled T2DM was associated with improvements in glycemic control without increased risk of major hypoglycemia at 24 weeks.

Baseline demographics and clinical outcomes after 24 weeks of treatment

		>65 years	≤65 years
n		1967	9890
Baseline characteristics			
Age (years)		71.5 (5.0)	50.5 (8.6)
Male (%)		42.6	57.3
Body mass index (kg/m^2)		26.8 (5.0)	28.4 (5.3)
Duration of diabetes (years)		11.2 (7.3)	6.9 (4.8)
Clinical outcomes			
A1C (%)	Baseline	9.5 (1.7)	9.5 (1.6)
	Change	-1.9 (1.6)*	-2.1 (1.6)*
FPG (pre-breakfast) (mg/dl)	Baseline	197.8 (62.0)	201.9 (57.6)
	Change	-71.4 (64.8)*	-75.7 (56.7)*
PPPG (post-breakfast) (mg/dl)	Baseline	260.9 (79.2)	271.5 (74.0)
	Change	-80.6 (83.1)*	-101.0 (73.8)*
Hypoglycemia (overall) (event/person-year [% with event])	Baseline	1.22 (4.1)	1.11 (4.0)
	Final visit	1.76 (6.0)†	1.27 (4.2)‡
Body weight (kg)	Baseline	70.0 (14.6)	77.6 (16.3)
	Change	0.4 (3.7)*	-0.5 (4.1)*
Insulin dose (U/kg)	Day 1	0.23 (0.13)	0.24 (0.13)
	Final visit	0.35 (0.19)	0.35 (0.18)
Quality of life (VAS 0-100)	Baseline	61.6 (17.3)	62.2 (16.9)
	Change	12.3 (18.5)*	16.0 (18.3)*

Mean (SD) or %; *p≤0.001 from baseline, †p=0.007, ‡p=0.481FPG, fasting plasma glucose; PPPG, postprandial plasma glucose; VAS, visual analog scale

1104-P

Pramlintide-Induced Shift Towards Euglycemia Based on SMBG Profiles in T2DM

KATHRIN HERRMANN, JUAN P. FRIAS, STEVE CHEN, STEPHAN MILLER, KEVIN SHAN, DAVID MAGGS, *San Diego, CA, La Jolla, CA*

To further understand the effects of pramlintide (PRAM) on glycemia we conducted a post-hoc analysis of the proportion of pre- and postprandial readings from 7-point glucose profiles that fell above, below, or within glycemic targets (based on AACE and ADA guidelines) in an open-label, 6-mo clinical practice trial in insulin-using patients with T2DM. Four time periods were analyzed: baseline (BL), Wk 1-4, Wk 5-15, and Wk 16 to study end (4-6 mo).Of 166 ITT patients who received PRAM for 6 mo, 138 had sufficient glucose readings to qualify for the analysis. BL characteristics were: age 54±10 y, T2DM duration 13±9 y, A1C 8.3±1.4%, weight 112±25 kg, and BMI 38.8±7.8 kg/m^2 (mean±SD). Patients initiated PRAM at 60 mcg with major meals and titrated to 120 mcg. Mealtime insulin dose was reduced upon PRAM initiation. A shift to more favorable glycemia (more euglycemia, less hyperglycemia) was seen by Wk 1-4 and sustained through the study. The percent of measurements within the ADA-defined euglycemic range (preprandial 70-130 mg/dL, postprandial 70-180 mg/dL) increased from 37.2±2.6% (mean±SE) at BL to 54.6±3.1% during the final time period (4-6 mo, P<0.0001). Conversely, percent of measurements in the ADA hyperglycemic range (preprandial >130 mg/dL, postprandial >180 mg/dL) decreased from 61.3±2.7% to 41.9±3.2% (P<0.0001). Results based on AACE glycemia guidelines (preprandial 70-<110 mg/dL, postprandial 70-<140 mg/dL) showed the same trend for euglycemia [BL 19.7±1.9%, 4-6 mo 28.4±2.8% (P<0.01)] and hyperglycemia [BL 78.8±2.0%, 4-6 mo 68.1±3.0% (P<0.002)]. Percent of measurements in the hypoglycemic range <70 mg/dL was low and increased from 1.6±0.45% to 3.5±0.9% (P<0.02) between BL and 4-6 mo. The incidence rate of severe hypoglycemia was 0.04 events/patient year (ITT). Nausea was the most frequently reported AE (29.5% of ITT patients).In this analysis adjunctive use of PRAM + insulin in T2DM improved glycemic control vs insulin alone, shifting overall glycemia towards the euglycemic range.

1105-P

Safety, Pharmacokinetics, and Pharmacodynamics of a Single Subcutaneous Dose of VRS-859 in Patients With Type 2 Diabetes

JEFFREY L. CLELAND, RONNIE ARONSON, ERIC HUMPHRISS, CAMILLE SHORE, RONG ZHOU, MARK S. KIPNES, *Redwood City, CA, Toronto, ON, Canada, Cincinnati, OH, San Antonio, TX*

VRS-859, a GLP-1 analog XTEN fusion protein, was compared vs placebo, in a dose-ranging study of a single subcutaneous dose, in patients with type 2 diabetes mellitus (T2DM) using concurrent metformin monotherapy. In each group, 8 patients received VRS-859 and 3 patients received placebo (PBO) in a randomized blinded manner. Fasting glucose (FG), insulin, and oral glucose tolerance (OGTT) tests were performed on Days -1, 4, 8, 11, 15, 18, 22, 25, and 30. Glycated albumin, HbA1c, body weight, and immune responses to drug were measured on Day -1 and Day 30.70 patients were randomized in the study (56% M, 52 y, 93 kg, 8.2% HbA1c, 171 mg/dL FG; mean). 52 T2DM patients were treated with VRS-859 and 18 T2DM patients were treated with placebo. No serious adverse events were reported and no patients dropped out of the study. No changes in QTc interval were observed and no anti-VRS-859 antibodies were detected. Safety assessments, including lipase, amylase, and calcitonin levels, were unremarkable at screening and through Day 30. VRS-859 was well tolerated even at the maximum dose, 200 mg, where 3 of 8 patients had mild transient gastrointestinal (GI) adverse events (resolved within 48 hrs post-dose). VRS-859 pharmacokinetics were dose linear with an average T_{max} of 90 hr, and an average $t_{1/2}$ of 128 hr. Reductions in FG and glucose excursions after OGTTs increased with dose and the reduction in FG was significant through Day 25 at the 200 mg dose.

Day	PBO (n=16)	12.5 mg (n=8)	25 mg (n=8)	50 mg (n=7)	100 mg (n=8)	150 mg (n=7)	200 mg (n=8)
	Change from Day -1 FG (mg/dL)						
4	-1.4	-30.9[a]	-28.7[a]	-33.2[a]	-59.9[d]	-50.3[d]	-48.6[d]
8	2.2	-8.4	-20.4	-21.7	-51.8[d]	-51.1[d]	-68.4[d]
11	3.3	-2.3	-7.8	-20.4	-43.0[d]	-35.4[b]	-43.5[d]
15	0.51	4.2	0.3	-15.0	-27.5[a]	-15.6	-31.8[b]
18	0.74	-3.2	9.6	-0.8	-24.3[a]	-3.0	-34.9[b]
22	7.9	7.1	10.5	-1.3	-19.2[a]	10.1	-26.4[b]
25	6.1	12.1	19.2	-3.4	-3.2	10.4	-28.4[b]
30	10.6	7.6	20.8	20.0	3.1	-2.2	-7.0
	Change from Day -1 Post-OGTT AUC (mg/dL-hr)						
4	22.7	-49.7[a]	-81.8[c]	-120.6[d]	-169.3[d]	-195.7[d]	-215.5[d]
8	21.6	1.6	-48.3[a]	-79.2[b]	-144.1[d]	-144.4[d]	-150.2[d]
11	24.2	-10.7	-16.1	-68.6[b]	-128.2[d]	-62.3[b]	-135.4[d]
15	18.5	11.1	0.8	-32.1	-56.2[b]	-44.3[a]	-64.3[b]
18	12.8	-3.3	6.1	2.9	-52.2[a]	23.9	-42.2[a]
22	15.3	10.7	18.9	-4.9	-50.9[a]	58.6	-10.4
25	14.4	35.5	36.1	10.2	-27.3	4.6	-12.7
30	7.6	39.0	49.7	-15.8	-27.9	-5.4	-1.2

P values compared to PBO: (a) < 0.05; (b) < 0.01; (c) < 0.001; (d) < 0.0001

In summary, VRS-859 provided glycemic control in T2DM patients enabling dosing with extended dosing intervals up to monthly with minimal GI side effects.

1106-P

Acyl CoA:Diacylglycerol Acyltransferase 1 (DGAT1) Inhibitor Blocks Ectopic Lipid Accumulation and Prevents the Loss of Insulin Content by Nutrient Overload in Human Islets

STEPHANIE B. VERNIER, BHARGAV PATEL, TERYN V. BRENEGAN, WILLIAM L. NEUMANN, JOSEPH SCHOBER, PAUL WANDA, GUIM KWON, *Edwardsville, IL*

Recent studies indicate that targeting acyl CoA: diacylglycerol acyltransferase 1 (DGAT1), a key enzyme in triglyceride (TG) synthesis, may provide a novel approach to treating obesity and type 2 diabetes mellitus (T2DM). Small molecules that inhibit DGAT1 have been shown to reduce weight gain and insulin resistance in rodents. The effects of DGAT1 inhibitors on ectopic lipid accumulation and associated β-cell defects under nutrient overload, however, have not been studied yet. To this end, we synthesized a DGAT1 inhibitor BN99, 4-(4-(2-cyclohexy-lacetamido)phenyl)-N-(2,6-dichlorophenyl) piperazine-1-carboxamide, reported by Janssen and studied its effects in human islets under nutrient overload. Treatment of dispersed human islet cells with excess nutrients, 25 mM glucose and 500 μM FFAs (oleate:palmitate=1:1) complexed with BSA at a 3:1 ratio, caused lipid droplet formation in insulin-

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

positive cells in a time-dependent manner. BN99 blocked lipid droplet formation caused by excess nutrients in a concentration-dependent manner ranged in 0.01-1 μM. Immunohistochemistry of frozen sections of human islets treated with excess nutrients also showed significantly higher levels of lipid droplets as compared to those of control or BN99 (1μM) treated islets. Importantly, BN99 (1 μM) completely prevented the loss of insulin content caused by excess nutrients. Moreover, BN99 also partially prevented the distortion of islet architecture caused by excess nutrients. Taken together, these studies suggest that a DGAT1 inhibitor may protect human β-cell function under nutrient overload.

1107-P

Nonclinical Efficacy and Safety of PEGylated C-Peptide

MICHELLE MAZZONI, DENNIS NAAS, JAMES CALLAWAY, *La Jolla, CA, Poway, CA*

A long-acting C-peptide (Ersatta) is in clinical development for the treatment of diabetic peripheral neuropathy. Ersatta is synthetic human C-peptide with a 40 kDa polyethylene glycol (PEG) linked to the non-active portion of the peptide; half-life is days vs. minutes with native C-peptide. To compare the potency of PEGylated C-peptide to its native form, Sprague Dawley rats were made diabetic by intravenous streptozotocin (STZ; 33 mg/kg) and randomized into 7 treatment groups (N=15): vehicle and low, mid, and high Ersatta or native C-peptide. At 10 days post-STZ, rats were administered subcutaneously Ersatta or vehicle by injection every 3 days or native C-peptide via implanted pumps. Animals were hyperglycemic but maintained on daily insulin. Plasma levels of both forms of peptide demonstrated 3 distinct and matched exposure ranges (2-40 nM) over the 12-week treatment period. Ersatta showed a dose-response improvement in caudal nerve conduction velocity (NCV) vs. baseline as compared to vehicle controls. At the highest exposure, the 4.5 m/s relative increase in NCV with Ersatta was comparable to that for native C-peptide. Thus, consistent with previous work, PEGylation of C-peptide does not alter its biological activity. Furthermore, the nonclinical safety of Ersatta was assessed in GLP-compliant toxicology studies in Sprague Dawley rats and cynomolgus monkeys with 6 months of weekly subcutaneous dosing. No systemic toxicities or meaningful development of antibodies to PEGylated C-peptide in either species were observed. There were findings of vacuolated macrophages in the skin and draining lymph nodes at injection sites consistent with the known clearance process for PEGylated peptides/proteins. Based on area under the curve exposures, the safety margins for chronic dosing in humans considering a target Ersatta dose of 1 mg/week to replace C-peptide in type 1 diabetes patients are 400-fold (rat) and 340-fold (monkey). Thus, Ersatta has an excellent nonclinical safety profile that supports chronic human dosing.

1108-P

Real-World Practice Pattern and Outcomes of Patients With Type 2 Diabetes (T2DM) Initiating Injectable Therapy via Insulin Glargine Disposable Pen (GLA-P) or Liraglutide (LIRA)

JAY LIN, WENHUI WEI, ALEKSANDRA VLAJNIC, CHUNSHEN PAN, LIN XIE, ONUR BASER, PHILIP LEVIN, *Flemington, NJ, Bridgewater, NJ, Boca Raton, FL, Ann Arbor, MI, Baltimore, MD*

Initiation of injectable therapy is a major event for T2DM patients but has limited real-world data. This study examined real-world practice patterns, 1-yr clinical outcomes, and plan-paid health care costs of T2DM patients initiating injectables via GLA-P or LIRA.Using the IMPACT® database, 967 unmatched adult T2DM patients who initiated GLA-P (n=557) or LIRA (n=410) between 01/2010 and 06/2010 and had 1-yr follow-up were assessed descriptively.Significant baseline (6 months before initiation) differences existed between the 2 cohorts. GLA-P initiators, compared with LIRA, were older (10.7% ≥65 years vs 6.5%); more male (56.1% vs 47.1%); sicker (Charlson comorbidity index 0.63 vs 0.34); less obese (10.2% vs 16.5%); had higher A1C (mean 9.6% vs 7.9%; 8.2% in GLA-P had A1C <7% vs 31.2% in LIRA); had more hospitalizations (11.3% vs 3.1%), emergency room (ER) visits (23.1% vs 16.0%), and hypoglycemic events (4.4% vs 1.9%); and had higher health care costs ($8,499 vs $5,563).During follow-up, treatment persistence was 52.0% in GLA-P and 43.6% in LIRA. A1C reduction was –1.31% in GLA-P and –0.51% in LIRA; 20.6% of GLA-P initiators achieving A1C <7% and 33.8% for LIRA (among those with baseline A1C >7 % and follow-up A1C data available: n=276 for GLA-P and n=179 for LIRA). Overall hypoglycemia-related event rates were 25.7 (GLA-P) and 8.5 (LIRA) per 100 patients/year, but hypoglycemia-related hospital/ER event rates were low in both cohorts (2.5 and 1.5). Mean 1-yr total health care cost was $15,993 in GLA-P (7.2% from study drug) and $15,544 in LIRA (16.8% from study drug).These data show a trend of prescribing GLA-P and LIRA to different T2DM patients when initiating injectable therapy, suggesting challenges in looking at real-world comparative effectiveness. About 1/3 of LIRA initiators had A1C <7%, suggesting that a substantial number of patients might not have initiated LIRA primarily to improve glycemic control.

Supported by: sanofi-aventis

1109-P

Compensatory Effect of Endogenous Glucose Production (EGP) after Acute Urinary Glucose Excretion (UGE) from Selective SGLT2 Inhibition With Tofogliflozin (TOFO) or SGLT1/2 Inhibition With Phlorizin (PHZ) in Normal and Diabetic Rats

MASANORI FUKAZAWA, TAKUMI NAGATA, NAOAKI MURAO, MIZUKI YAMANE, MASAYUKI SUZUKI, TETSUYA MITSUI, YOSHIYUKI SUZUKI, KIYOFUMI HONDA, SACHIYA IKEDA, YOSHIKI KAWABE, *Gotemba, Shizuoka, Japan*

A difference in the compensatory effect for glucose loss by EGP between normal and diabetic conditions has been suggested by the instance of SGLT2 inhibitors only lowering plasma glucose (PG) in diabetic conditions despite the UGE induction in normal conditions. As SGLT1 and 2 both contribute differently to UGE (SGLT1; high affinity/low capacity transporter, SGLT2; low affinity/high capacity), clarifying the compensatory role of EGP under both normal and diabetic conditions after acute UGE when inhibiting either SGLT2 or both SGLT1 and 2 is important to understand the hypoglycemia potential. Here we evaluated PG and EGP simultaneously in anesthetized normal (Wistar) and diabetic (ZDF) rats after acute UGE by continuous infusion of TOFO, a highly selective SGLT2 inhibitor under clinical development, or PHZ, a SGLT1/2 dual inhibitor (IC50s for rat SGLT1 and 2 are: TOFO 8200 and 15 nM; PHZ 970 and 48 nM). In normal rats, induction of UGE with TOFO at a plasma concentration fully inhibiting SGLT2 but not SGLT1, reduced PG only slightly (to >100 mg/dL) and increased EGP. In diabetic rats, which showed higher EGP levels than normal rats, TOFO at an equipotent plasma concentration induced greater UGE and reduced PG to 130 mg/dL without further increase of EGP. In normal rats, PHZ at a plasma concentration inhibiting both SGLT1 and 2, increased EGP similarly to TOFO despite the greater UGE induction than TOFO, and PG was reduced to ~90 mg/dL. In conclusion, PG with UGE induction by selective SGLT2 inhibition was compensated for in normal rats but not in diabetic rats. Moreover, greater UGE by SGLT1 and 2 inhibition lowered PG further with only limited compensation by EGP under normal conditions. These suggest the lower hypoglycemia potential of highly selective inhibition of SGLT2 in terms of compensative capacity of EGP.

1110-P

The Comparison of the Therapeutic Effect of Allogeneic and Syngeneic Mesenchymal Stem Cell Transplantation in a Diabetic Model of Hindlimb Ischaemia

AARON LIEW, CLAAS BAUSTIAN, DILIP THOMAS, ERIN VAUGHAN, XIZHE CHEN, CLARA SANZ-NOGUES, MICHAEL CREANE, SENTHILKUMAR ALAGESAN, PETER OWENS, JASON HORAN, RHODRI CEREDIG, PETER DOCKERY, MATTHEW GRIFFIN, TIMOTHY O'BRIEN, *Galway, Ireland*

Diabetes Mellitus is associated with a worse outcome in patients with peripheral arterial disease. Mesenchymal stem cells (MSCs) have been shown to improve therapeutic neovascularisation. Allogeneic MSCs have an advantage in that they can be isolated from non-diabetic donors thus avoiding disease-induced cellular dysfunction. In addition, allogeneic cells may be used as 'off the shelf' product as they can be prepared in advance. There has been no study to date comparing the efficacy of transplantation of allogeneic and syngeneic MSC transplantation from diabetic and non-diabetic donors respectively into a diabetic animal model. Allogeneic and syngeneic MSCs were isolated from C57BL/6(H-2^b) and diabetic obese dbdb/C57BKS(H-2^d) mice respectively. Unilateral hindlimb ischaemia (HLI) was induced in diabetic obese mice. Normal saline, allogeneic or syngeneic MSCs ($1x10^6$) were administered intramuscularly into the ischaemic thigh following the induction of HLI. MSCs derived from both sources secrete various angiogenic factors and are able to form tubules *in vitro.* Allogeneic MSCs significantly improve blood perfusion as compared to the control group at all time points studied after transplantation (1, 2 and 3 weeks after induction of HLI). Syngeneic MSCs significantly improve blood perfusion as compared to the control group at week two only. There was no statistical difference in blood perfusion between the allogeneic and syngeneic MSC group. The percentage of toe necrosis were 50%(4/8), 86%(6/7) and 86%(6/7) in the allogeneic, syngeneic and control groups respectively. Toes amputation were seen in 14%(1/7) of the control group but not in the other groups. In conclusion, either autologous or allogeneic transplantation have beneficial effects in the diabetic setting.

Supported by: Science Foundation Ireland and Medtronic Ireland

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

1111-P

Exendin-4 Inhibits Palmitate-Induced Apoptosis of Human Cardiac Progenitor Cells

ANNA LEONARDINI, LUIGI LAVIOLA, MAURA R. ORLANDO, MARIA A. INCALZA, ANNALISA NATALICCHIO, SEBASTIO PERRINI, FRANCESCO GIORGINO, *Bari, Italy*

Dysfunction and increased apoptosis of cardiac progenitor cells (CPCs) may contribute to the cardiac abnormalities observed in type 2 diabetes. Glucagon-like peptide-1 (GLP-1)-based therapies may promote survival of cardiac cells. Thus, the aim of this study was to investigate the protective effects of the GLP-1 receptor agonist exendin-4 on palmitate-induced apoptosis of human CPCs isolated from biopsies of the right auricle during open heart surgery. Biopsy-obtained cells showed typical features of mesenchimal multipotent cells, including the differentiation toward the adipogenic, osteogenic and chondrogenic lineages. Acute exposure of CPCs to GLP-1 resulted in a time- and dose-dependent increase in intracellular cAMP levels and CREB phosphorylation, which were abolished in the presence of the GLP-1 receptor (GLP-1R) antagonist exendin 9-39 or following siRNA-mediated silencing of the GLP-1R. When CPCs were incubated in the presence of 25 mM palmitate for 16 h, a 4-fold increase in cell apoptosis was detected by measuring cytosolic oligosomes. However, incubation with palmitate for shorter times (10-120 min) did not induce cell apoptosis. Similarly, exposure to 25 mM glucose for up to 16 h had no effect on CPCs apoptosis. Noteworthy, preincubation of CPCs with the GLP-1R agonist exendin-4 (20 nM for 16 h) inhibited palmitate-induced apoptosis ($p<0.05$ vs. CPCs treated with palmitate alone). Thus, long-term exposure to palmitate specifically reduces the viability of human CPCs through increased apoptosis, whereas GLP-1R activation prevents this response. The GLP-1R-mediated effects may play a role in the cardioprotective action of GLP-1-based therapies in subjects with type 2 diabetes.

Supported by: Eli Lilly Foundation

1112-P

CNX-011-67, A Novel Orally Available GPR40 Agonist Enhances Glucose Dependent Insulin Secretion, Significantly Reduces Fed and Fasting Glucose and HbA1c Levels and Improves Pancreatic Insulin Content in Female ZDF Rats on a High Fat Diet

M.R. JAGANNATH, M.V. VENKATARANGANNA, B.P. SOMES, ANILKUMAR DANDU, YOGANAND MOOLEMATH, ANUP MAMMEN OOMMEN, M.K. VERM, K. APARN, M.K. GOVIN, NAGESH GOWDA, B. SANGHAMITR, JAIDEEP SINGH, RAVEENDRA GHODKE, V. SUNI, P.C. SHILP, P. NIKET, D.N. VIJAYARAGHAV, VASADHA KADAM, D. DHANANJAYA, *Bangalore, India*

We previously reported that CNX-011-67 delayed onset of diabetes in male ZDF rats. We now extend our observations to demonstrate that chronic treatment of diabetic female ZDF rats (n = 9) on high fat diet for 8 weeks with CNX-011-67 leads to a 18% reduction in fasting (230±37 (treated) Vs 272±39 (Zdf) mg/dl, n=9) and 20% reduction in random blood glucose levels (285±34 (treated) Vs 361±52 (Zdf) mg/dl, n=9). There was a significant reduction in post-OGTT glucose excursion with a prolonged control of (24h) post meal glucose levels. Treatment with CNX-011-67 enhanced phasic insulin secretion, improved insulinogenic index (0.5±0.1 (treated) Vs (0.3±0.1 (ZDF) and improved islet insulin content (as demonstrated by IFC staining) suggesting enhanced glucose responsiveness of beta cells. Treatment for 8 wks led to 1.1% reduction in HbA1c ($p<0.05$) and a concomitant 32% reduction in TBARS and 15% in HNE indicating better control of glucose excursion. Enhanced AKT phosphorylation (~20%, n=6) suggested improved peripheral insulin action in adipose, liver and muscle in rats treated with CNX-011-67. Immunohistochemistry studies revealed enhanced insulin content in islets from CNX-011-67 treated rats. In parallel studies, treatment of cultured Wistar rat islets with CNX-011-67 exposed to severe glucolipotoxic conditions (16.7mM glucose and 500µM Palmitate) showed increased IP3 generation (~25%), cytoplasmic and mitochondrial [Ca^{2+}] in NIT-1 cells (~20%). Thapsigargin-triggered endoplasmic reticulum stress-mediated inhibition of glucose stimulated insulin secretion in rat islets was significantly overcome by chronic treatment with CNX-011-67. In summary, these data suggest that long- term oral therapy with CNX-011-67 could be of clinical value to improve islet function by multiple mechanisms to maintain normoglycemia in T2D patients

1113-P

Liraglutide is Safe and Effective in Mild or Moderate Renal Impairment: The Association of British Clinical Diabetologists (ABCD) Nationwide Liraglutide Audit

KEN Y. THONG, CHRISTOPHER WALTON, ROBERT E. RYDER, ABCD NATIONWIDE LIRAGLUTIDE AUDIT CONTRIBUTORS, *Birmingham, United Kingdom, Hull, United Kingdom*

We evaluated the safety and efficacy of liraglutide among patients with mild or moderate renal impairment. Data was obtained from a nationwide audit of liraglutide use in UK. Among 4129 patients, we excluded patients with follow-up <6 months, previously on exenatide, used liraglutide 1.8 mg (too few to analyse), or lacked baseline data to estimate creatinine clearance (CrCl) using the Cockcroft-Gault formula. Remaining 1081 patients were divided into CKD group 1 (normal, eCrCl>90 ml/min) (n=872), CKD group 2 (mild renal impairment, eCrCl 60-90 ml/min) (n=169) and CKD group 3 (moderate renal impairment, eCrCl 30-59 ml/min) (n=40). Effect of CKD group on changes of A1c, weight, systolic blood pressure (SBP) and creatinine (Cr) at 6 months were analysed using ANCOVA using baseline values as covariates, while proportion of patients reaching A1c ≤7%, suffering gastrointestinal (GI) side effects (adjusted for gender), or hypoglycaemia (adjusted for insulin and sulfonylurea use) using logistic regression. A1c and weight reduction for all three groups were significantly reduced from baseline; CKD group 1, -1.0% (0.1) and -3.6 kg (0.2), CKD group 2, -0.9% (0.1) and -3.3 kg (0.4), and group 3, -0.8% (0.2) and 2.5 kg (0.9). There were no influences of CKD group on A1c reduction (p=0.46) or weight reduction (p=0.95). Similarly, no effect of CKD group was seen on SBP reduction (-4 mmHg v -3 mmHg v -6 mmHg, p=0.74), rates of GI side effects (15.3% v 12.4% v 17.5%, CKD 2 v 1 OR [95%CI] 0.8 [0.5,1.2], p=0.26) or rates of reported hypoglycaemia (1.7% v 1.2% v 0%, CKD 2 v 1 OR 0.5 [0.1,2.2] (p=0.36). A small but significant reduction of Cr was observed with advancing CKD group (+1 µmol/L v -3 µmol/L v -7 µmol/L, p=0.02). 1 case of acute renal failure attributed to dehydration from prolonged vomiting was reported in CKD group 2. We conclude that liraglutide 1.2 mg is safe and effective in real life clinical practice among patients with mild or moderate renal impairment.

Supported by: Novo Nordisk, Inc.

1114-P

Efficacy and Safety of Dapagliflozin for Type 2 Diabetes Mellitus Patients With a History of Cardiovascular Disease

LAWRENCE A. LEITER, WILLIAM T. CEFALU, TJERK W. DEBRUIN, INGRID GAUSE-NILSSON, JENNIFER SUGG, SHAMIK J. PARIKH, *Toronto, ON, Canada, Baton Rouge, LA, Wilmington, DE, Moindal, Sweden*

Dapagliflozin (DAPA) is a selective SGLT2 inhibitor with glucuretic effects for the treatment of type 2 diabetes mellitus (T2DM). To assess DAPA benefit risk, 2 Phase 3 trials were conducted. Here DAPA was evaluated in patients with HbA1c ≥ 7.0 - ≤ 10.0% and documented cardiovascular disease (CVD). Patients (N=964) were randomized to receive double-blind 10 mg/d DAPA or placebo (PBO) for 24 wks (80-wk extension ongoing) and stratified by age (< 65 or ≥ 65 y), insulin (INS) use, and time from most recent qualifying CV event (NCT01042977). INS doses were reduced by 25% at randomization. Mean age was 64 y, and 47% were ≥ 65 y. Mean T2DM duration was 13 y. The majority of patients reported the use of 1-2 oral anti-hyperglycemic agents. Twenty percent received only INS and 41% used INS in combination with other treatments. A history of hypertension was present in 93% of patients. The independent primary end points were change from baseline (BL) in HbA1c as well as patients (%) reaching a 3-item end point (reduction of ≥ 0.5% in HbA1c, ≥ 3 % in body weight [BW], and ≥ 3 mm Hg in seated systolic blood pressure [SBP]). Reductions from BL were greater for DAPA vs PBO (P <0.0002) in HbA1c (BL 8.1%; -0.3 vs 0.1 %), BW (BL 93.9 kg; -2.5 vs -0.6 %), and SBP (BL 134.7 mm Hg; -2.7 vs 0.3 mm Hg). More DAPA patients achieved the 3-item end point (10.0% vs PBO: 1.9%, P <0.0001). In those receiving INS, the mean daily INS dose increased 10% (5.3 IU/d) with PBO vs no change on DAPA (nominal P <0.05). Stratified analyses yielded results consistent with the overall analysis; however, SBP reduction was not significantly different at 24 wks in patients ≥ 65 y. Incidences of adverse events (AEs) and serious AEs were balanced between groups, but more patients on DAPA had events suggestive of genital and urinary tract infections. When added to standard of care, DAPA improved glycemic control and BP, induced weight loss, and was well-tolerated in an older, high CV risk population with advanced T2DM and comorbid CVD.

Supported by: AstraZeneca/Bristol-Myers Squibb

1115-P

ARRY-981, a Novel GPR119 Agonist With Durable Reductions in Blood Glucose Levels

JAY B. FELL, LANCE M. WILLIAMS, MARALEE MCVEAN, PATRICE LEE, NICKOLAS A. NEITZEL, PAUL LARSON, BRIAN BAER, THOMAS D. AICHER, STEVEN A. BOYD, RONALD J. HINKLIN, TIMOTHY M. TURNER, JOHN P. FISCHER, JAMES D. WINKLER, KEVIN KOCH, *Boulder, CO, Fort Collins, CO, Ann Arbor, MI, Pittsburgh, PA*

GPR119 has emerged as a promising new target for the treatment of type 2 diabetes mellitus. The expression of this G-protein coupled receptor on the β-cells of the pancreas and the L-cells of the gastrointestinal tract provides a unique opportunity for a single drug to promote insulin secretion via two distinct pathways. However, of recent concern is the loss of activity seen *in vivo* with select GPR119 agonists. Tachyphylaxis in ZDF rats was reported by Neurocrine Biosciences upon subchronic treatment with their GPR119 agonist NBI104 (ADA 2010 #0697-P). GlaxoSmithKline announced that their clinical GPR119 agonist, GSK1292263, did not reduce 24 hour glucose profiles after 14 days of dosing (ADA 2011 #0996-P). We have identified a novel GPR119 agonist, ARRY-981, that showed durable blood glucose reductions over 28 days of QD dosing in the high fat fed female ZDF rat and the DIO mouse models. ARRY-981 is a selective GRP119 agonist which does not bind to numerous other receptors or enzymes. In animals, administration of this drug elevated GLP-1 levels 7-fold over control, confirming its on-target activity. ARRY-981 was selected from a proprietary series of compounds optimized for efficacy in multiple diabetic animal models. In high fat fed female ZDF rats, dosed QD for 7 days at 10 mg/kg, this drug demonstrated 47% $AUC_{glucose}$ lowering, as well as both fasted and non-fasted blood glucose lowering. Additive $AUC_{glucose}$ lowering was observed when ARRY-981 was dosed at 3 mg/kg QD for one week in combination with either metformin, sitagliptin or dapagliflozin. In addition, fasted and non-fasted blood glucose levels were normalized in these combination studies. Finally, ARRY-981 significantly lowered serum triglycerides 48% versus control in a hyperlipidemic animal model when dosed QD for 28 days at 10 mg/kg.

1116-P

Evaluating the Clinical and Cost Effectiveness and Patient Preference of Incretin Therapies When Used in Accordance With National Guidelines in Routine UK Primary Care Practice

MARC EVANS, PHIL MCEWAN, RICHARD O'SHEA, ALISON CLARKE, LINDSAY GEORGE, *Cardiff, United Kingdom, Swansea, United Kingdom*

This study assessed the clinical effects and patient preference with respect to liraglutide, exenatide and DPP-4 inhibitors when used in routine primary care according to current UK treatment guidelines. Anonymised data on multiple parameters including HbA_{1c}, weight, adverse events and treatment discontinuation was collected from GP practices for patients receiving an incretin therapy according to current UK guidelines. Consecutive patients considered appropriate for an incretin therapy were also surveyed for treatment preference. Based on observed treatment effects, UKPDS 68 risk equations were applied over a 20-year time horizon to calculate the cost effectiveness of liraglutide, exenatide and DPP-4 inhibitors in the respective patient groups prescribed any of these agents (using the acquisition cost of the most commonly prescribed DPP-4 inhibitor, sitagliptin). Data (Mean ±SD) from 1114 patients were obtained. Greater reduction in HbA_{1c} was observed for liraglutide compared to exenatide or DPP-4 inhibitors (1.23% (±0.14), 0.79% (±0.19) and 0.72% (±0.23), $p<0.05$). Weight changes were -3.9kg (±5.7), -2.9kg (±5.8) and -0.8kg (±3.1) for those receiving liraglutide, exenatide or a DPP-4 inhibitor. More patients expressed a preference for a drug with a liraglutide profile over one with a sitagliptin-like profile (62.5 vs 37.5%, $p<0.05$). Based on the latest measured observations, the calculated life years gained per patient was 0.12, 0.08 and 0.07 for those prescribed liraglutide, exenatide or a DPP-4 inhibitor compared to their respective baseline. The observed cost/QALY vs baseline for patients receiving liraglutide, exenatide or a DPP-4 inhibitor was £16,505, £16,648 and £20,661. In conclusion, clinical practice experience reflects clinical trial data, with liraglutide demonstrating superior cost effectiveness, while patients appeared to favour a drug with a liraglutide-like profile.

1117-P

Effects of PF-04620110, a Novel Diacylglycerol Acyltransferase 1 (DGAT-1) Inhibitor, in Type 2 Diabetes (T2DM) Subjects With Insufficient Glycemic Control on Metformin

JIE LI, GIANLUCA NUCCI, WEI GAO, DOUGLAS S. LEE, CLAIRE M. STEPPAN, ROBERTO CALLE, JAMES M. RUSNAK, *Cambridge, MA, Groton, CT*

PF04620110, a DGAT1 inhibitor, was previously evaluated in healthy obese subjects (HOV). There was a decrease in triglycerides (TG) and insulin with an increase in GLP-1; however, the dose was limited to 5 mg QD due to GI AEs. This double-blind, placebo-controlled study investigated the efficacy and safety of PF04620110 over 4 weeks in 48 T2DM subjects. The subjects received either PF 04620110 5 mg QD, 2.5 mg BID or placebo. The BID arm was initiated at 2.5 mg QD, escalated to 2.5 mg BID on Day 15, with BID continuing through Day 28. Subjects were confined at the CRU for the study duration and followed an isocaloric diet. The 4-hour area under the curve (AUC) for glucose, GLP-1, TG and insulin as well as the 24 hour weighted mean glucose concentrations were measured at baseline (Day -1) and study end (Day 28). PK was comparable to that observed previously in HOV and total exposure was similar between QD and BID. There were no clinically relevant laboratory test abnormalities, vital signs, and ECG changes and no withdrawals due to AEs. The most common AEs were nausea, diarrhea, and headache with nausea reported in 43.8% of subjects at 2.5 mg BID and 37.5% in 5 mg QD. PF04620110 provided minimally additional pharmacodynamic benefit over a robust placebo effect in T2DM subjects.

Descriptive Summary of the Changes from Baseline (90%CI) on Day 28 by Treatment Group

	2.5 mg BID N=15	**5 mg QD** N=16	**Placebo** N=15
Glucose AUC (mg*hr/dL)	-118.25 (-240.56, 4.06)	-142.97 (-246.29, -39.64)	-117.66 (-189.25,-46.07)
Insulin AUC(IU*hr/mL)	12.40 (-16.64, 41.44)	0.61 (-69.19, 70.40)	41.0 (20.08, 61.91)
TG AUC(mg*hr/dL)	-184.96[a] (-400.84, 30.93)	-100.46 (-218.08, 17.15)	-110.27 (-221.85, 1.30)
Total GLP-1 AUC(pmol*hr/L)	25.28 (12.59, 37.97)	4.73 (-8.66, 18.13)	-17.52[b] (-59.57, 24.54)
24-hour weighted mean glucose (mg/dL)	-25.42 (-53.10, 2.26)	-23.40 (-42.00,-4.79)	-18.28 (-31.74,-4.81)

[a] N= 13, [b] N= 14.

1118-P

Signal Detection for Quantitative Identification of Subgroups of Patients With Type 2 Diabetes Mellitus (T2DM) Likely to Achieve Metabolic Control With Basal Insulin Therapy

VANITA ARODA, ROBERT RATNER, MANON GIRARD, RACHELE BERRIA, ALEKSANDRA VLAJNIC, JOHN STEWART, MATTHEW RIDDLE, *Hyattsville, MD, Quebec, QC, Canada, Bridgewater, NJ, Portland, OR*

Signal detection methods offer an alternative way to analyze clinical studies, generating decision trees that can quantitatively identify subgroups of patients who may or may not benefit from treatment. We used recursive partitioning, a forward iterative process, to identify variables that quantify clinical trial data to allow prediction of response to T2DM treatment in an individual patient.Patient-level data from 11 studies evaluating initiation and titration of insulin glargine for ≥24 weeks in patients with T2DM were pooled for analysis (N=2251: mean [SD] age 58.4 [10.1] years, 55.1% men, T2DM duration 8.9 [6.2] years, baseline A1C 8.8 [1.1] %, baseline fasting plasma glucose [FPG] 198 [52.4] mg/dL, baseline weight 89.2 [18.4] kg), baseline metformin [MET] or sulphonylurea [SU] use 59.3% and 85.1%, respectively). Treatment response was defined as A1C <7.0% at Week 24. Composite endpoints of A1C <7.0% with no hypoglycemia, and A1C <7.0% with no hypoglycemia and no weight gain, were also examined. Seven candidate baseline variables were entered into models: age, gender, T2DM duration, A1C, FPG, and MET or SU use. Each variable was processed within each data subgroup to determine the best cut-off for partitioning data, until the cut-off was not significant ($P>0.05$) or <10 patients were in a subgroup.Overall, 51% of patients achieved A1C <7.0% with insulin glargine. Probability of reaching target was 64% if baseline A1C ≤8.8%, increasing to 83% if the patient also had an FPG >156 mg/dL and no SU therapy at baseline. Probability of reaching target was only 33% if T2DM duration was >5 years and baseline FPG >220 mg/dL. Similar factors were identified for the two composite endpoints. This analysis identifies readily available clinical variables that may help predict a response to treatment, thus facilitating individualization of therapy by physicians for patients with T2DM according to their characteristics.

Supported by: sanofi-aventis

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

1119-P

Insulin Degludec has Similar Pharmacokinetic Properties in Subjects With Hepatic Impairment when Compared to Subjects With Normal Hepatic Function

GERHARD AROLD, VIERA KUPČOVÁ, MARIANNE THRANE, MALENE HØJBJERRE, HANNE L. HAAHR, *Berlin, Germany, Bratislava, Slovakia, Copenhagen, Denmark, Aalborg, Denmark, Søborg, Denmark*

Insulin degludec (IDeg) is a new-generation basal insulin that forms soluble multi-hexamers upon subcutaneous injection, resulting in a flat and stable ultra-long action profile. This open-label, parallel-group study investigated the pharmacokinetic (PK) properties of IDeg in subjects with different grades of hepatic impairment and in subjects with normal hepatic function following single-dose administration of 0.4 U/kg IDeg.A total of 24 subjects (mean age: 47.4 yrs; females/males: 16/8; mean BMI: 26.0 kg/m^2) were allocated to one of 4 hepatic function groups (N=6 per group): mild, moderate, severe hepatic impairment, or normal hepatic function. In the severe hepatic impairment group, 3 subjects had diabetes. Blood samples for PK analysis were collected before and up to 120 hrs after IDeg administration.The mean PK profiles of IDeg were similar for subjects with normal and impaired hepatic function. In addition, hepatic impairment had no statistically significant effect on total exposure ($AUC_{IDeg,0\text{-}120h,SD}$), maximum concentration ($C_{max,IDeg,SD}$) or apparent clearance ($CL/F_{IDeg,SD}$). A test of monotonous trend between $AUC_{IDeg,0\text{-}120h,SD}$ and grade of hepatic impairment was not significant (p-value: 0.63). IDeg was safe and well tolerated.In conclusion, the ultra-long PK properties of IDeg are preserved in subjects with hepatic impairment; there were no differences in the PK properties of IDeg between subjects with normal hepatic function and those with different grades of hepatic impairment.

Table 1: Pair-wise comparison of PK endpoints for IDeg after single dose

Grade of hepatic impairment	$AUC_{IDeg,0\text{-}120h,SD}$	$C_{max,IDeg,SD}$	$CL/F_{IDeg,SD}$
	Ratio [90% CI]	Ratio [90% CI]	Ratio [90% CI]
Mild vs. normal	0.95 [0.77; 1.16]	0.90 [0.67; 1.20]	1.05 [0.86; 1.29]
Moderate vs. normal	1.00 [0.82; 1.22]	0.77 [0.58; 1.03]	0.98 [0.80; 1.19]
Severe vs. normal	0.92 [0.74; 1.14]	0.75 [0.55; 1.02]	1.06 [0.85; 1.31]

CI: confidence intervalGrade of hepatic impairment according to the Child-Pugh classification

Supported by: Novo Nordisk A/S

1120-P

WITHDRAWN

1121-P

SR-135, a Peroxynitrite Decomposing Catalyst, Prevents Weight Gain and Reduces Fasting Blood Glucose Levels in B6D2F1 Mice Fed With a High Fat Diet

MICHAEL JOHNS, SMITA RAUSARIA, ANDREW KAMADULSKI, HARRY ZOLLARS, STEPHANIE B. VERNIER, BHARGAV PATEL, TERYN V. BRENEGAN, WILLIAM L. NEUMANN, JOSHUA S. WOOTEN, PAUL WANDA, GUIM KWON, *Edwardsville, IL*

Peroxynitrite has been recently implicated in β-cell dysfunction and the pathogenesis of type 2 diabetes. Chemical catalysts capable of destroying peroxynitrite, therefore, may have therapeutic value for treating type 2 diabetes. We have recently reported a new class of Mn(III)-bis(hydroxyphenyl) dipyrromethene peroxynitrite decomposition catalysts. From this class, SR-135, was shown to have potent 2-electron peroxynitrite reducing catalytic activity and membrane solubilizing properties (logP = +4.05). Herein we show that SR-135 inhibited lipid droplet formation and prevented the loss of insulin content caused by nutrient overload (4 day treatment with 25 mM glucose+500 μM free fatty acids (1:1=oleate: palmitate)) in a concentration-dependent manner (0.1-10 μM) in rat and human primary β-cells. Immunohistochemistry of frozen sections of rat and human islets treated with the same experimental conditions also corroborated these findings. To confirm these findings in an in vivo obesity-induced diabetes model, 6 week old B6D2F1 mice (the F1 hybrids of C57BL/6 and DBA/2) were fed with a lean- or a high fat-diet (HFD) for 6 weeks and monitored bodyweights and fasting blood glucose levels. After 6 weeks, the average bodyweights and fasting blood glucose levels of HFD-fed mice were 10 g and 20 mg/dL higher than those of lean diet-fed mice, respectively. Daily intra-peritoneal injection of SR-135 (5 mg/kg) for 7 days significantly reduced the body weight (36.9±1.4 vs. 32.3±1.0) and fasting blood glucose levels (158±8.7 vs. 109±3.4) of HFD-fed B6D2F1 mice (n=6). Vehicle-treated HFD-fed mice also showed a slight decrease in bodyweights and fasting blood glucose levels but substantially less than SR-135 treated mice. These results suggest that peroxynitrite might be one of the key toxic molecules that cause β-cell defects under nutrient overload and a pharmacological agent such as SR-135 may provide a therapeutic intervention.

1122-P

Oral Mimetic of Roux-en-Y Gastric Bypass Surgery

JOSEPH FAYAD, SCOTT V. MONTE, JEROME J. SCHENTAG, *Buffalo, NY*

Roux-en-Y Gastric Bypass (RYGB) surgery hormonally mediates inflammation and obesity and very rapidly improves blood glucose, insulin resistance, and hepatic function. These RYGB hormonally mediated changes precede weight loss. Oral mimetics of RYGB surgery would be expected to follow the effects of orally ingested food materials and would therefore be active on the so-called "Ileal Brake". We are developing Brake, an oral compound mimetic of the RYGB effect on the ileal brake. Brake is a combination of carbohydrates formulated for release in the distal intestine and therefore exhibiting hormone-metabolic effects similar to that of RYGB. In 18 retrospectively studied obese patients compared with 15 prospectively studied RYGB patients, we found that, after 6-months of treatment, subjects treated with Brake had a reduction in insulin resistance that was 63% of the value of RYGB patients (38.3% vs. 60.8%). The comparison of Brake to RYGB reduction for HbA_1C was 55% (11.2% vs. 20.5%); for Triglycerides the comparison was 81% (32.5% vs. 40.3%); for AST 158% (41.3% vs.26%); for ALT 187% (50.5% vs. 26.1%). Thus, the hormonal effects of Brake approach that seen with RYGB. Total body weight reduction of Brake effect to that of RYGB on was only 21% (5.3% vs. 25.2%). We hypothesize the lower weight loss seen with Brake is due to lack of meal restriction, malabsorption, and less of the hypertrophic response associated with RYGB surgery. On Brake, patients ingest normal meals, and have better metabolic homeostasis as mediated by activation of the ileal brake.

Supported by: University at Buffalo

1123-P

Glycemic Control and Clinical Outcome in Nursing Home Residents With Diabetes: A Multicenter Observational Study

DAWN SMILEY, DARIN E. OLSON, SHADI SADEGHI-YARANDI, WINTER POWELL, ALEXANDRA MIGDAL, RAKHEE CHABRIA, INGRID PINZON, MARCOS TOYOSHIMA, ZOBAIR NAGAMIA, CHRISTOPHER NEWTON, THEODORE M. JOHNSON II, LIMIN PENG, GUILLERMO UMPIERREZ, *Atlanta, GA*

We analyzed the type of diabetic care, glycemic control, and clinical outcome in 1,409 residents (59% female, age 79.7±12 yrs, BMI 25.7±7 kg/m^2) admitted to 3 community nursing homes (NH) between 1/1/08-12/31/08. Residents with diabetes (DM, prevalence 33%) had higher rates of comor-

bidities vs non-diabetic residents: hypertension (92% vs 81%, p<0.001), dyslipidemia (55% vs 33%, p<0.001), coronary artery disease (35% vs 25%, p<0.001), heart failure (29% vs 21%, p=0.002), and chronic kidney disease (23% vs15%, p<0.001). Prior to admission, DM residents were treated with diet alone (42%), oral antidiabetic agents (OAD, 29%) or insulin therapy (16%) or combination therapy (12%). In the NH, DM residents received diet alone (12%), sliding scale regular insulin alone (16%), OAD alone (8%) or with insulin (28%), or combinations of insulin (36%). Mean daily BG in DM residents was 145±40 mg/dl with median admission A1c of 6.5% (range 5.1-11.8). During the study period, DM residents had more complications (54% vs 45%, p<0.001) and more emergency room (ER) and hospital transfers (37% vs 30%, p=0.013). A Cox proportional hazards model revealed higher mortality in DM residents (hazard ratio: 1.44, p=0.027). 44% of DM residents had at least one BG <70 mg/dl (7% with BG<40 mg/dl). There were no differences in frequency of hypoglycemia among treatment groups. DM residents with hypoglycemia had longer median length of stay (LOS, 56 vs 27 days, p<0.001), more ER or hospital transfers (44% vs 30%; p= 0.004) and higher mortality (18% vs 10%, p=0.015) compared to DM without hypoglycemia.In summary, diabetes is common in nursing home residents and associated with increased comorbidity, resource utilization, and mortality. Hypoglycemia is also common and associated with more emergency room visits, hospitalization, LOS, and mortality. Randomized studies of different approaches to glycemic control, especially those that limit hypoglycemia, could improve clinical outcome in nursing homes.

Supported by: sanofi-aventis

1124-P

PERSISTence on Glimepiride-Metformin (Amaryl M®) Fixed Combination in Everyday Practice in Asian Type 2 Diabetes Patients

SYED A.A. JAVAZ, PRADANA SOEWONDO, EDWARD WANG, KARIM ADMANE, *Bangalore, India, Jakarta, Indonesia, Bridgewater, NJ, Paris, France*

The PERSIST study was an observational, multicountry, multicenter, prospective product registry. The primary objective was to assess the persistence of Amaryl M® fixed combination after 6 months in Asian patients with type 2 diabetes (T2D) in everyday practice. Statistical tests were performed using SAS® software. Data were summarized using descriptive statistics. Means, medians, standard deviations, and ranges were used to describe numerical variables; counts and percentages were used to summarize categorical variables. The study included 1309 T2D patients (55.7% male, 44.3% female). The mean ± SD age of the patients was 52.3 ± 10.4 years and the mean duration of diabetes was 4.6 ± 4.4 years. More than 80% (87.2% [1142/1309] in the intention-to-treat [ITT] population) were found to be continuing Amaryl M therapy at 6 months. More than 90% of participants (92.1% [1205/1309] in the ITT population) were still on Amaryl M at 3 months. At baseline, mean A1C was 8.92%. Amaryl M effectively improved glycemic control, leading to statistically significant reductions in A1C at Month 3 (7.73%) and Month 6 (7.17%) relative to baseline ($P < 0.001$). Only 3.06% (40/1309) of patients discontinued treatment during the observation period, with lack of efficacy being the most common reason for discontinuation. Amaryl M was found to be safe in Asian T2D patients. The most common adverse event was hypoglycemia (39 patients, 2.98%); no instance of hypoglycemia resulted in a serious adverse event. There was a low incidence of serious adverse events (4 patients, 0.3%). The management of Asian patients with T2D with Amaryl M is associated with a high rate of treatment persistence, effective improvements in glycemic control, and a favorable safety profile.

Supported by: sanofi-aventis

1125-P

Efficacy and Safety of Saxagliptin in Combination With Insulin in Patients With Long-Standing Type 2 Diabetes

GIANMARIA MINERVINI, BERNARD CHARBONNEL, ANTHONY H. BARNETT, JOHN MONYAK, NAYYAR IQBAL, *Wilmington, DE, Nantes, France, Birmingham, United Kingdom, Princeton, NJ*

In a phase 3 trial in type 2 diabetes (T2D) patients with inadequate response to insulin or insulin plus metformin, glycemic control improved more with saxagliptin 5 mg/d than with placebo as add-on therapy. Because patients with long-standing disease may experience different treatment effects than those more recently diagnosed, we assessed outcomes in patients stratified by T2D disease duration (<10 y or ≥10 y). After 24 weeks, glycemic improvement was greater with saxagliptin than with placebo in both T2D duration categories (interaction of treatment by duration: P=0.561 for HbA_{1c}; P=0.894 for fasting plasma glucose; P=0.971 for postprandial glucose; Table 1). The incidence of adverse events was similar with saxagliptin and placebo in both T2D duration categories (Table 2); 1 death occurred (unrelated to saxagliptin treatment) in a patient who had T2D for ≥10 years. The results of this analysis show that the efficacy and safety of saxagliptin 5 mg/d added to insulin with or without metformin appear consistent regardless of duration of T2D.

Table 1.

	T2D Duration, y			
	<10		≥10	
	SAXA + INS (n=135)	PBO + INS (n=57)	SAXA + INS (n=169)	PBO + INS (n=94)
HbA_{1c}, %				
Baseline mean (SE)	8.74 (0.08)	8.58 (0.12)	8.62 (0.07)	8.70 (0.08)
Adjusted mean (SE) change*	–0.6 (0.1)	–0.3 (0.1)	–0.8 (0.1)	–0.3 (0.1)
Difference vs PBO (95% CI)	–0.34 (–0.62, –0.06)		–0.47 (–0.70, –0.25)	
FPG, mg/dL				
Baseline mean (SE)	174 (4.5)	169 (7.5)	173 (4.4)	176 (5.8)
Adjusted mean (SE) change*	–8.3 (4.2)	–5.9 (6.3)	–11.5 (3.8)	–6.2 (5.1)
Difference vs PBO (95% CI)	–2.42 (–17.14, 12.29)		–5.35 (–17.45, 6.75)	
PPG, mg/dL				
Baseline mean (SE)	242 (6.7)	248 (10.3)	259 (6.5)	260 (9.1)
Adjusted mean (SE) change*	–24.7 (6.3)	–2.3 (9.7)	–29.2 (5.8)	–5.4 (7.7)
Difference vs PBO (95% CI)	–22.37 (–44.90, 0.17)		–23.87 (–42.40, –5.34)	
Response (HbA_{1c} <7%),* % of patients	16.5	8.9	18.0	5.4
Difference vs PBO (95% CI)	7.6 (–2.2, 17.4)		12.6 (5.2, 20.0)	

FPG=fasting plasma glucose; INS=insulin or insulin + metformin; PBO=placebo; PPG=120-min postprandial glucose; SAXA=saxagliptin 5 mg/d; T2D=type 2 diabetes.*Week 24.

Table 2.

Patients with events over 24 wk, %	T2D Duration, y			
	<10		≥10	
	SAXA + INS (n=135)	PBO + INS (n=57)	SAXA + INS (n=169)	PBO + INS (n=94)
Adverse events (AEs)	56.3	54.4	57.4	62.8
Treatment-related AEs	14.1	14.0	14.2	19.1
Serious AEs	5.9	1.8	2.4	5.3
Treatment-related serious AEs	1.5	0	0	0
AEs leading to discontinuation	0.7	0	1.8	3.2
Deaths	0	0	0.6	0

Supported by: Bristol-Myers Squibb/AstraZeneca

1126-P

Does Liraglutide Confer Greater Glycemic Benefits than Exenatide When Used With Oral Agents Versus Insulin in Clinical Practice?

PHILIP LEVIN, ENGELS CHOU, TEHSEEN SALIMI, MAEVA GERME, HONGWEI WANG, TONY YANG, QUANWU ZHANG, *Baltimore, MD, Bridgewater, NJ, Paris, France, Marlboro, NJ*

In randomized trials, adding LIRA (liraglutide) versus EXEN (exenatide) to oral agents (OADs) result in greater improvements in A1C and fasting plasma glucose but not in prandial glucose excursions. This study evaluated real world glycemic effects of LIRA vs EXEN when adding to oral agents or insulin. Patients with A1C ≥7% were identified from IMPACT™ claims database (Jan 2009-Dec 2010) and evaluated according to the intention to treat A1C response, defined as a ≥0.8% reduction plus any A1C value ≤7% within 6 months after initiation of LIRA or EXEN. The mean age of patients was 52 years for both LIRA (n=878) and EXEN (n=1,638). Previous use of OAD only was 66 vs 71% and majority of insulin therapy was basal, 21 vs 18% in LIRA vs EXEN respectively. Baseline A1C (8.7% vs 8.9%) and comorbidity burden (Charlson comorbidity score: 1.68 vs 1.85) were comparable in LIRA vs EXEN. Six-month A1C response rate was 26% in Lira and 15% in EXEN (P<0.01), with a hazard ratio (HR) of 1.76 (95% CI: 1.47-2.11) after adjustment of baseline A1C, concomitant medications, comorbidity, and other baseline characteristics. GLP-1 medication adherence was also used as a covariate and strongly associated with A1C response (HR=3.58; 2.54-5.04). Propensity matched (1:1) response estimates remained unchanged with 26% in LIRA vs 16% in EXEN (Odds Ratio=1.82; 1.42-2.33). Stratified by OAD vs basal insulin therapy, response rate was 28 vs 17% in OAD only (OR=1.95; 1.45-2.61), and 13 vs 14% in basal insulin (OR=0.89; 0.46-1.73) for LIRA vs EXEN. While the data is consistent with clinical trials in patients only on OADs, no A1C advantage was observed when adding LIRA in comparison with EXEN to basal insulin, with a decreased response rate in LIRA relative to that in the

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

combination with OADs. This suggests the clinical need for an alternative GLP-1 therapy with a complementary mode of glucose lowering action to basal insulin to optimize glycemic control.

Supported by: sanofi-aventis

1127-P

Interactions of the Glycosaminoglycan Heparin With Amylin Fibrils

ANDREI T. ALEXANDRESCU, SUMAN JHA, SHARADRAO M. PATIL, JASON GIBSON, NATHAN N. ALDER, CRAIG E. NELSON, *Storrs, CT*

Amylin is an endocrine hormone that helps regulate blood glucose levels and controls appetite. In patients with type 2 diabetes, amylin misfolds into amyloid plaques that have been implicated in the destruction of the pancreatic β-cells that synthesize insulin and amylin. The plaques found *in situ* contain not only amylin but heparan sulfate proteoglycans that attach to the fibrils through their glycosaminoglycan chains. We investigated the interaction of amylin with heparin fragments of defined length, that model the glycosaminoglycan chains associated with amyloid deposits. We found that heparin enhances fibrillization in a manner that depends on the length of the polysaccharide fragments. We used NMR to establish that the negatively charged heparin fragments bind to the positively charged N-terminal half of amylin. We used FRET to determine that heparin associates with amylin fibrils rather than enhancing fibrillization catalytically. We used TIRFM to show that fluorescein-labeled heparin is co-localized with amylin fibrils. The mechanism of binding appears to involve electrostatic complementation between the negatively charged heparin helix structure and the positively charged cross-β sheet structure of amylin fibrils. To see how heparin affects the biological function of amylin, we used a fluorimetric assay of cytotoxicity towards a mouse model of pancreatic β-cells. With heparin fragments longer than 20 saccharides, cell death was similar to when amylin was added alone. By contrast, short heparin fragments of 2 to 8 saccharides protect against cytotoxicity and as such may be leads for drugs to treat type 2 diabetes.

1128-P

Efficacy and Safety of Gemigliptin Compared With Sitagliptin Added to Ongoing Metformin Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Alone

EUN JUNG RHEE, KYUNG WAN MIN, HAK CHUL JANG, IL SEONG NAM-GOONG, CHOON HEE CHUNG, JOONG YEOL PARK, HAK YEON BAE, DOO-MAN KIM, SEI HYUN BAIK, MOON-KYU LEE, BYUNG-JOON KIM, SANG AH CHANG, CHUL WOO AHN, YONG SEONG KIM, KUN HO YOON, KYONG SOO PARK, HAE JIN KIM, VYANKATESH K. SHIVANE, ARAVIND R SOSALE, MALA DHARMALINGAM, PRAMOD GANDHI, SANDEEP KUMAR GUPTA, SHAILESH PITALE, PANKAJ KUMAR AGARWAL, NADEEM RAIS, V. MOHAN, UMA MAHESH, JEONG AE KIM, PAN KYUNG KIM, SUN WOO KIM, *Seoul, Republic of Korea, Gyeonggi, Republic of Korea, Ulsan, Republic of Korea, Gangwon, Republic of Korea, Gwangju, Republic of Korea, Daejeon, Republic of Korea, Incheon, Republic of Korea, Mumbai, India, Bangalore, India, Nagpur, India, Lucknow, India, Ghaziabad, India, Tamil Nadu, India, Chennai, India*

This study was designed to assess the efficacy and safety of a DPP IV inhibitor, gemigliptin (LC15-0444) 50mg versus sitagliptin100mg in patients with type 2 diabetes continuing metformin treatment.We conducted a 24-week, double-blind, randomized, active-controlled trial in 425 patients (296 from Korea, 129 from India) with type 2 diabetes inadequately controlled with metformin alone. Eligible patients were randomized to one of 3 treatment groups and gemigliptin 50mg qd or gemigliptin 25mg bid or sitagliptin 100mg qd was added to ongoing metformin treatment for 24 weeks. HbA1c and fasting plasma glucose (FPG) were measured periodically, and oral glucose tolerance tests were performed at baseline, and week 24.At week 24, gemigliptin 50mg/day added to ongoing metformin therapy resulted significant improvement of glycemic control supported by the followings. Reduction in HbA1c of gemigliptin 50mg qd (-0.77%) was non-inferior to those once daily sitagliptin 100mg(-0.83%).Proportion of patients achieving HbA1c <7% or 6.5% in gemigliptin 25mg bid (50%) and gemigliptin 50mg qd (54.07%) was comparable to the results with once daily sitagliptin100 mg (48.87%). There was decrease in FPG, postprandial glucose, $AUC_{0\text{-}2h}$ glucose, DPP 4 activity and increase in GLP-1, sensitivity of beta cells to glucose (supported by HOMA-β, HOMA-IR, postprandial (2h) c-peptide, insulinogenic index, and postprandial proinsulin to insulin ratio) in patients who were administrated with gemigliptin 50mg/day added to ongoing metformin therapy. There was no increased risk of adverse experience with gemigliptin 50 mg/day compared with sitagliptin100 mg qd.In conclusion, gemigliptin 50 mg/day as an add-on therapy to metformin was efficacious and well tolerated in type 2 diabetes mellitus patients.

1129-P

Association of Measures of Glycemic Variability With Glycemic Control and Hypoglycemic Events

SILVIO E. INZUCCHI, GUILLERMO UMPIERREZ, ANDRES DIGENIO, RONG ZHOU, BORIS P. KOVATCHEV, *New Haven, CT, Atlanta, GA, Bridgewater, NJ, Cincinnati, OH, Charlottesville, VA*

Glycemic variability (GV) is an emerging factor in diabetes control. Measures of global GV include calculations of standard deviation (SD) and mean amplitude of glycemic excursions (MAGE), but these fail to capture extremes of the glycemic spectrum (hyper- and hypoglycemia). Here we investigate how various measures of GV relate to A1C levels and hypoglycemic events.This pooled analysis included six published Phase 3, randomized controlled studies in adults with type 2 diabetes (N=1699) who completed a 24-week treatment regimen with basal insulin glargine or comparator (target FPG≤100 mg/dL) and for whom complete 7-point blood glucose (BG) profiles are available. The GV measures SD (mg/dL), MAGE (mg/dL), mean absolute glucose (MAG; mg/dL), low BG index (LBGI), high BG index (HBGI), and average daily risk range (ADRR) were calculated from BG profiles for patients at 24 weeks. For the outcomes of an A1C ≥ 7.0% at 24 weeks and on-trial development of hypoglycemia, the area under the curve (AUC: calculated from curve of sensitivity vs. [1-specificity]; range: 0-1; 1 = best association) of the receiving operating characteristic (ROC) curve was calculated for each GV measure.All GV measures were significantly associated with both outcomes (Table). HBGI showed the strongest association with A1C ≥ 7.0% and LBGI with hypoglycemia.GV tools that selectively assess both ends of the BG scale correlate better with not achieving optimal glycemic control and the incidence of hypoglycemia than do global measures. Their predictive utility to identify patients at greatest risk should be evaluated in future studies.

Variability parameter	A1C ≥ 7.0% (AUC mean [SD])	A1C ≥ 7.0% (95% CI)	Hypoglycemia (AUC mean [SD])	Hypoglycemia (95% CI)
SD	0.55 (0.014)	0.52-0.58	0.56 (0.014)	0.53-0.58
MAGE	0.55 (0.014)	0.54-0.58	0.56 (0.014)	0.53-0.58
MAG	0.55 (0.014)	0.52-0.57	0.55 (0.014)	0.52-0.57
LBGI	NA[a]	NA[a]	0.60 (0.014)	0.57-0.63
HBGI	0.68 (0.013)	0.66-0.71	NA[a]	NA[a]
ADRR	0.59 (0.014)	0.56-0.62	0.54 (0.014)	0.52-0.57

[a]LBGI and HBGI were specifically designed to look at the low and high ends of the BG scale, respectively; thus, each measure's use in predicting the reverse is inconsistent with its definition.SD=standard deviation, CI=confidence interval

Supported by: sanofi-aventis

1130-P

The Liver-Directed/Pancreas-Sparing Pharmacokinetic Profile of GKM-001, a Glucokinase Modulator With Robust Glucose Lowering Properties and Low Hypoglycemia Risk

KASIM A. MOOKHTIAR, DHANANJAY UMRANI, SIDDHARTHA DE, DEBNATH BHUNIYA, *Pune, India*

Glucokinase (GK) regulates glucose homeostasis via dual control of insulin secretion in pancreas and glucose disposal in liver. Though GK activators have shown anti-hyperglycemic effects in animals and Type-2 Diabetes (T2D) patients, hypoglycemia, due to their dual hepatic and pancreatic action, is a concern. GKM-001 was designed to selectively target liver GK and spare pancreas GK and, thereby, lower hypoglycemia risk. Previously, the liver-directed/pancreas-sparing action of GKM-001 was demonstrated by glycogen accumulation in rat hepatocytes, absence of insulin secretion in rat islets and increase in glucose infusion rate during a hyperglycemic clamp in rats, without change in plasma insulin levels. Here, the pharmacokinetic profile of GKM-001 in mice, rats and dogs, and its liver vs. plasma and pancreas distribution are described.GKM-001 showed oral bioavailability of ~ 25%, with preferential hepatic distribution and very low pancreatic levels, resulting in a high liver:plasma ratio in mice (≥ 20:1), and a high liver:pancreas ratio in rats (≥ 30:1) and dogs (≥ 60:1). GKM-001 was excreted via the biliary route (90% of IV-administered compound recovered in feces over 24 hr in rats; 20-30% in dogs), indicating hepatic extraction. The ADME profile of GKM-001 showed poor permeability and high plasma protein binding, resulting in a significantly lower free fraction (0.65 μM*hr) in plasma, below the EC_{50} value (4.3 μM) for rat GK activation. These data suggest a reduced ability for GKM-001 to reach pancreas and activate GK within β-cells, resulting in functional tissue selectivity observed *in vivo*.Consistent with its PK profile and ADME properties, and as we have hypothesized, no hypoglycemia was observed in any pre-clinical models (≥10-fold above efficacy dose) or in a 14-day repeated dose toxicity study in rats at > 60-fold above efficacy dose. GKM-001 is currently in clinical development for the treatment of T2D.

1131-P

Long-Term Efficacy and Safety of Saxagliptin in a Triple-Therapy Regimen With Insulin and Metformin for Type 2 Diabetes

BERNARD CHARBONNEL, ANTHONY H. BARNETT, JOHN MONYAK, GIANMARIA MINERVINI, NAYYAR IQBAL, *Nantes, France, Birmingham, United Kingdom, Wilmington, DE, Princeton, NJ*

In a phase 3 trial, type 2 diabetes (T2D) patients with inadequate response to insulin or insulin plus metformin had significant glycemic improvement when adding saxagliptin 5 mg/d vs placebo, without increased risk of hypoglycemia or weight gain. This subanalysis compares glycemic and safety outcomes after 52 weeks of treatment with saxagliptin vs placebo in patients receiving triple (add-on to insulin + metformin) or dual therapy (add-on to insulin). Reduction in HbA_{1c} and percentage of patients achieving HbA_{1c} <7% were greater with saxagliptin than placebo in both triple and dual therapy after 52 wks of treatment (Table 1). The incidence of adverse events was similar with saxagliptin and placebo (Table 2); 2 deaths occurred but were considered unrelated to treatment. In the triple- and dual-therapy cohorts, the incidences of reported hypoglycemia and confirmed hypoglycemia (fingerstick glucose ≤50 mg/dL and associated symptoms) were similar with saxagliptin vs placebo add-on treatment (Table 2). This subanalysis shows that saxagliptin 5 mg/d is effective and well tolerated in combination with insulin or insulin plus metformin over 52 weeks of treatment in patients with T2D.

Table 1	SAXA + INS + MET (n=209)	PBO + INS + MET (n=105)	SAXA + INS (n=95)	PBO + INS (n=46)
Mean (SE) HbA_{1c} at baseline, %	8.66 (0.06)	8.65 (0.09)	8.69 (0.09)	8.67 (0.11)
Adjusted mean (SE) change in HbA_{1c},*,‡ %	-0.81 (0.06)	-0.44 (0.09)	-0.65 (0.10)	-0.28 (0.14)
Difference (95% CI) SAXA vs PBO	-0.37 (-0.59, -0.15)		-0.36 (-0.69, -0.04)	
Response (HbA_{1c} <7%), % of patients†,‡	23.8	8.7	16.0	8.7
Difference (95% CI) SAXA vs PBO	15.0 (7.1, 23.0)		7.3 (-3.7, 18.3)	

*Repeated measures analyses; †last observation carried forward; ‡at week 52.INS=insulin; MET=metformin; PBO=placebo; SAXA=saxagliptin 5 mg/d.

Table 2 Patients with events over 52 wk, %	SAXA + INS + MET (n=209)	PBO + INS + MET (n=105)	SAXA + INS (n=95)	PBO + INS (n=46)
Adverse event (AE)	67.5	72.4	64.2	69.6
Treatment-related AE	16.7	20.0	22.1	28.3
Serious AE	7.7	9.5	9.5	6.5
AEs leading to discontinuation	2.9	1.9	3.2	2.2
Deaths	0.5	0	1.1	0
Reported hypoglycemia	22.5	23.8	23.2	32.6
Confirmed hypoglycemia	7.2	4.8	8.4	10.9

Supported by: Bristol-Myers Squibb/AstraZeneca

1132-P

Effects of Add-On Treatment With Sitagliptin on Reducing the Range of Glucose Variations in Japanese Type 2 Diabetic Patients Receiving Insulin Therapy

KAZUNORI SEZAKI, YUKIKO TANIGUCHI, YUTAKA MORI, MASAZUMI ERIGUCHI, *Higashimurayama, Japan, Komae, Japan*

Objective: In this study, we investigated whether sitagliptin might help reduce the magnitude of glucose variations in type 2 diabetic patients on insulin therapy by using CGM.Patients and Methods: This study included a total of 10 type 2 diabetic patients in whom stable glycemic control had been achieved after admission for glucose control. Insulin regimens used included long-acting insulin once daily in 4 patients and biphasic insulin twice daily in 6, with the daily insulin dose being 14.2 ± 10.1 U. The patients were given insulin therapy alone on days 1 and 2 and add-on sitagliptin 50 mg/day on days 3 to 6 with their daily insulin doses maintained. Variables examined included 24-hour mean glucose levels and their SDs (mg/dL), total area for the range of 24-hour glucose variations (total area between the 24-hour mean glucose level and the continuous glucose curve) (mg · hr/dL), MAGE (mg/dL), proportion of time in hyperglycemia (≥ 180 mg/dL) and hypoglycemia (≤ 70 mg/dL).Results: The 24-hour mean glucose level with and without sitagliptin was 142.3 ± 46.8 mg/dL and 169.9 ± 59.5mg/dL, respectively. Add-on sitagliptin led to significant decreases in the SDs of 288 glucose levels over 24 hours ($P < 0.01$), the total area for the range of 24-hour glucose variation ($P < 0.001$), MAGE ($P < 0.01$), and the proportion of time in hyperglycemia ($P < 0.01$), compared to insulin therapy alone, while there was no significant change in the proportion of time in hypoglycemia with or without sitagliptin. Conclusions: This study demonstrated that insulin therapy alone does not provide adequate glycemic control in type 2 diabetic patients. In contrast, add-on sitagliptin was shown to decrease not only the 24-hour mean glucose levels but also the postprandial glucose increases, suggesting that add-on sitagliptin is effective in postprandial glucose control in type 2 diabetic patients on insulin therapy.

1133-P

"Diabetes Interactive Diary" Telemedicine System vs. Standard Carbohydrate Counting Education in Type 1 Diabetes: Results of a Randomized Trial

MARIA CHIARA ROSSI, ANTONIO NICOLUCCI, GIUSEPPE LUCISANO, PAOLO DI BARTOLO, VALERIO MISELLI, ROBERTO ANICHINI, GIACOMO VESPASIANI, DID STUDY GROUP, *Santa Maria Imbaro (CH), Italy, Ravenna, Italy, Scandiano (RE), Italy, Pistoia, Italy, San Benedetto del Tronto (AP), Italy*

Carbohydrates (CHO) counting is effective in promoting dietary freedom and glycaemic control. Its use is limited by the complex education required. The Interactive Diary for Diabetes (DID) is an electronic diary/bolus calculator/telemedicine system based on communication by mobile phone short messages. It enables patients to match insulin to CHO intake on a meal by meal basis. Aim of this multicentre, randomized study was to compare DID vs. traditional education in T1DM adults treated with insulin glargine + prandial insulin glulisine.Patients were randomized to the DID program (Group A, N=64) or to CHO counting education (Group B, N=64). Patients were seen after 3 and 6 months to evaluate HbA1c levels (primary end-point), fasting blood glucose (FBG), body weight, daily insulin doses, hypoglycemic episodes, and quality of life (Diabetes Specific Quality of Life Scale -DSQOLS). A generalized hierarchical linear regression model for repeated measures was used to compare changes between groups. Poisson regression was used to compare incidence rates of hypoglycemic episodes.Overall, 128 patients were enrolled (48% males; age 36.9±10.5 yr; T1DM duration 16.3±9.3 yr). After 6 months, HbA1c levels decreased from 8.2±0.7 to 7.8±0.8 in group A and from 8.3±0.9 to 7.8±0.8 in group B (p=0.38); FBG changed from 186±78 to 188±68 mg/dl in group A and from 182±73 to 148±85 mg/dl in group B (p=0.03); body weight increased by 0.36±2.7 Kg in group A and 0.30±2.8 Kg in group B (p=0.98). Fewer moderate hypoglycaemic episodes were registered in group A (IRR=0.32, 95%CI 0.22-0.48, p<0.0001). A borderline significant difference in favor of DID was found in the fear of hypoglycemia dimension of DSQOLS. Mean daily doses of short- and long-acting insulin were slightly lower in group A than in group B.DID is at least as effective as traditional CHO counting education and is associated with a lower incidence of moderate hypoglycemia.

1134-P

Comparison of Liraglutide and Exenatide Evaluated by Continuous Glucose Monitoring (CGM) in Patients With Diabetes Associated With Liver Cirrhosis

KANAKO MORI, YOSHIYUKI HAMAMOTO, SACHIKO HONJO, YUKIKO KAWASAKI, HISATO TATSUOKA, KANTA FUJIMOTO, ATSUKO MATSUOKA, HIROKI IKEDA, YOSHIHARU WADA, HIROYUKI KOSHIYAMA, *Osaka, Japan*

Liver cirrhosis is a consequence of chronic hepatic injury caused by viral infection, toxins such as alcohol, or fatty liver disease such as nonalcoholic steatohepatitis known as NASH. Cirrhosis is often accompanied by a significant postprandial blood glucose elevation through decreased insulin sensitivity in the liver and requires high dose of insulin to adjust it. GLP-1 receptor agonist (GLP-1RA) improves glycemic control not only augmenting insulin secretion but also suppressing glucagon secretion and hepatic glucose production. Therefore, we examined the effect of GLP-1RAs on diurnal glycemic control evaluated by CGM (MMT-7102W, Medtronic) in diabetic patients with cirrhosis.Seven patients were hospitalized and given insulin therapy before GLP-1RA administration. Liraglutide (Lira) 0.6mg daily or exenatide (Ex) 5 μg twice daily were randomly administered for two consecutive days per each in cross-over manner, and blood glucose levels (BG) were monitored by CGM. A day was divided into four time periods by every 6 hours started from 6 a.m. and the area-under-the-curve (AUC) of glycemia was calculated for each period, postprandial period (2 hours after each meal) and the whole day (WD). The mean HbA1c value was 8.7±0.7% (±SE). CGM revealed that while there were 3 obvious peaks of BG after each meal observed with Lira

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

administration, only 2 peaks could be observed after lunch and midnight with Ex administration. The AUC of WD was significantly lower in Lira than Ex because of better BG in daytime and midnight. While the 2-Hour AUC after breakfast and dinner were significantly higher, that after lunch was lower in Lira compared with Ex. The mean BG was significantly lower in Lira, but the time spent in hypoglycemia was significantly longer in Ex than Lira. Our results showed that GLP-1RAs had high potency to improve glycemic metabolism in patients with cirrhosis, and that liraglutide had a higher efficacy to control glycemia than exenatide.

1135-P

Two-Year Use of Exenatide Once Weekly in Type 2 Diabetes Mellitus (T2DM) Patients Taking Thiazolidinedione

MICHAEL TRAUTMANN, PAUL NORWOOD, ELLA PINTILEI, JOANNE LIUTKUS, HARRY HABER, MARILYN BOARDMAN, *Indianapolis, IN, San Francisco, CA, Lasi, Romania, Cambridge, ON, Canada, Ann Arbor, MI*

Exenatide once weekly (EQW) has been studied in combination with several antidiabetes medications for T2DM treatment. This single-arm, open-label trial investigated the long-term efficacy and safety of EQW in combination with a thiazolidinedione (TZD) for 2 years. Pts with T2DM unable to achieve glycemic control (A1C >7% and ≤10%) after receiving TZD with or without metformin (MET) for at least 4 mo began 2-mg EQW (naïve) or switched to 2-mg EQW from exenatide BID (switched). Of 134 pts enrolled at study start (TZD, n=16; TZD+MET, n=118), 85 completed 104 wks of treatment. At baseline (for all randomized pts), 55% were male with a mean±SD age 55±10 years, duration of diabetes 6±5 years, body weight 98.1±18.7 kg, A1C 7.2%±1.0, and fasting blood glucose (FBG) 150±46 mg/dL. Pts showed improvements in mean A1C and FBG, and no changes in body weight at 104 wks (Table). The most frequent (≥10%) treatment-emergent AEs were nausea (17.2%), injection-site nodule (11.9%), nasopharyngitis (11.9%), and upper respiratory tract infection (10.4%). The majority of AEs were mild (32.1%) or moderate (30.6%) in intensity. A total of 21 pts (15.7%) experienced an SAE; no SAEs were reported in more than 1 pt. Known TZD-related AEs (edema, weight gain, and congestive heart failure) did not occur at a higher frequency than reported with TZD use alone. Minor hypoglycemia (BG <54 mg/dL) was reported in 5 pts (3.7%). No major hypoglycemia (BG <54 mg/dL and impairment requiring assistance) was reported. This study demonstrated that pts treated with EQW+TZD experienced improvements in measures of glycemia over 2 years of treatment.

	Overall	Naïve	Switched
A1C, %	**N=133**	**N=44**	**N=89**
Baseline Week 104	7.2±0.96.6±0.9	7.7±1.06.6±1.0	7.0±0.86.6±0.8
FBG, mg/dL	**N=130**	**N=43**	**N=87**
BaselineWeek 104	151±45128±35	152±38135±49	150±49125±28
Body weight, kg	**N=134**	**N=44**	**N=90**
Baseline Week 104	98.1±18.799.0±18.8	96.3±17.196.0±16.9	99.0±19.5100.1±19.4

FBG=fasting blood glucose. Data are mean±SD. Only patients with baseline value and ≥1 postbaseline value were included.

1136-P

Long-Term DPP4 Inhibition Decreases Liver Fat Content in Patients With IGT or Type 2 DM

MASANOBU TSUCHIYA, YOSHIHIKO NISHIO, HIROSHI MAEGAWA, *Yanai, Japan, Kagoshima, Japan, Otsu, Japan*

Nonalcoholic fatty liver disease is frequently associated in patients with type 2 DM. The aim of this study is to clarify whether long-term Alogliptin(ALO), a kind of DDP4 inhibitor may decrease liver fat content in patients with impaired glucose tolerance (IGT) or newly diagnosed type 2 diabetes (DM). Thirteen patients comprised of 9 patients with IGT and 4 patients with DM (IGT+DM group) were recruited. The 13 patients were treated with ALO (25 mg daily for 48 weeks). A 75-g OGTT, laboratory measurements and computed tomography (CT) to determine liver CT values (Hounsfield unit, HU) were performed at baseline , 12weeks and 48 weeks after the treatment. Early insulin secretion assessed by delta IRI / delta PG for 30 min. Liver CT values and spleen CT values were evaluated in terms of the mean values for three different sites respectively. 12 weeks after the treatment, the treatment with ALO significantly decreased plasma glucose level at 0m(P<0.05), 30 m (P<0.01), 60 min (P<0.001) and 120m(p<0.001) after the glucose load. ALO administration showed higher liver CT values (50.8 ± 11.3, 56.3± 8.9 HU, P<0.01), the liver-to-spleen ratio (0.89 ± 0.17, 1.00 ± 0.17 HU, P<0.01), and had lower AST (20.5 ± 4.8, 17.5 ± 4.6 mg/dl, P<0.05), ALT (22.3±8.0, 17.7±6.4 P<0.01) as compared with those of the baseline. 48 weeks after the treatment, the treatment with ALO significantly decreased plasma glucose level at 0m(P<0.05), 30 m (P<0.05), 60 min (P<0.001), 120m(p<0.001) after the glucose load and also showed higher IRI/ PG(0.63±0.32, 1.44±0.98 P<0.05). ALO treatment showed higher liver CT values (50.8 ± 11.3, 55.7± 8.2 HU, P<0.05), the liver-to-spleen ratio (0.89 ± 0.17, 0.99 ± 0.16 HU, P<0.01), and had lower ALT (22.3±8.0, 18.8±9.2 P<0.05) as compared with those of the baseline. In this treatment, before and after treatment, there were no differences in BMI, HOMR-IR. In conclusion, Long-term DPP4 inhibition may decrease liver fat content in patients with IGT or type 2 DM.

1137-P

LX4211, a Dual Inhibitor of SGLT1 and SGLT2, Results in Postprandial Glucose Reductions in Healthy Subjects

IKE OGBAA, DAVID POWELL, PHILLIP BANKS, ANNE TURNAGE, KENNY FRAZIER, KRISTI A. BOEHM, JOEL FREIMAN, ARTHUR SANDS, BRIAN ZAMBROWICZ, *The Woodlands, TX*

SGLT2 is the target of several investigational compounds that aim to treat type 2 diabetes mellitus (T2DM). LX4211 is a potent systemic inhibitor of SGLT2 that also inhibits SGLT1 locally in the gastrointestinal (GI) tract. In prior clinical studies, dual inhibition by LX4211 provided glycemic control and metabolic benefits without triggering clinically significant GI side effects. In this study we explored the impact of timing of the dosing regimen on a variety of pharmacodynamic (PD) parameters including postprandial glucose (PPG), fasting plasma glucose (FPG), and insulin.12 healthy subjects were enrolled, sequestered, and randomly assigned to LX4211 (n=10) or placebo (n=2). Subjects received LX4211 two (2) hours prior to breakfast for 7 days to establish a steady state, followed by dosing at 5 different times relative to meal, in a Latin Square design balanced for first order carryover effects, on Days 8-12. PD parameters, including PPG, FPG, and insulin were assessed. Safety and tolerability were also evaluated throughout the study.All 12 subjects completed the study. Results across dosing times were comparable. All adverse events (AE) were mild and infrequent; no events were deemed to be related to the administration of LX4211.

Days 8-12, change from baseline (Day -1):

Dose Schedule→ PD Variable↓	Immediately prior to breakfast	Split dose[a] (AM/PM)
FPG (mg/dL) (95% CI)	-6.12 (-8.26, -3.98)†	-6.68 (-8.81, -4.54)†
PPG (mg•hr/dL) $AUC_{0\text{-last}}$, (95% CI)[b]	-74.71† (-99.75, -49.67)	-103.19† (-128.23, -78.15)
Insulin (µU•hr/mL) $AUC_{0\text{-last}}$, (95% CI)[b]	-193.71† (-189.51, -134.14)	-163.65† (-191.33, -135.97)

† p≤0.001 of within schedule comparison vs Day -1
[a] Split dose was taken 1 hour prior to both breakfast and dinner
[b] $AUC_{0\text{-last}}$ were calculated from 0-minutes to 13-hours postdose

LX4211 produced marked suppression of postprandial glucose excursion and hyperinsulinemia after breakfast with either morning or split dose, without producing hypoglycemia or diarrhea in healthy subjects.

1138-P

Effects of Sitagliptin Versus Mitiglinide on Insulin, Proinsulin, Glucagon and GLP-1 Responses after Oral Glucose Load: A Randomized, Cross-Over Study

MASAFUMI MATSUDA, TOMOKO MORITA, NATSUKO OSHITANI, YOSHITAKA AKIYAMA, YUUKO OONO, YOSHIMASA ASO, TOSHIHIKO INUKAI, MASAFUMI KAKEI, MASANOBU KAWAKAMI, TAKUYA AWATA, SHIGEHIRO KATAYAMA, *Kawagoeshi, Japan, Koshigaya-shi, Japan, Saitama-shi, Japan, Moroyama-machi, Japan*

Both sitagliptin (SIT) and mitiglinide (MIT) have potency to reduce the plasma glucose (PG) conc. after an oral glucose load. However, the differences through affecting hormonal levels after an oral glucose load are not studied well, when similar levels of PG are achieved. We compared directly these two agents in 16 type 2 diabetic patients (M/F=10/6, Age: 66±3 y.o., BMI: 24±4kg/m^2, HbA1c: 6.6±0.5%, FPG: 116±27mg/dl). Pioglitazone (n=2) and metformin (n=9) were continued in 11 subjects. Patients received SIT (50mg qd for 1 week and 100mg qd for an additional week) or MIT (10mg tid for 2 weeks). After 2 weeks, patients crossed-over to an alternative treatment. 75 g oral glucose tolerance tests (OGTT) were conducted before the study and after interventions. The average of area under the curve (aAUC) up to 180 min of PG response was similar in both agents and lower than before (CON) (SIT 179±53, MIT 174±50 vs CON 222±60 mg/dl, p<0.0001). Insulinogenic index was highest in MIT (0.3±0.3 vs SIT 0.2±0.2, p<0.01; vs CON 0.1±0.1, p<0.01), while the Matsuda index was similar in 3 OGTTs (MIT 10±5, SIT 11±7, CON 11±7). aAUC of GLP-1 was increased in SIT (15±14 vs MIT 6±5,

p<0.001; vs CON 5±4 pmol/L, p<0.001). The incremental aAUC of glucagon was lower in SIT (-2.4±12.9 vs MIT 6.2±14.0, p<0.05; vs CON -0.7±15.0 ng/ml), although basal glucagon levels were paradoxically higher in SIT (77±17, vs MIT 71±18 p<0.05; vs CON 74±20 ng/ml). aAUC of proinsulin was decreased in SIT (15.0±3 8, vs MIT 21.4±9.8, p<0.01; vs CON 17.2±8.6 pmol/L, p<0.05). Triglyceride levels were reduced by MIT. There were no differences between subjects who randomly started with SIT first and those with MIT first. While clinical doses of SIT and MIT resulted in a similar PG control, SIT enhanced less insulin secretion with less glucagon responses and much less proinsulin responses compared with MIT. Thus these changes of hormonal profiles by SIT favor islet functions compared with MIT in clinical use.

Supported by: The Waksman Foundation of Japan

1139-P

Self-Management Comparison of Adults With Type 1 Diabetes in Latin America and the Middle East: Data From the International Diabetes Management Practices Survey (IDMPS)

JUAN JOSE GAGLIARDINO, PABLO ASCHNER, JULIANA CHAN, JEAN-MARC CHANTELOT, ELIZABETH GENESTIN, MARIE-PAULE DAIN, HASAN ILKOVA, FERNANDO JAVIER LAVALLE-GONZÁLEZ, AMBADY RAMACHANDRAN, *La Plata, Argentina, Bogotá, Colombia, Shatin, Hong Kong, Paris, France, Istanbul, Turkey, Monterrey, Mexico, Chennai, India*

IDMPS is an ongoing 5-year multinational observational study documenting the current quality of care provided to people with type 1 or type 2 diabetes. Feasibility analyses were previously performed to validate the chances of pooling the data collected during 4 years in Latin America (2693 patients) and 3 years in Middle East (1316 patients). The aim was to identify type 1 diabetes mellitus (T1DM) patient profiles for self-management in both regions. Self-management (SM) was defined as both self-monitoring blood glucose (SMBG) and insulin self-adjustment (ISA) performance. Patient profiles were determined by using logistic regression analysis. SM performance was greater in Latin America than in the Middle East (58.1 vs 51.3%). The frequency of SMBG (27.4 vs 21.0%) and ISA (25.9% vs 18.9%) was also higher in Latin America. In Latin America, SM was significantly associated with age (< 40 years vs > 65; OR = 2.4, $P = 0.002$), level of education (university) (OR = 2.3, $P < 0.001$), health insurance coverage (OR = 1.7, $P = 0.004$), diabetes education (OR = 1.7, $P = 0.001$), time since diagnosis (for 5-year changes: OR = 1.1, $P = 0.004$), insulin pen use (vs vials-syringes use: OR = 1.7, $P = 0.001$), basal-prandial regimen (vs basal regimen: OR = 3.6, $P < 0.001$; vs other regimens: OR = 2.6, $P < 0.001$) and patient recruited by specialists (OR = 1.6, $P = 0.005$). In the Middle East, SM was significantly associated with age (< 40 years vs 40 to 65 years; OR = 2.1, $P = 0.003$; vs > 65 years; OR = 7.1, $P = 0.001$), level of education (university) (OR = 2.3, $P < 0.001$), diabetes education (OR = 2.5, $P < 0.001$), time since diagnosis (for 5-year changes: OR = 1.3, $P < 0.001$), insulin pen use (vs vials-syringes use; OR = 1.9, $P = 0.002$) and basal-prandial regimen (vs other regimens: OR = 2.0, $P = 0.001$). In both regions, SM was associated with better glycemic control. A specific effort should be made to empower adults with T1DM to improve their care quality and outcomes.

Supported by: sanofi-aventis

1140-P

Fish Oil Supplementation Reduces Adipose Inflammation and Improves Capillary Density in Insulin Resistant Subjects

MICHAEL L. SPENCER, MUNIRA NASSER, LINDSEY SHIPP, AKOSUA ADU, RESAT UNAL, BRIAN FINLIN, PHILIP A. KERN, *Lexington, KY*

In addition to their beneficial effects on blood lipids, ω-3 fatty acids (fish oils, FO) reduce inflammation. We hypothesized that FO supplementation would reduce the adipose inflammation associated with obesity/insulin resistance. Twenty-one obese (BMI 27-40) non-diabetic insulin resistant subjects were recruited. After baseline FSIGT and adipose biopsy, the subjects were randomized to either 4 g/day of FO supplement (Lovaza) or placebo for 12 weeks, followed by repeat studies. There were no significant changes in SI or in either total or HMW plasma adiponectin post-treatment. Immunohistochemisty revealed no changes in adipocyte size or collagen deposition. However, the FO treated subjects demonstrated improvements in inflammation and vascularity. Adipose tissue macrophage (ATM) number was reduced in the FO subjects from 67±10 / mm^2 to 39±11 /mm^2 (p<0.05). The ATM were predominantly M2 (CD206+), and the proportion of M1 (CD86) and M2 macs was not changed post-treatment. Following FO (but not placebo) treatment, capillary number increased from 16 ±1.2 /mm^2 to 20 ±1.3 /mm^2 (p<0.05), with no change in large vessels. Nanostring gene expression analysis of >100 targets showed relatively few changes, although MCP1 was decreased after FO treatment.Thus, 12 weeks of treatment with FO reduced ATM number and increased capillary number, both of which would be expected to improve the adipose dysfunction associated with metabolic syndrome. However, these changes in adipose tissue did not result in a measurable improvement of insulin sensitivity or plasma adiponectin.

Supported by: R01 DK80327

1141-P

TAK-875, a GPR40 Agonist, Improves Postprandial Hyperglycemia Additively With Sulfonylurea and Is Effective in Rats With Sulfonylurea Failure

RYO ITO, YOSHIYUKI TSUJIHATA, MASAMI SUZUKI, KAE MATSUDA-NAGASUMI, KAZUMASA MIYAWAKI, NOBUYUKI NEGORO, KOJI TAKEUCHI, *Fujisawa, Japan*

GPR40, a G protein-coupled receptor highly expressed in pancreatic β-cells, mediates free-fatty-acid-induced insulin secretion. TAK-875 (TAK) is a potent and selective GPR40 agonist that lowers plasma glucose via glucose-dependent insulin secretion. Sulfonylureas (SUs) are widely used oral insulin secretagogues, but have adverse effects such as hypoglycemia and secondary failure. In the present study, we compared the glucose-lowering effects, risk of hypoglycemia and risk of secondary failure between TAK and SUs, and evaluated their effects in combination. We also assessed the efficacy of TAK in a rat model with SU failure. In an oral glucose tolerance test (OGTT) using type 2 diabetic N-STZ-1.5 rats, acute dosing of TAK (3-30 mg/kg) dose-dependently improved glucose tolerance, and the decrease in glucose AUC was greater than that seen with the SU glibenclamide (GB) at maximal doses (TAK: -37.6%; GB: -12.3%). Moreover, combination treatment with TAK (3 mg/kg) and the SU glimepiride (GM, 10 mg/kg) additively decreased glucose AUC (TAK: -25.3%; GM: -20.0%; TAK+GM: -43.1%). While GM (10 mg/kg) induced hypoglycemia in fed normal rats, TAK (3 mg/kg) did not affect normoglycemia, and no further exaggeration was observed in their combination. In N-STZ-1.5 rats receiving GB (10 mg/kg/d) for 4 weeks, the efficacy of GB was lost in OGTT. In contrast, even after 15-week treatment with TAK (10 mg/kg/d), secondary failure was not observed in these rats. Interestingly, acute dosing of TAK (3 mg/kg) was effective in the rats with SU secondary failure (glucose AUC: -29.3% for TAK [$p \leq 0.01$ vs vehicle] vs -4.3% for GB). These results indicate that TAK has the lower risk for hypoglycemia and secondary failure and is a more potent antihyperglycemic agent than SUs; TAK and GM combination may be useful for further improving glycemic control. In addition, our results suggest that TAK treatment may be a valuable strategy in type 2 diabetic patients with SU failure.

1142-P

SDF-1β Protects Palmitate-Induced Fibrotic Response in Cardiac Cells via Activation of AMPK and p38 MAPK-Mediated IL-6 Excretion

YUGUANG ZHAO, JUNYING DAI, GUANJUN WANG, LU CAI, WEI LI, *Changchun, China, Louisville, KY*

Elevated saturated free fatty acids including palmitate often occur in the patients with obesity and diabetes, and are also primary trigger for cardiac remodeling and dysfunction. Stromal cell-derived factor-1beta (SDF-1β) was cardiac protective, but whether it also protects the heart from palmitate-induced fibrosis remains unknown. Using H9c2 cardiac cell line, we studied the possible protection of SDF-1β from palmitate-induced fibrotic response. Exposure of H9c2 cells to palmitate at 62.5 nM for 15 h caused a significant fibrotic effect, shown by up-regulation of connective tissue growth factor (CTGF) and tissue growth factor beta (TGF-β). Pretreatment with SDF-1β significantly prohibited palmitate-induced fibrosis along with significant increases in AMPK and p38 MAPK-mediated IL-6 production. AMPK activator significantly prevents palmitate-induced cardiac fibrosis while both AMPK and p38 MAPK inhibitors prohibited SDF-1β's protective effects. Direct addition of recombinant human IL-6 to cell cultures prevented palmitate-induced fibrosis whereas IL-6 siRNA abolished the protective effect of SDF-1β. These results suggest that SDF-1β prevents palmitate -induced cardiac fibrosis via activating AMPK and p38 MAPK-mediated IL-6 excretion. Using type 2 diabetes model, we further confirmed that SDF-1β can prevent diabetes-induced cardiac fibrosis by its activation of AMPK. This important finding opens a new road for the research of SDF-1β's cardiac protection that is irrelevant with its well-known function of stem cell mobilization.

1143-P

Ipragliflozin, A Novel SGLT2-Selective Inhibitor, Improves Glycemic Control and Reduces Body Fat in the Diabetic Goto-Kakizaki (GK) Rats

TOSHIYUKI TAKASU, YUKA HAYASHIZAKI, JIRO HIROSUMI, HIDEAKI MINOURA, NOBUAKI AMINO, EIJI KUROSAKI, *Tsukuba-shi, Ibaraki, Japan*

Ipragliflozin (IPRA; ASP1941) is a novel, selective sodium glucose co-transporter 2 (SGLT2) inhibitor that is currently under clinical development for

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

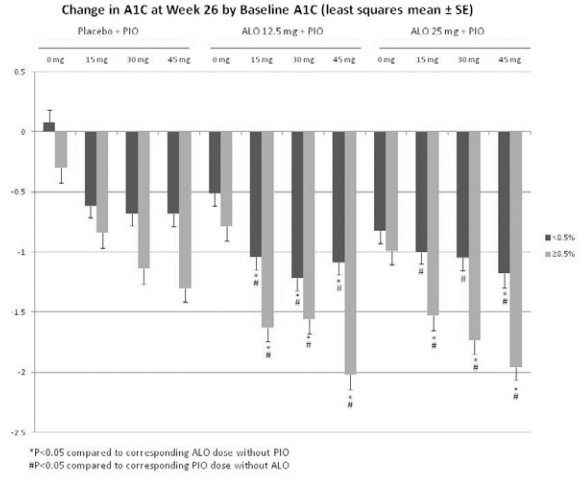
the treatment of patients with type 2 diabetes mellitus. In a previous study, IPRA exerted anti-obesity effects in diet-induced obese rats by promoting fatty acids utilization, while these effects on non-obese diabetes were concerned. In this study, in order to examine the effect of IPRA on the body composition in a non-obese model, the diabetic Goto-Kakizaki (GK) rats was selected. GK rats were treated for 9 weeks with IPRA once daily (1, 3, and 10 mg/kg or 10 mg/kg under feed restriction (FR)). The body composition was analyzed using dual-energy X-ray absorptiometry after 9-week treatment: hemoglobin A1c (A1c), blood glucose and plasma insulin were also measured after 4 and 8-week treatment.After 9-week treatment under free-access feeding condition, the body weight was not significantly changed although the cumulative food intake was significantly increased compared with vehicle group (8, 20, and 38% increase in IPRA 1, 3, and 10 mg/kg respectively vs vehicle). In the IPRA 10 mg/kg, FR group, the body weight was significantly decreased (390.7 ± 7.5 g in IPRA 10 mg/kg and, 355.4 ± 5.1 g in IPRA 10 mg/kg, FR vs 413.7 ± 7.9 g in vehicle). Regardless the feeding condition, the lean body mass was not affected significantly by IPRA, while the body fat mass was reduced significantly in the IPRA treated groups compared to that of vehicle group (51.4 ± 2.5 g in IPRA 10 mg/kg and, 39.1 ± 2.2 g in IPRA 10 mg/kg, FR vs 82.5 ± 4.6 g in vehicle).After 8-week treatment, reductions in A1c levels were significant at doses ≥1 mg/kg (4.2±0.1% in IPRA 1 mg/kg vs 4.9±0.1% in vehicle group) and the reduction in plasma insulin levels were significant at doses ≥1 mg/kg.In conclusion, IPRA improves glycemic control and selectively reduced fat mass without affecting lean body mass in non-obese diabetic model and induced anti-diabetic effects.

1144-P

Effect of Alogliptin in Combination With Pioglitazone on Glycemic Control by Baseline A1C

PENNY FLECK, CRAIG WILSON, *Deerfield, IL*

This phase 3, randomized, double-blind, placebo-controlled, 12-treatment arm study assessed the efficacy and safety of alogliptin (A) alone or combined with pioglitazone (P) in patients with type 2 diabetes on metformin with inadequate glycemic control. Treatment arms included A alone at doses of 12.5 or 25 mg QD; P alone at doses of 15, 30, or 45 mg QD; combinations of each A dose with each P dose; and a placebo arm. The primary analysis compared P alone (doses pooled; 387) with A 12.5 mg + any dose of P (n=390) or A 25 mg + any dose of P (n=390). The change from baseline (BL) A1C at week 26 by BL A1C was determined using 2 subgroups: <8.5% and ≥8.5%. Subjects in the combination groups achieved significantly larger decreases from BL in A1C levels at week 26 compared with subjects in the P alone group (P<0.001); greater reductions were observed for subjects with higher BL A1C levels. The majority of the A + P arms exhibited a statistically significant decrease in A1C levels at week 26 compared with corresponding doses of A alone and P alone (P<0.05), regardless of BL A1C; however, decreases were larger in subjects with higher BL A1C levels (Figure). The incidence of adverse events (AEs) was similar across all 12 arms, ranging from 54.3% (placebo) to 69.2% (A 25 mg + P 15 mg); serious AEs ranged from 0.8% (P 15 mg and A 25 mg + P 15 mg) to 7.8% (P 45 mg). Few subjects discontinued due to an AE, with the most occurring in the P 45 mg arm (7/129; 5.4%). Few subjects reported hypoglycemic events. In conclusion, A + P was significantly more effective than either monotherapy, with greater reductions being achieved in patients with higher BL A1C levels in all active treatment groups.



1145-P

Analysis of Factors Correlated With Hepatic Triglyceride Content in 32 Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease

FANGPING LI, YINQIONG HUANG, SHENG-NENG XUE, *Guangzhou, China*

Objectives: In this study we investigated the correlation between hepatic triglyceride content and glucose lipid metabolism ,insulin resistance and β cell function. Methods: 32 patients with type 2 diabetes and Nonalcoholic fatty liver disease were investigated in this study. We measured hepatic triglyceride content with liver proton magnetic resonance spectroscopy. OGTT was carried out in all participants, with measurements of plasma glucose and insulin level. The homeostasis model assessment insulin resistance index (HOMA-IR), hepatic insulin resistance (HIR) and Matsuda Index(M-SI) were used to assess insulin resistance. The homeostasis model assessment beta cell function(HOMA-βF), early insulin secretion index(EISI) and late insulin secretion index(LISI) were used to assess β cell function. Results: Hepatic triglyceride contents had positive correlations with BMI, waist circumference, Body fat, ALT, AST, TG, HOMA-IR, HIR, while had negative correlations with MSI. Stepwise regression analysis showed that: body fat and HOMA-IR were independently risk factors for hepatic triglyceride contents. Conclusion: Hepatic triglyceride contents is closely correlated with obesity, liver function, blood lipid and insulin resistance, among which obesity and insulin resistance are the most important factors.

1146-P

Does Pioglitazone Increase Bladder Cancer Risk in Japanese Type 2 Diabetes?

KANTA FUJIMOTO, YOSHIYUKI HAMAMOTO, SACHIKO HONJO, YUKIKO KAWASAKI, ATSUKO MATSUOKA, KANAKO MORI, HISATO TATSUOKA, YOSHIHARU WADA, HIROKI IKEDA, JUN FUJIKAWA, HIROYUKI KOSHIYAMA, *Osaka, Japan*

The concern about a possible risk of developing bladder cancer associated with pioglitazone has emerged. It has been reported that the prevalence of bladder cancer is relatively lower in Japan when compared with western countries. On account of this concern, we investigated the prevalence of bladder cancer in patients with type 2 diabetes in relation to pioglitazone treatment.We retrospectively examined the frequency of bladder cancer in patients with type 2 diabetes using the database in our institute. The data investigated were during the period of 13 years from 1998 to 2011.The numbers of total subjects with diabetes and those with bladder cancer were 21335 and 682 respectively. In the patients with diabetes, 170 were found to have bladder cancer, indicating that the prevalence of bladder cancer in patients with diabetes was 0.80%. Among the patients with diabetes, 663 patients (491 men and 172 women) were taking pioglitazone, in which 9 (6 men and 3 women) of them were found to have bladder cancer, and the prevalence of bladder cancer in patients taking pioglitazone was 1.36% (hazard ratio 1.753 [95%CI 0.892-3.446]). There was no statistically significant difference by the duration of pioglitazone therapy.Our study showed that bladder cancer was seen in 0.8% of patients with type 2 diabetes, and the treatment with pioglitazone might increase the risk. Although our study has limitation because of relatively small number of subjects from one institute, further study with large number of subjects will be justified.

1147-P

Exenatide Injection of 5 Micro-g Three Times a Day Stabilized the Daily Glucose Profile in Japanese Subjects

KENTARO SAKAMOTO, TOSHIHIDE HAYASHI, SUMIE OKAHATA, TERUO SHIBA, *Tokyo, Japan*

To investigate the acute effects of exenatide (Ex) on glucose and compare the effect of tid to bid on daily profile in Japanese, 21 consecutive inpatients of T2DM who consented to use of Ex were enrolled. 9 patients were on mono-therapy, and others were with oral hypoglycemic agents. Patients were treated with insulin to neutralize glucose toxicity in a week and then solid meal tests (460kcal containing 51% carbohydrates and 35% fats) were performed under the continuous glucose monitoring (CGMS). Ex was injected after the test and again, the test was performed on the 3rd day, in which plasma glucose (PG mg/dl), insulin (IRI microU/ml), and C-peptide (CPR) were examined at fasting, 15, 30, 60, and 120 min after load. Initial dose of Ex was 5 micro-g bid, and 8 patients who consented were administered tid from the 3rd day.The mean age, BMI, and initial HbA1c(%) were 50.8±10.1, 29.3±4.4, and 10.3±1.8, respectively. Whereas fasting PG did not change (pre- / post-: 128.2±22.7/131.0±22.5) by the Ex administration bid, the whole post-challenge PG decreased significantly (15min: 139.7±23.2/127.9±22.8, 30min: 173.8±31.2/132.5±30.8, 60min: 215.0±43.2/128.5±34.7, 120min: 217.4±54.2/117.8±43.8)*. IRI, along with CPR, increased at the fasting

(10.3±8.0/12.2±7.2) and 15 min (15.4±8.9/24.1±17.4), and decreased significantly at 120 min (39.7±24.3/26.2±23.0).CGMS revealed negative glucose excursion (*) by exenatide injection after breakfast or supper on the 2nd day, whereas overt positive excursion of glucose was observed after lunch. Additional bolus of Ex before lunch attenuated the mean(146.6±31.2/134.6±31.5), maximum (201.9±36.3/184.9±39.1), and SD (25.8±8.4/19.0±7.1) of the glucose by CGMS significantly.Ex bid acutely improved glucose by augmenting early phase insulin secretion in Japanese. 5 micro-g Ex tid stabilized the daily glucose profile to reduce the maximum PG near 180 (ADA recommended), which has the potential to reduce cardiovascular events.

1148-P

Pharmacokinetics (PK) of the Novel, Long-Acting Basal Insulin LY2605541 in Subjects With Varying Degrees of Renal Function

HELLE LINNEBJERG, SIAK LENG CHOI, ERIC CHEN QUIN LAM, KENNETH F. MACE, TERI S. HODGSON, VIKRAM P. SINHA, *Windlesham, Surrey, United Kingdom, Indianapolis, IN*

The basal insulin LY2605541 (LY) is PEGylated insulin lispro designed to have a large hydrodynamic size which delays insulin absorption and reduces clearance, resulting in prolonged duration of action.This Phase 1, multi-site, open-label study was designed to investigate the PK of LY in subjects with renal impairment. The PK of LY after a single subcutaneous dose (3 nmol/kg) was evaluated in 5 groups of subjects [Table]. Serial PK samples were collected up to 12 days post-dose. For subjects with end stage renal disease (ESRD), LY was given approximately 48 h before subjects resumed their normal dialysis schedule (2-4 hemodialysis sessions over the 12-day PK sampling period).The apparent clearance (CL/F) and half-life ($t_{1/2}$) across the groups were not affected by renal function; the relationship between CL/F and the estimated creatinine clearance (CrCL) was not significant (slope=0.000863 [p=0.885]). Dose-normalized C_{max} values (C_{max}/Dose) in subjects with moderate and severe renal impairment were slightly lower compared to control subjects, but with similar overall LY serum exposure (dose-normalized $AUC_{(0-\infty)}$ [$AUC_{(0-\infty)}$/Dose]). Dialysis did not result in a significant LY elimination (≤25%) relative to the overall AUC in subjects with ESRD. LY was well tolerated in healthy subjects and those with renal impairment.In conclusion, the PK properties of LY appear to be unaffected by renal impairment. Therefore no specific dose adjustment due to PK would be needed with increasing renal impairment.

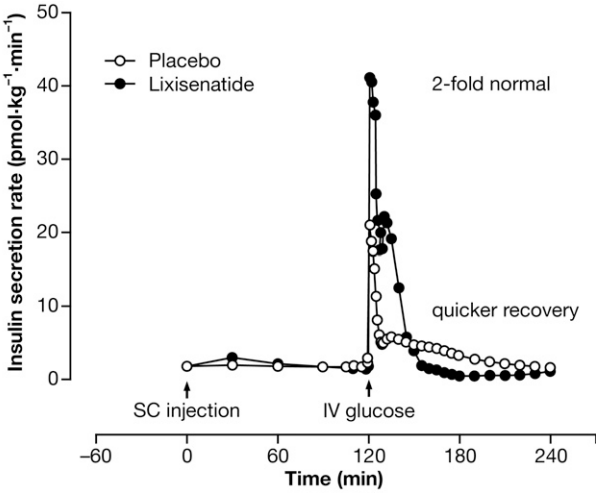
	Estimated Creatinine Clearance (CrCl, mL/min)				
	Normal Function (>80)	Mild Impairment (51-80)	Moderate Impairment (30-50)	Severe Impairment (<30)	ESRD (Dialysis for >3 months)
Demographics [N or Mean (SD)]					
N (M/F)	12 (9/3)	8 (7/1)	8 (5/3)	9 (4/5)	9 (6/3)
Age (years)	45.5 (15.3)	66.9 (8.9)	61.0 (13.3)	61.8 (11.5)	44.4 (10.7)
Weight (kg)	81.3 (15.1)	84.5 (13.0)	73.7 (16.0)	66.7 (10.1)	79.9 (19.3)
Pharmacokinetic Parameters [Geometric Mean (% CV)]					
$AUC_{(0-\infty)}$/Dose (pmol•hr/L/pmol)	0.352 (36)	0.452 (31)	0.429 (38)	0.424 (39)	0.323 (61)
CL/F (L/hr)	2.84 (36)	2.21 (31)	2.33 (38)	2.36 (39)	3.10 (61)
$t_{1/2}$ (hr)	34.9 (50)	37.2 (31)	43.7 (48)	42.4 (16)	45.7 (24)
C_{max}/Dose (pmol/L/pmol)	0.00713 (78)	0.00863 (79)	0.00623 (37)	0.00532 (68)	0.00518 (155)

1149-P

Augmentation of 1st-Phase Insulin Release With Lixisenatide in Non-Diabetic Subjects

REINHARD H. BECKER, JENS STECHL, CHRISTOPH KAPITZA, JEROME MSIHID, *Frankfurt, Germany, Neuss, Germany, Chilly-Mazarin, France*

Lixisenatide restores insulin release and accelerates glucose disposition in type 2 diabetes. We investigated the physiological response in non-diabetic subjects. In a 2-period, 2-treatment, 2-sequence, single-center, single-dose, crossover study, subjects (14 male, 6 female, mean age 36 yr, BMI 25 kg/m^2) received single doses of lixisenatide 20 µg SC or matching placebo 2 h prior to an intravenous glucose challenge (IVG; 0.3 g/kg over 30 s). First- ($AUC_{0-10min}$) and 2nd- ($AUC_{10-120min}$) phase insulin secretion [IS] was integrated from IS-rate (based on C-peptide measurement). Maximum plasma lixisenatide concentration (C_{max} 145 pg/mL; CV% 44) occurred 2 h (range 1-3 h) after injection, with weak transient effects on fasting BG and pre-IVG insulin levels. Lixisenatide enhanced 1st-phase IS 2.4-fold (90% CI 2.1-2.6), while 2nd-phase release was unchanged overall, 0.9-fold (90% CI 0.81-1.01), but was elevated up to 30 min and subsequently dropped sharply to baseline, differing significantly *vs* placebo, which remained elevated. First- and 2nd-phase insulin concentration increased 3.2-fold (90% CI 2.7-3.8) and 3.4-fold (90% CI 2.7-4.2), followed by 2.3-fold (90% CI 1.9-3.0) accelerated glucose disposition, reducing BG below counter-regulatory thresholds (<3.9 mmol/L) in some subjects. Glucagon suppression was initially augmented and recovered faster in those with BG<3.9 mmol/L. A single dose of lixisenatide 20 µg SC boosts insulin release to IVG and accelerates glucose disposition in non-diabetic subjects without affecting counter-regulatory interplay of insulin and glucagon release, thus retaining euglycemia.



Supported by: sanofi-aventis

1150-P

Selective SGLT2 Inhibition by Tofogliflozin (TOFO) Reduces Renal Glucose Reabsorption (RGR) Only in Hyperglycemic Conditions but not in Hypo- or Euglycemic Conditions in Rats

TAKUMI NAGATA, MASANORI FUKAZAWA, MASAYUKI SUZUKI, MIZUKI YAMANE, KOJI YAMAGUCHI, MOTOHIRO KATO, TETSUYA MITSUI, KIYOFUMI HONDA, SACHIYA IKEDA, YOSHIKI KAWABE, *Gotemba, Shizuoka, Japan*

Although it was generally believed that the contribution to RGR of SGLT2 (90%) was higher than SGLT1 (10%), recent studies have proposed a greater contribution of SGLT1 to RGR under hypo- and euglycemic conditions, but there is no direct evidence indicating the contribution of SGLT1 and 2 to RGR under different glycemic levels. Moreover, larger contribution to RGR under hypo- or euglycemic conditions may have an impact on hypoglycemia risk potential of SGLT inhibitors. Here we examined the contribution of SGLT2 and SGLT1 under different glycemic conditions by comparing the inhibitory effects of TOFO, a highly specific SGLT2 inhibitor under clinical development for T2D, and phlorizin (PHZ), a SGLT1/2 inhibitor, on RGR with glucose titration and clamp protocols in normal rats. TOFO has 3-fold greater activity against rSGLT2 (IC50=15nM) than PHZ, but 8-fold weaker activity against rSGLT1 (IC50=8200nM) than PHZ. To compare the contribution of SGLT1 and 2 inhibition, plasma concentrations of the two compounds were maintained by continuous iv infusion at levels sufficient to inhibit rSGLT2 completely, while inhibiting rSGLT1 to different degrees (~30% for PHZ and ~1% for TOFO). Under hyperglycemic conditions, over 50% equipotent inhibition of RGR was achieved by TOFO and PHZ, as expected from SGLT2 inhibitory activity. Under hypoglycemic and euglycemic conditions, PHZ reduced RGR by about 20-40%. In contrast, the RGR reduction by TOFO was minimal (1-5%). In conclusion, the contribution of SGLT1 to RGR is greater under lower glycemic conditions than under hyperglycemic conditions, and selective SGLT2 inhibition by TOFO exhibits greater reduction on RGR only in hyperglycemic conditions. This suggests that SGLT2-selective inhibitors, such as TOFO, have a lower risk of hypoglycemia than SGLT1/2 inhibitors.

1151-P

Insulin Degludec has Similar Pharmacokinetic Properties in Subjects With Renal Impairment and Subjects With Normal Renal Function

ISTVAN KISS, GERHARD AROLD, SUSANNE G. BØTTCHER, MARIANNE THRANE, HANNE L. HAAHR, *Budapest, Hungary, Berlin, Germany, Søborg, Denmark, Copenhagen, Denmark*

Insulin degludec (IDeg) is a new-generation basal insulin forming soluble multi-hexamers upon subcutaneous injection, resulting in a flat and stable ultra-long action profile. This open-label, parallel-group trial investigated the pharmacokinetic (PK) properties of IDeg in subjects with different grades of renal impairment and subjects with normal renal function (NRF) following single doses of 0.4 U/kg IDeg. In addition, the influence of hemodialysis on clearance of IDeg was investigated in end-stage renal disease (ESRD)

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

subjects by administration of two single doses of IDeg, one before and one just after hemodialysis.A total of 30 subjects (mean age: 65.6 yrs; females/males: 15/15; mean BMI: 28.4 kg/m^2) were allocated to one of five renal function groups (N=6 per group): NRF, mild, moderate, severe renal impairment, or ESRD.PK profiles of IDeg were similar for subjects with normal and impaired renal function. Renal impairment had no statistically significant effect on total exposure ($AUC_{0\text{-}120h,SD}$), maximum concentration ($C_{max,SD}$) or apparent clearance (CL/F_{SD}). PK profiles of IDeg for subjects with ESRD were similar irrespective of whether subjects received hemodialysis or not. Hemodialysis did not affect CL/F_{SD}, and no unaltered IDeg was detected in dialysate samples collected during dialysis from subjects with ESRD.In conclusion, the ultra-long PK properties of IDeg are preserved in subjects with renal impairment; renal impairment did not result in differences in the PK properties of IDeg compared to subjects with NRF. Hemodialysis did not affect the clearance of IDeg.

Table 1: PK endpoints vs. creatinine clearance

	$AUC_{IDeg,0\text{-}120h,SD}$	$C_{max,IDeg,SD}$	$CL/F_{IDeg,SD}$
Estimated slope	-0.138	-0.171	0.129
95% CI	[-0.390; 0.113]	[-0.415; 0.073]	[-0.120; 0.378]
Statistical significance	NS	NS	NS

Estimated slope: a measure of correlation between creatinine clearance and PK endpoint; CI: confidence interval; NS: non-significant (p≥0.05).Renal impairment was classified based on creatinine clearance (CL_{CR}) estimated by the Cockcroft & Gault formula, and subjects were grouped as: Normal (CL_{CR} >80 mL/min), mild (CL_{CR} >50-≤80 mL/min), moderate (CL_{CR} >30-≤50 mL/min), severe (CL_{CR} ≤30 mL/min) or end-stage renal disease (ESRD).

Supported by: Novo Nordisk A/S

1152-P

Exenatide Once Weekly was Associated With Improved Glycemic Control regardless of Baseline Body Weight

STEVEN C. BRUNELL, RICHARD PENCEK, YAN LI, BYRON J. HOOGWERF, *San Diego, CA, Indianapolis, IN*

The pharmacokinetic profile of a drug can be affected by variables such as volume of distribution, which is often a function of body weight. Consequently, body weight can influence the drug efficacy. The purpose of these analyses was to examine changes from baseline in several biomarker endpoints, stratified by baseline body weight quartiles, in patients treated with exenatide once weekly (EQW). Subjects with type 2 diabetes who received EQW in 7 randomized, comparator-controlled studies (N=1719; age [mean±SD], 55±10.3 y; A1C, 8.5±1.1%; analysis endpoints at 24-30 wks) were included in these analyses. Changes in A1C and body weight from baseline to endpoint were comparable across weight quartiles, indicating that baseline body weight did not have a substantial effect on these endpoints (Table). There were potential trends for greater reductions in fasting glucose in the lowest weight quartile and attenuated reductions in pulse pressure in the highest weight quartile. The most common adverse event overall was hypoglycemia (16.4%), which was more prevalent in patients receiving a concomitant sulfonylurea (28.0%) than in those who were not (7.5%). Other common adverse events were nausea (14.7%) and diarrhea (10.9%). Results from these analyses show that patients treated with EQW experienced clinically-meaningful improvements from baseline in A1C, fasting glucose, body weight, and pulse pressure, irrespective of baseline body weight.

	Body Weight Quartiles			
	Q1(n=435)	Q2(n=424)	Q3(n=430)	Q4(n=430)
Baseline body weight, mean (SD), kg	63.5 (6.4)	78.7 (3.7)	92.5 (4.4)	115.2 (12.2)
Baseline A1C, mean (SD), %	8.6 (1.1)	8.5 (1.1)	8.4 (1.0)	8.5 (1.1)
A1C, mean (95% CI) Δ, %	-1.5 (-1.6, -1.4)	-1.4 (-1.5, -1.3)	-1.4 (-1.5, -1.3)	-1.4 (-1.5, -1.3)
Fasting glucose, mean (95% CI) Δ, mg/dL	-41.2 (-45.5, -36.9)	-33.3 (-38.2, -28.5)	-32.4 (-36.8, -28.1)	-34.7 (-40.1, -29.5)
Weight, mean (95% CI) relative Δ, %	-2.6 (-3.0, -2.2)	-2.8 (-3.1, -2.4)	-2.5 (-2.9, -2.1)	-2.8 (-3.2, -2.4)
Pulse pressure, mean (95% CI) Δ, mmHg	-2.7 (-3.9, -1.5)	-2.5 (-3.5, -1.4)	-2.4 (-3.5, -1.4)	-1.5 (-2.6, -0.4)

1153-P

Efficacy and Safety of a Basal-Plus Regimen of Insulin Glargine Plus Insulin Glulisine in Patients With Type 2 Diabetes: A Pooled Analysis of 4 Clinical Trials

STEFANO DEL PRATO, MARK LANKISCH, JAY LIN, EDWARD WANG, DAVID R. OWENS, *Pisa, Italy, Düsseldorf, Germany, Flemington, NJ, Bridgewater, NJ, Cardiff, United Kingdom*

The "basal-plus" regimen is an increasingly common initial step in insulin therapy intensification. This pooled analysis evaluated overall efficacy and safety of adding a single bolus dose of insulin glulisine to basal insulin glargine in persons with type 2 diabetes mellitus (T2DM).Data from subjects with poor glycemic control on oral antihyperglycemic drugs who were initiated on basal insulin glargine to which insulin glulisine (basal-plus) was added once daily for up to 6 months were pooled from 4 randomized, multicenter studies. Glargine was titrated to protocol-defined blood glucose targets in 2 of 4 studies. Glulisine was titrated in all 4 studies to protocol-defined fasting (FBG) or postprandial glucose (PPG) targets. PPG was measured 2 h after glulisine injection. A1C, FBG, PPG, insulin dose, and demographics were measured at baseline and endpoint.A total of 713 subjects were included (46.6% female, mean age, 59.9 y, a mean duration of diabetes, 11.0 y). The basal-plus regimen resulted in a significant decrease in A1C and PPG at endpoint (Table). Glargine and glulisine dose significantly increased, whereas there was no significant change in body weight, body mass index, or FBG. Subjects with A1C < 7% increased from 20.2% at baseline to 45.2% at endpoint. The prevalence of severe hypoglycemia (as defined in each trial) was 1.7%.The results suggest that basal-plus treatment using glargine + glulisine improves glycemic control without affecting body weight and with a low prevalence of severe hypoglycemia in T2DM subjects who are uncontrolled on oral agents.

	Baseline	Endpoint	*P* Value
A1C, %	7.6 (0.8)	7.1 (0.9)	< 0.001
FBG, mg/dL	119 (37)	123 (37)	0.051
PPG, mg/dL	195 (44)	140 (39)	< 0.001
Weight, kg	89.7 (19.8)	90.6 (20.5)	0.4
BMI, kg/m^2	31.9 (6.0)	32.2 (6.2)	0.3
DoseGlargine,	36.8 (26.5)	41.9 (33.2)	0.002
UGlulisine, U	4.9 (2.2)	13.2 (11.1)	< 0.001

Values are mean (SD); BMI, body mass index

Supported by: sanofi-aventis

1154-P

Efficacy and Safety of Add-On Vildagliptin to Metformin in Comparison to Uptitrating Metformin Therapy

NAN HEE KIM, YEON-AH SUNG, CHUL WOO AHN, SEOK WON PARK, SOO LIM, CHUL HEE KIM, DONG SUN KIM, YOUNG GOO SHIN, KYU JEUNG AHN, JAE HYEON KIM, SEI HYUN BAIK, *Gyeonggi, Republic of Korea, Seoul, Republic of Korea, Gangwon, Republic of Korea*

Aims: To show whether vildagliptin added to metformin 1500mg is non-inferior to uptitrating metformin in reducing HbA1c levels from baseline.Methods: A randomized, open-labeled, multicenter study of type 2 diabetic patients inadequately controlled by 1500mg of metformin monotherapy (7%≤HbA1c≤11%). They were randomized to add vildagliptin 50mg bid on metformin 1500mg or uptitrating metformin dose up to 2000mg or 2500mg.Results: Intention to treat analysis was done in 132 patients from vildagliptin plus metformin therapy and 125 patients from metformin uptitration therapy. From the similar baseline HbA1c values (8.16 vs 8.14%, vildagliptin plus metformin vs metformin uptitration), changes in HbA1c after 24 weeks were not inferior with vildagliptin plus metformin combination therapy compared to metformin uptitration therapy [adjusted mean change (±SE) of HbA1c; -1.25±0.05% vs. -0.90±0.06%, (95% CI for non-inferiority: -0.51 to -0.20), p<0.0001]. In the superiority analysis, vildagliptin plus metformin combination therapy showed significant reduction for HbA1c than metformin uptitration therapy (p<0.0001). Similarly, vildagliptin plus metformin therapy also controlled fasting plasma glucose more effectively thanmetformin uptitration therapy. (-26.0±1.7 vs -17.8±1.8 mg/dl (mean±SE), p=0.001). Changes of insulin resistance, insulin secretion, and lipid profile were not different between two therapies. There was no difference in the hypoglycemic events with either therapy. The incidence of adverse drug reaction was lower in the vildagliptin plus metformin combination therapy than in metformin uptitration therapy (3.8% vs. 10.7%), mostly due to the difference of gastrointestinal side effect (3.0% vs 9.2%, p=0.0420).Discussion: When metformin alone fails to maintain sufficient glycemic control, the addition of vildagliptin provides comparable efficacy to metformin uptitration therapy, and displays more favorable adverse effect profile.

Supported by: HANDOK Pharmaceuticals Co.

1155-P

Postprandial Incretin, Insulin and Glucagon Secretion in T2DM Patients Treated With Sitagliptin Alone or in Combination With Metformin

JOSE DE JESUS GARDUNO GARCIA, JOHN ADAMS, CAROLINA SOLIS-HERRERA, CURTIS TRIPLITT, RALPH A. DEFRONZO, EUGENIO CERSOSIMO, *San Antonio, TX*

To assess hormonal changes in response to sitagliptin (S) monotherapy or in combination with metformin (S+M), 16 T2DM patients (age 47±10 y, 9 male/7 female, diagnosis < 1 year, BMI 34±5 kg/m^2, HbA_{1C} 8.8± 1%) were randomized to receive 4 weeks of therapy with Placebo (P), Metformin (M), S, or S+M, at maximum doses (2-week washout between each therapy). After each therapy, patients received a 6-h meal tolerance test (MTT) (600 kcal, 20g protein, 25g fat, 75g glucose). Fasting plasma glucose (FPG), insulin (FPI), glucagon (FPGn) levels and AUCs during MTT were measured over 360 minutes. Plasma incretin levels (active GLP-1 and GIP) and insulin secretory rate (ISR) (plasma C-peptide deconvolution) were determined. The decrement in FPG with S+M was greater than with other therapies (S+M=125±2, M=149±3 S=154±3, P=161±4 mg/dl) ($p< 0.05$). Mean PG post-MTT was 208±15 mg/dl in P and decreased to 182±15 (S), 181±11 (M) and 155±9 (S+M) [$p<0.01$]. FPI (~12 µU/ml) did not change in any group. The peak ISR (12.3 pmol/kg·min) during MTT with S+M was higher than all other groups (M=11.0±1.3, S=11.2±1.2, P=10.2±1.2). FPGn was similar in all 4 groups. During MTT the percent glucagon suppression was greater with S+M (29%) versus S (21%), M (17%), and P (21%) ($P<0.05$). Baseline GLP-1 was higher in S+M (121±7) versus 5 (78±15) and both were higher than in M (28±6) and P (32±6) ($p<0.05$). Post MTT GLP-1 AUC was markedly increased in S+M (4.5-), S (4.1-), M (1.8-) fold compared to P ($p<0.05$). Fasting GIP levels were similar in all 4 groups and post MTT levels increased only in S+M by 1.3 fold vs P. Conclusion: The reduction in fasting and post-meal plasma glucose levels caused by sitagliptin is enhanced with the addition of metformin. The improvement in glucose tolerance results from a greater stimulation of insulin and enhanced suppression of glucagon, which may be related to higher GLP-1 and GIP levels observed with S+M versus alone.

1156-P

Exenatide Once Weekly Resulted in Sustained Improvement in Glycemic Control With Weight Loss through 4 Years

LEIGH MACCONELL, YAN LI, RICH PENCEK, CHRISTINE SCHULTEIS, LISA PORTER, *San Diego, CA*

In the 30-wk, randomized, open-label DURATION-1 study, the once-weekly formulation of the GLP-1 receptor agonist exenatide (EQW) significantly reduced A1C compared with twice-daily exenatide (LS mean ΔA1C: -1.9% vs -1.5%; *P*=0.002), with similar weight loss, in 295 ITT patients with T2DM treated with diet/exercise, metformin, sulfonylurea (SFU), and/or thiazolidinedione. Persistence of glycemic control and safety was studied in 258 (87%) patients receiving EQW in a subsequent extension. A total of 176 (68%) patients completed 4 y of EQW treatment (baseline [mean±SD]: A1C 8.2±0.9%; FPG 166±41 mg/dL; weight 100±18 kg; duration of diabetes 7±5 y); some patients increased or decreased oral antidiabetes medication doses. Long-term EQW treatment was associated with significant A1C reduction (LS mean [95%CI]: -1.7% [-1.9, -1.5]). At 4 y, mean±SE A1C was 6.9±0.1%, with 55% of patients achieving A1C <7.0%. Clinically significant improvements in FPG (-37 mg/dL [-44, -31]) and weight (-2.5 kg [-3.8, -1.2]) were observed, as were LS mean reductions in cardiovascular risk markers: systolic blood pressure (-1.6 mmHg [-4.0, 0.9]), total cholesterol (-10.9 mg/dL [-16.6, -5.1]), LDL cholesterol (-8.0 mg/dL [-12.9, -3.2]), and triglycerides (-13% [-19, -6]; geometric LS mean % change). Mostly mild nausea, the most common adverse event (AE) with EQW during the initial controlled period, decreased with ongoing therapy. The annual event rate (events/100 y patient exposure) for nausea with EQW was 85 in wks 1-30 and 15 over the 4-y study duration. Six (2%) EQW patients withdrew due to gastrointestinal AEs over 4 y. No major hypoglycemia was observed; minor hypoglycemia occurred primarily with SFU use. Annual event rates for cardiac and renal/urinary disorders were 5 and 6, respectively, for EQW over 4 y. Overall, long-term EQW treatment was associated with significant, sustained improvement in glycemic control and improvements in cardiometabolic measures, with no unexpected safety findings.

1157-P

Two Post-Cardiac Surgery IV Insulin Protocols Targeting Blood Glucose 110–140mg/dL in Patients With and Without Diabetes

VASUDEV MAGAJI, AMY DONIHI, SHRIDDHA NAYAK, SRINIVAS JAMPANA, LAUREN WILLARD, PARACHUR NIVEDITA, RAYMOND A. EDER, JANN M. JOHNSTON, MARY T. KORYTKOWSKI, *Pittsburgh, PA*

Blood Glucose (BG) targets after cardiac surgery were revised in 2009 to 110-140mg/dL, prompting changes to IV insulin infusion protocols (IVIIPs). We compared two UPMC IVIIPs targeting 110-140mg/dL in patients grouped according to diabetes (DM) status. IVIIP1 adjusts insulin infusion rates (IIR) based on BG and its rate of change using 4 algorithms. IVIIP2 adjusts IIR based on current BG, its rate of change, and current IIR with a single table. Consecutive cardiac surgery patients receiving IVIIP1 and IVIIP2 were studied retrospectively. Exclusion criteria: sepsis, organ transplantation, steroids, enteral/parental nutrition. BGs and IIRs were collected for 48 hours postoperatively. Efficacy (%BG 110-140mg/dL) and safety (%BG 40-69 & <40mg/dL) were analyzed. Baseline data and glycemic control in first 48 hours of IVIIP are described in the tables.Both IVIIPs were safe and effective. All groups had mean BGs in goal with minimal hypoglycemia. DM status did not effect glycemic control with IVIIP1, but DM patients had slightly higher BGs with IVIIP2.Differences in glycemic control may be due to differences in the IVIIPs or in the study populations,such as higher pressor use in IVIIP2 DM group.

Table1- Baseline Characteristics

	IVIIP1 Diabetes Group (N=49)	IVIIP2 Diabetes Group (N=43)	p value IVIIP1 Diabetes Group vs IVIIP2 Diabetes Group	IVIIP1 No Diabetes Group (N=57)	IVIIP2 No Diabetes Group (N=79)	p value IVIIP1 No Diabetes Group vs IVIIP2 No Diabetes Group
Age in years Median [min-max]	63[33-92]	62*[37-83]	0.769	66[33-89]	59*[26-85]	0.003
Gender(M/F), %	63.2/36.7	72/28	0.367	63.1/36.9	64.5/35.5	0.867
BMIMedian [MIN-MAX]	30.2[18.9-47]	32*[21-50]	0.263	29.3[19.8-50]	28.66*[18-50]	0.309
Preoperative A1C (%) Median [min-max]	7.0‡[4.6-11.8]	6.5†[4.3-11.1]	0.008	5.8‡[4.9-6.4]	5.6†[4.3-6.4]	0.004
Hematocrit, post-operative (%)	28[21-42]	27[19-39]	0.130	27[20-38]	28[21-39]	0.092
Use of pressors, %	55.1	79*	0.015	61.4	58.2*	0.710
BaselineBGM (mg/dL)	141±37	159±36	0.023	155±42	147±39	0.245

Table 2 - Glycemic control

	IVIIP1 Diabetes Group (N=49)	IVIIP2 Diabetes Group (N=43)	p value IVIIP1 Diabetes Group vs IVIIP2 Diabetes Group	IVIIP1 No Diabetes Group (N=57)	IVIIP2 No Diabetes Group (N=79)	p value IVIIP1 No Diabetes Group vs IVIIP2 No Diabetes Group
% BGs in 110-140 mg/dL	41.78	35.93†	0.033	45.93	47.81†	0.208
% BGs in 141-180 mg/dL	23.32	30.38*	0.006	20.43	26.10*	0.015
% BGs > 180 mg/dL	7.25	12.5†	0.017	4.88	4.87†	0.851
% BGs 70-109 mg/dL	26.31	20.45	0.038	28.04	20.33	0.001
% BGs 40-69 mg/dL	1.27	0.75	0.274	0.72	0.89	0.448
% BGs < 40 mg/dL	0.07	0.00	0.352	0.00	0.00	—
Average BG after goal (mg/dL)	123±11	133±14†	<0.001	121±10	126±9†	0.003
Time to Goal (hours) Median [MIN-MAX]	5.2[0.8-19.4]	6.63†[1.8-12.7]	0.995	2.8[0.2-9.85]	4.1†[0.9-19.8]	0.028

For Table1 and Table2* $p<0.05$ for Diabetes vs NoDiabetes with IVIIP2† $p<0.01$ for Diabetes vs NoDiabetes with IVIIP2‡ $p<0.01$ for Diabetes vs NoDiabetes with IVIIP1

For author disclosure information, see page 797.

Guided Audio Tour poster

ADA-Funded Research

1158-P

Alogliptin plus Metformin Combination Therapy vs. Alogliptin or Metformin Monotherapy for Type 2 Diabetes Mellitus

RICHARD PRATLEY, CRAIG WILSON, PENNY FLECK, *Orlando, FL, Deerfield, IL*

The efficacy and safety of alogliptin (ALO) plus metformin combination therapy (A+M) in doses of 12.5/500 and 12.5/1000 mg BID vs monotherapy with ALO 12.5 mg BID (A12.5) or MET 500 or 1000 mg BID (M500 or M1000) was evaluated in a 7-arm study of 784 subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise alone; 2 arms, placebo and ALO 25 mg QD, were included for the purposes of secondary analyses. In the primary efficacy analysis, the 2 combination therapy regimens were compared with their monotherapy regimens (A+M 12.5/500 vs A12.5 and M500, and A+M 12.5/1000 vs A12.5 and M1000). The majority of subjects were white (72%), women (52%), mean age of 54 years, body mass index of 31, diabetes duration of 4 years, and baseline A1c of 8.4%. Reductions in A1c at week 26 (primary endpoint) were -1.22% and -1.55% with A+M 12.5/500 and 12.5/1000, vs -0.56%, -0.65%, and -1.11% with A12.5, M500, and M1000 (P<0.001 for all comparisons). Significantly more subjects achieved A1c <7% with A+M (47.1% and 59.5% with 12.5/500 and 12.5/1000) vs monotherapy with A12.5, M500, or M1000 (20.2%, 27.2%, and 34.3%) (P<0.01 for all comparisons). Reductions in FPG were -31.7 and -45.9 mg/dL with ALO+MET 12.5/500 and 12.5/1000, vs -9.7, -11.5, and -31.9 mg/dL with A12.5, M500, and M1000 (P<0.05 for all comparisons). Significantly fewer A+M subjects were rescued for hyperglycemia: 12.3% and 2.6% with 12.5/500 and 12.5/1000, vs 17.3%, 22.9%, 10.8% with A12.5, M500, and M1000 (P<0.05 for all comparisons). Greater reductions in proinsulin/insulin ratios and increases in HOMA-BCF (beta cell function) with A+M vs ALO or MET monotherapy were observed. Modest weight decreases were observed with A+M and MET, while ALO monotherapy was weight neutral. All arms were well tolerated with few reports of hypoglycemic events. In summary, A+M combination therapy provided significantly better glycemic control than ALO or MET monotherapy, with a safety profile consistent with its individual components.

1159-P

Improved Diabetes Treatment Satisfaction and Weight-Related Quality of Life for Asian Patients Treated With Exenatide Once Weekly Versus Twice Daily

MANJIRI PAWASKAR, MELANIE CHAN, TAKESHI IMAOKA, JENNIE BEST, MARILYN BOARDMAN, *Indianapolis, IN, Toronto, ON, Canada, Kobe, Japan, San Diego, CA*

This trial evaluated efficacy and safety of exenatide once weekly (EQW) vs twice daily (EBID) in Asian patients (pts) with type 2 diabetes suboptimally controlled with metformin, sulfonylurea, thiazolidinediones, or any 2 combined. This report examines patient-reported outcomes.This open-label comparator-controlled trial randomized 678 pts to add EBID or EQW to the current oral regimen for 26 wks. Pts in China, S Korea, India, and Taiwan completed the Impact of Weight on Quality of Life (IWQOL-Lite) questionnaire; pts in Japan completed the Diabetes Treatment Satisfaction Questionnaire (DTSQ).For questionnaires, changes from baseline (BL) to endpoint were tested by paired t-test (ITT population). Treatment group comparison on changes was performed using LOCF ANCOVA model. A1C and body weight (wt) were analyzed using MMRM ANCOVA.BL mean age = 56 y, A1C = 8.7%, wt = 70 kg. Both EQW and EBID significantly reduced A1C (P<0.001) at 26 wks. The difference in change in A1C from BL to 26 wks was greater for EQW vs EBID (-1.4 vs -1.1; P<0.001). Both groups had reduced mean wt at 26 wks (P<0.001); the difference in change in wt from BL was greater for EBID vs EQW (-2.5 vs -1.6 kg; P<0.001). Both groups had a significant increase from BL in IWQOL-Lite total score (Table). EQW patients had a significant increase from BL in DTSQ total score vs EBID.EQW and EBID pts who completed the IWQOL had significant improvement in wt-related quality of life at 26 wks. Japanese pts treated with EQW had significant improvement in overall treatment satisfaction vs EBID at 26 wks.

		EBID (N=338)		EQW (N=340)		Treatment Comparison
		Baseline	Change	Baseline	Change	*P* value
IWQOL (N=523) Patients in China, S Korea, India, and Taiwan	Total score transformed	86.56 (0.97)	2.38 (0.78)*	86.94 (0.95)	2.40 (0.77)*	0.987
DTSQ (N=155) Patients in Japan	Total treatment satisfaction	24.34 (0.66)	0.05 (0.72)	24.64 (0.66)	4.03 (0.71)*	<0.001

Data presented as LS Mean (SE). *Within group P<0.05

1160-P

Long-Term Safety and Tolerability of Saxagliptin Add-On Therapy in Elderly Patients With Type 2 Diabetes

NAYYAR IQBAL, ELSIE ALLEN, MARK DONOVAN, PETER ÖHMAN, *Princeton, NJ, Wilmington, DE*

Safety is a particular concern in elderly patients receiving treatment for type 2 diabetes (T2D). This pooled analysis examined adverse events (AEs) of interest (treatment-related AEs, serious AEs, AEs leading to discontinuation, and events of special interest) in elderly patients ≥65 y who received saxagliptin added to metformin, glyburide, or thiazolidinedione over 76-206 weeks of treatment in 3 placebo-controlled trials. Time at risk for each AE type was calculated for patients from day of first dose to specified event or last dose. Weighted incidence rates (IRs/100 person-years±SE) and IR ratios (IRRs) with 95% CIs for saxagliptin vs placebo were calculated (Mantel Haenszel). Treatment-related AE IRs were similar between saxagliptin 5 mg and placebo for patients ≥65 y (Table). Results were consistent with those obtained for pooled analysis of all doses of saxagliptin. In the elderly subpopulation, there were few events for confirmed hypoglycemia (saxagliptin 5 mg, 1 event; placebo, 2 events), hypersensitivity (2 events each for saxagliptin 5 mg and placebo), and acute cardiovascular events (saxagliptin 5 mg, 3 events; placebo, 2 events), resulting in wide CIs. There were 2 deaths (1 elderly) in the saxagliptin group and 6 (0 elderly) in the placebo group. This analysis demonstrates that long-term use of saxagliptin as add-on therapy is well tolerated in elderly patients with T2D.

IR/100 person-y±SE	≥65 y			<65 y		
	SAXA 5 mg n=99	PBO n=106	IRR (95% CI) SAXA vs PBO	SAXA 5 mg n=531	PBO n=524	IRR (95% CI) SAXA vs PBO
Treatment-related AEs	34.1±5.8	27.1±4.9	1.26(0.77, 2.04)	24.0±2.0	27.8±2.3	0.86(0.69, 1.08)
Serious AEs	5.7±2.0	9.9±2.7	0.57(0.24, 1.40)	6.5±0.9	6.6±1.0	0.99(0.66, 1.49)
AEs leading to D/C	9.3±2.6	4.4±1.8	2.13(0.85, 5.329)	4.7±0.8	3.4±0.7	1.36(0.81, 2.27)
Acute cardiovascular-related events	2.1±1.3	1.5±1.1	1.42(0.26, 7.79)	0.8±0.3	1.6±0.5	0.48(0.18, 1.31)
Reported hypoglycemia	12.6±3.2	12.3±2.9	1.03(0.51, 2.05)	10.2±1.2	10.7±1.3	0.95(0.68, 1.32)
Confirmed hypoglycemia	0.8±0.8	1.2±0.8	0.65(0.06, 7.33)	1.2±0.4	1.3±0.4	0.90(0.36, 2.29)
Hypersensitivity	1.4±1.0	1.3±0.9	1.03(0.14, 7.83)	1.7±0.5	0.3±0.2	5.7(1.29, 24.92)

AE=adverse event; D/C=discontinuation; IR=incidence rate; IRR=incidence rate ratio; PBO=placebo; SAXA=saxagliptin; SE=standard error.

Supported by: Bristol-Myers Squibb/AstraZeneca

1161-P

Less Nocturnal Hypoglycemia for Insulin Degludec vs. Insulin Glargine in Subjects With T1DM and Baseline A1c of 7.5–8.5%: A Meta-Analysis

IRL B. HIRSCH, LUIGI F. MENEGHINI, LENA LANDSTEDT-HALLIN, SØREN RASMUSSEN, NATHAN LASSOTA, JITEN VORA, *Seattle, WA, Miami, FL, Stockholm, Sweden, Soeborg, Denmark, Liverpool, United Kingdom*

The risk of hypoglycemia increases as A1c levels approach recommended targets. Insulin degludec (IDeg) is a new basal insulin that forms soluble multi-hexamers upon sc injection, resulting in an ultra-long action profile with a low day-to-day variability. We performed a patient level meta-analysis to investigate whether these characteristics of IDeg would allow improved glycemic control together with lower rates of hypoglycemia compared to insulin glargine (IGlar) in T1DM patients with a baseline A1c of 7.5-8.5%. Changes in A1c and fasting plasma glucose (FPG) were analyzed with a linear model and rates of hypoglycemia with a negative binomial regression model. Hypoglycemia was defined as rates of self-reported confirmed hypoglycemia (PG <56 mg/dL [3.1 mmol/L] or severe episodes requiring assistance) and nocturnal confirmed hypoglycemia (onset between 00:01 to 05:59, incl.). The analysis included all open-labeled randomized treat-to-target phase 3a trials in T1DM of 26 or 52 weeks, where IDeg (n=223) and IGlar (n=109) were dosed once-daily in a basal-bolus regimen. A1c decreased from 8.0% at baseline in both groups to 7.6 vs. 7.5% at end of trial for IDeg vs. IGlar, respectively (treatment difference: 0.05 $[-0.12; 0.22]_{95\% CI}$). FPG decreased from 175 to 143 mg/dL for IDeg vs. 177 to 163 mg/dL for IGlar, a treatment difference of -18.27 mg/dL $[-35.05; -1.49]_{95\% CI}$. There was no difference in overall hypoglycemia (rate ratio (RR): 0.99 $[0.80; 1.24]_{95\% CI}$) or severe hypoglycemia (RR: 1.05 $[0.50; 2.22]_{95\% CI}$) between IDeg and IGlar. Despite the lower FPG achieved with IDeg, the rate of nocturnal hypoglycemia was lower with IDeg compared to IGlar (RR: 0.68 $[0.50; 0.93]_{95\% CI}$). In conclusion, for patients with T1DM and a baseline A1c of 7.5-8.5%, treatment with IDeg results in comparable im-

provement in A1c with a significantly lower rate of nocturnal hypoglycemia (32%) and a greater reduction in FPG compared to IGlar.

Supported by: Novo Nordisk A/S

1162-P

Effects of Long-Term Liraglutide on Diurnal Glucose Variations and Post-Load Insulin Secretion in Japanese Type 2 Diabetic Patients

YUKIKO TANIGUCHI, KAZUNORI SEZAKI, YUTAKA MORI, MASAZUMI ERIGUCHI, *Higashimurayama, Japan, Komae, Japan*

Objective: In this study, we investigated whether the inhibitory effect of liraglutide on glucose variations in type 2 diabetic patients might be maintained over the long term and how long-term liraglutide might affect post-load insulin secretion in these patients.Methods: The study included a total of 15 patients who were available for long-term follow-up with the dose of liraglutide maintained at 0.9 mg/day. The patients were examined for glucose variation before, 1 week and 6 months after the start of liraglutide 0.9 mg/day. Also, in those receiving liraglutide monotherapy, an OGTT was performed without giving liraglutide to assess their insulin-secretory capacity.Results: There was a mean reduction of 5.4 kg in body weight and 1.3% in HbA1c value in the patients after 6 months of treatment with liraglutide 0.9 mg/day, compared to baseline. The nearly flat glucose variation achieved and maintained over a 24-hour period after 1 week of treatment with liraglutide 0.9 mg/day remained nearly intact even after 6 months, with significant decreses seen in 24-hour mean glucose levels, the total area for the range of 24-hour glucose variations, and MAGE. Of these, 3, 6 and 1 had NGT, IGT, and diabetes, respectively, at the OGTT performed 1 week after the start of liraglutide 0.9 mg/day; 5, 3, and 2 had NGT, IGT, and diabetes, respectively, at the OGTT performed after 6 months. Additionally, the increase in pre- and post-load insulin secretion seen after 1 week of treatment with liraglutide 0.9 mg was no longer seen after 6 months, with no improvement in insulinogenic index.Conclusions: The glucose variations continued to be flattened over the long term with liraglutide in those whose body weight had been favorably controlled even after hospital discharge, while the pre- and post-load increases in insulin secretion after 1 week of treatment with liraglutide disappeared with long-term body weight control, with no improvement in early-phase insulin secretion.

1163-P

Linagliptin is Efficacious and Well Tolerated in Asian Patients With Inadequately Controlled Type 2 Diabetes

ZHENGPEI ZENG, DONG SEOP CHOI, VISWANATHAN MOHAN, ANGELA EMSER, KAMRAN SIDDIQUI, YAN GONG, SANJAY PATEL, HANS-JUERGEN WOERLE, *Beijing, China, Seoul, Republic of Korea, Chennai, India, Ingelheim, Germany, Singapore, Singapore, Bracknell, United Kingdom*

A series of randomized, double-blinded, placebo-controlled, multinational trials for the DPP-4 inhibitor linagliptin examined its safety and efficacy for glycemic control as monotherapy, as add-on to metformin, as add-on to metformin + sulfonylurea, or in combination with pioglitazone in patients with type 2 diabetes (T2D). Given the need for evaluation of new antidiabetic agents in different ethnicities, we analyzed pooled patient data for efficacy and safety of linagliptin in Asian patients with T2D. For efficacy endpoints (e.g. HbA1c), trials with treatment ≥24 weeks were pooled. For safety endpoints, data from all placebo-controlled linagliptin trials in patients with T2D were pooled. Efficacy data were pooled for 743 linagliptin- and 286 placebo-treated patients from 4 RCTs (24-week treatment preceded by 4-week washout [when applicable] and 2-week placebo run-in). Baseline demographics (mean±SD) for linagliptin and placebo were similar: HbA1c: 8.2% (±0.9%) in both arms; BMI: 26.0 (±4.0) and 26.1 (±3.7) kg/m^2; mean age: 54.5 (±10.0) and 54.0 (±10.5) years, respectively. HbA1c change from baseline at 24 weeks (mean ±SE) was −0.60% (±0.03) with linagliptin and 0.20% (±0.05) with placebo, resulting in placebo-corrected HbA1c change of −0.80% (±0.06; 95% CI: −0.91 to −0.68; p<0.0001) favoring linagliptin. A total of 1477 Asian patients who participated in 12 trials (≥12 days up to 24 weeks) were analyzed for safety; 1037 and 440 received linagliptin or placebo, respectively (treated set [TS]). Overall adverse event (AE) rates with linagliptin and placebo including background medication in the TS were similar (56.6% and 56.8%, respectively). Drug-related AEs and serious AEs were reported by 11.6% and 8.4%, and 2.4% and 2.7%, respectively (TS). In Asian patients with T2D, linagliptin offers an efficacious and well-tolerated treatment option as monotherapy or in combination with other commonly used oral antidiabetic therapies.

Supported by: Boehringer Ingelheim

1164-P

Effect of Alogliptin Combined With Pioglitazone on Lipids and Lipoprotein Particles in Patients With Type 2 Diabetes

PENNY FLECK, CRAIG WILSON, *Deerfield, IL*

Lipid abnormalities are a common consequence of insulin resistance and type 2 diabetes mellitus (T2DM). We evaluated effects of alogliptin (A), a highly selective dipeptidyl peptidase-4 inhibitor, combined with pioglitazone (P), a thiazolidinedione, on fasting lipids, lipoprotein particles, and high-sensitivity C-reactive protein (hsCRP) in patients with T2DM. Lipid parameters were assessed from 2 phase 3 multicenter, randomized, double-blind, placebo-controlled studies. Patients were 18-80 years of age, had an established diagnosis of T2DM and were previously treated with antidiabetic therapy. Patients in study 1 were randomized to receive placebo, A (12.5 - 25 mg), P (15 - 45 mg), or A + P (P groups with common A doses were pooled for primary analysis) once daily for 26 weeks. In study 2, patients were randomized to A 25 mg, P 30 mg, A 12.5 + P 30 mg or A 25 + P 30 mg. Changes in particle size were determined by NMR fractionation. Lipid variables were assessed in 1553 patients in study 1 and 654 in study 2. In study 1, free fatty acids were significantly (P=0.002) reduced from baseline with A 25 + P vs P alone (all doses) at week 26. In study 2, patients receiving A 25 + P 30 showed significant (P≤0.001) improvement from baseline in triglycerides and HDL at week 26 compared to A 25. Significant (P≤0.01) reductions from baseline in very low-density lipoprotein (VLDL) and total LDL particles (medium-small, small, and very small) were observed in both studies among the A + P combinations vs comparator at 26 weeks. No significant findings for hsCRP were observed for A + P combination arms in study 1 vs P alone; in study 2, hsCRP was significantly reduced from baseline to week 26 with A 25 + P 30 vs A 25 (P=0.004), but not vs P 30. Lipid analyses from these 2 clinical studies indicate that VLDL and total LDL particles are consistently improved with A + P therapy vs comparator. Overall, the combined regimen appears to have a favorable effect on lipids in the studied population.

1165-P

Comparative Trial Between Combination of Glargine and Lispro Insulin Versus NPH and Regular Insulin Using a Basal/Bolus Approach in Hospitalized Patients With Type 2 Diabetes

ALVARO PUIG, LUZ PRIETO, DIANA ALBA, MARIA P. SOLANO, *Miami, FL, Tallahassee, FL*

There is a paucity of data comparing different basal-bolus insulin regimens in the inpatient setting.We performed a prospective randomized trial of patients with type 2 diabetes admitted to the medical service. We sought to determine whether treatment with once daily glargine plus pre-meal and supplemental lispro insulin would result in better inpatient glycemic control (measured by mean daily blood glucose concentration), with a lower rate of hypoglycemic events than treatment with twice daily neutral protamine Hagedorn (NPH) insulin plus pre-meal and supplemental regular insulin. Thirty-seven insulin naive subjects with a blood glucose level (BG) between 140 and 400 mg/dl were randomized to receive either glargine and lispro (n=17) or NPH and regular insulin (n=20). The initial total insulin dose was 0.4 U/kg/d for patients with BG 140-200 mg/dl or 0.5 U/kg/d for BG 201-400 mg/dl. Equivalent glycemic control was achieved in both groups from a mean daily BG of 255±57 and 230±45 mg/dl to a mean daily BG after the first day of 188±28 and 189±40mg/dl in the glargine/lispro and NPH/Regular insulin groups respectively (p=0.94). During treatment, 1 patient (5.8%) in the glargine/lispro group and 3 patients (15%) in the NPH/regular group had at least one episode of hypoglycemia (BG <60 mg/dl) during the hospital stay (P=0.37). There were no episodes of severe hypoglycemia (<40 mg/dl) in either group. The mean total daily insulin dose was comparable in both groups (48±19 in the glargine/lispro group and 47±15 units in the NPH/regular group(p=0.85).Basal/bolus insulin therapy in the inpatient setting was equally effective using insulin analogs or human insulin without a significant difference in the risk of hypoglycemia.

1166-P

PPAR-α Activation Reduces the Negative Effects of PPAR-γ Agonism on Bone Mass and Bone Strength at the Proximal Femur in the Ovariectomized Rat

SUSAN Y. SMITH, RANA SAMADFAM, LUC CHOUINARD, MALAIKA AWORI, AGNES BENARDEAU, FRIEDER BAUSS, ELENA SEBOKOVA, MATTHEW B. WRIGHT, *Senneville, QC, Canada, Basel, Switzerland, Penzberg, Germany*

Treatment of type 2 diabetes with thiazolidinedione (TZD) PPAR-γ agonists e.g. pioglitazone (Pio) is associated with bone loss and increased fracture risk, including a potential increase in hip fractures. Data regarding bone effects of PPAR-α agonists (e.g. fenofibrate [Feno]) are limited, although

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

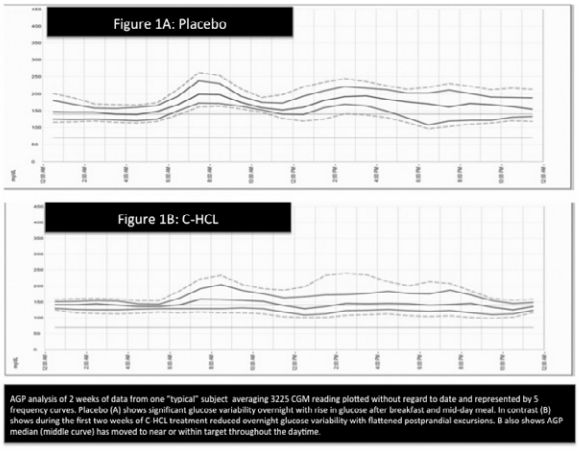
recent animal studies suggest Feno may increase bone mass. Our objectives were to investigate, at the proximal femur (a site relevant to hip fractures in the clinic), the effects of Pio, Feno, or combined Pio+Feno in the ovariectomized (OVX) rat model.Four weeks after ovariectomy rats were treated orally with vehicle, Pio (10 mg/kg/day), Feno (25 mg/kg/day) or Pio+Feno for 13 weeks. Whole-body composition analysis (bone mineral content, bone mineral density, muscle and fat mass) and bone densitometry analysis at the proximal femur were performed in vivo using dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography. A femoral shear neck test was performed ex vivo at the end of treatment.DXA analysis showed that OVX-induced loss of bone mass at the proximal femur was exacerbated by Pio. In contrast, Feno greatly reduced OVX-induced bone loss. Co-administration of Feno with Pio partially prevented Pio-induced bone loss. Consistent with these results, OVX resulted in slight decreases in peak load and stiffness (up to 14%) with an increase (9%) in work to failure (energy required to break the bone). Pio exacerbated losses in bone strength compared to OVX (up to 6%) whereas Feno completely prevented OVX-induced decreases in bone strength. Feno+Pio partially prevented Pio-induced loss of bone strength. Whole-body bone mass parameters were generally consistent with findings at the proximal femur.At the proximal femur, dual agonism of PPAR-α and -γ reduced negative bone effects associated with agonism of PPAR-γ alone. These data suggest that dual PPAR-α/γ agonism may have less risk for fractures versus TZDs.

1167-P

Diurnal Glucose Patterns Based on Continuous Glucose Monitoring of Patients With Type 2 Diabetes Treated With Colesevelam HCl

ROGER MAZZE, ELLIE STROCK, ARLENE MONK, MATTHEW MURPHY, RICHARD BERGENSTAL, MIN XI, *Minneapolis, MN*

Colesevelam HCl (C-HCl), a biologically engineered bile acid sequestrant, significantly improves HbA1c in type 2 diabetes. During this randomized, double-blind, placebo-controlled, cross-over study, continuous glucose monitoring (CGM) was employed with ambulatory glucose profile (AGP) analysis to determine how C-HCl effects diurnal glucose patterns. Twenty-one subjects treated with concomitant oral agent therapy were randomized to 12 weeks C-HCl followed by 12 weeks placebo (PLCB) (N=11) or PLCB followed by C-HCl (N=10). There was no significant difference between groups for age (60±8 years), gender (30/70,M/F), weight (233±57lbs), BP (134±16/78±7mmHg), diabetes duration (9.2±6 years), HbA1c (7.5±0.3%), HDL (43.6±10.6 mg/dL) and LDL (90.9±18.6 mg/dL). Regardless of treatment sequence, both groups when treated with C-HCL experienced a decline in HbA1c (0.42±0.4%, p<0.001). AGP analysis of CGM detected an immediate, sustained and significant decline in hourly glucose exposure (13.9±17.5 mg/dL/hr (p<0.001). As shown in Figure 1, overnight and daytime glucose exposure decreased immediately upon C-HCL treatment. Overall, C-HCL treatment lowered overnight exposure by 9.1±13.9mg/dL/hr, p<0.007 and daytime by 15.7±19.8 mg/dl/hr, p<0.001. There was no significant increase in hypoglycemia. There was a significant (p<0.007) decrease in LDL (12.5±13.9 mg/dL) with no change in HDL or triglycerides.C-HCL treatment immediately and significantly lowered both overnight and daytime glucose exposure without an increased risk of hypoglycemia.



AGP analysis of 2 weeks of data from one "typical" subject averaging 3225 CGM reading plotted without regard to date and represented by 5 frequency curves. Placebo (A) shows significant glucose variability overnight with rise in glucose after breakfast and mid-day meal. In contrast (B) shows during the first two weeks of C-HCL treatment reduced overnight glucose variability with flattened postprandial excursions. B also shows AGP median (middle curve) has moved to near or within target throughout the daytime.

1168-P

Liraglutide + Metformin in Type 2 Diabetes: Clinical Benefits Associated With Switch or Use Early in the Disease Process

STEPHEN C. BAIN, JOCHEN SEUFERT, ANNE B. THOMSEN, SABINA FURBER, DAVID D'ALESSIO, *Swansea, United Kingdom, Freiburg, Germany, Soeborg, Denmark, Cincinnati, OH*

Metformin (Met) is generally considered the most appropriate first-line pharmacotherapy for type 2 diabetes (T2DM). When Met becomes insufficient, however, there is no general consensus on how to intensify treatment. This post-hoc analysis compared clinical benefits achieved by adding liraglutide in patients previously receiving Met only (Met-add-on) vs substituting liraglutide for sulfonylurea (SU) in subjects previously receiving Met + SU (SU-switch). Data were obtained from a large clinical trial (n=988) in which patients receiving met alone or Met + SU had their therapy changed to Met + liraglutide 1.8 mg. Baseline age (mean [SD]: 58 ([9.3] vs 56 [9.8], respectively) and A1c (Table) were similar, while duration of diabetes was significantly longer in the SU-switch subjects (9.0 [6.2] vs 6.5 [5.4]; $p<0.0001$). Among subjects who completed 12 weeks of treatment, the SU-switch group lost more weight, likely due to the termination of SU treatment, and subjects in the Met-add-on group had a greater reduction in A1C. These data are consistent with greater clinical efficacy of liraglutide among patients with less advanced T2DM, with ~70% of the Met add-on group reaching a target A1C of 7%. The further reduction in mean A1C among the SU switch-subjects, with ~45% reaching the glycemic goal, suggests benefits of liraglutide vs SU. These findings support the conclusions that the glycemic response to liraglutide varies across the spectrum of diabetes progression, and that changing from SU to liraglutide can bring additional benefits to some patients.

	Met-add-on group (n=532)		Met-SU-switch group (n=285)	
	Baseline	**Change from baseline**	**Baseline**	**Change from baseline**
A1C (%)	8.0 (0.86)	-1.3 (0.04)*	7.7 (0.48)	-0.6 (0.04)
Patients reaching A1C <7.0% at 12 weeks (%)	—	69.7	—	44.6
Body weight (kg)	99.4 (21.44)	-3.7 (0.18)	98.4 (20.03)	-4.4 (0.21)**
Fasting plasma glucose (mmol/L)	9.8 (2.24)	-2.2 (0.09)	9.3 (1.84)	-0.8 (0.12)
Systolic blood pressure (mmHg)	134.2 (16.09)	-4.2 (0.79)***	135.1 (15.65)	-3.7 (0.91)

Data are for patients completing 12 weeks' treatment. Baseline data: mean (SD); change data: mean (SE) with no imputation for missing values.*$p<0.0001$ vs Met-SU-switch group; **$p=0.019$ vs Met-add-on group; ***NS vs Met-SU-switch group.

1169-P

Improving Glycemic Control With Biphasic Insulin Aspart 30 in Chinese Patients With Type 2 Diabetes Inadequately Controlled on Oral Glucose-Lowering Drugs: A Subgroup Analysis from the A_1chieve Study

WENYING YANG, YUXIU LI, LIMING CHEN, YONGQUAN SHI, YONGDE PENG, MINXIANG LEI, *Beijing, China, Tianjin, China, Shanghai, China, Changsha, China*

This subgroup analysis of A_1chieve study was to evaluate clinical safety and effectiveness of biphasic insulin aspart (BIAsp 30) in Chinese patients with type 2 diabetes (T2D) treated only with oral glucose-lowering drugs (OGLDs) previously. A_1chieve was a prospective, open-label, 24-week observational study in patients with T2D initiating insulin analogues therapy in 28 countries across Asia, Africa, Europe, and Latin America. In China, 11020 patients were enrolled, and among them 4100 patients previously treated only with OGLDs initiated BIAsp 30±OGLDs (54.2% males, mean ± SD age 56.2 ± 13.6 yr, BMI 24.7 ± 3.2 kg/m^2, duration of T2D 6.8 ± 5.4 yr, duration of OGLD 6.2 ± 5.2 yr). Glycemic control was significantly improved after 24 weeks as measured by A1C, fasting plasma glucose (FPG) and postprandial plasma glucose (PPPG) (table). The proportion of patients achieving A1C target <7.0% increased from 9.7% at baseline to 54.2% at Week 24. Percentages of patients treated with OD, BID, TID, >TID dosing were 1.1%, 82.3%, 16.6%, 0.0% at baseline and 1.9%, 83.3%, 14.4%, 0.3% at Week 24. Total daily insulin dose was 0.44 ± 0.18 U/kg at baseline and 0.47 ± 0.18 U/kg at Week 24. No serious adverse drug reactions were reported. Rates of total, major, nocturnal hypoglycemic events (events/patient/year) were 1.47, 0.10, 0.31 at baseline and 1.35, 0.00, 0.22 at Week 24. Overall, BIAsp 30 improved glycemic control with low risk of hypoglycemia in Chinese patients with T2D inadequately controlled on OGLDs in A_1chieve study.

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

Table. Change in endpoints of the study patients

	Baseline	Week 24	Change
A1C, %	9.3 (2.1)	7.0 (1.0)	-2.3 (2.0)*
FPG, mg/dL	184.2 (59.8)	121.9 (22.8)	-62.2 (60.8)*
PPPG, mg/dL	258.9 (83.3)	158.8 (32.0)	-100.2 (84.7)*
Body weight, kg	68.4 (11.3)	68.7 (10.7)	0.3 (3.0)*

Mean (SD); * p<0.001; A1C, HbA_{1c}.

1170-P

Beginning a Basal plus Mealtime Insulin Regimen Using Prandial Insulin Aspart in Insulin-Naïve Adults With Type 2 Diabetes: Results from the A_1chieve Study

JIHAD HADDAD, LEÓN E. LITWAK, RACHID MALEK, ALEXEY V. ZILOV, PRAFUL N. CHAKKARWAR, MOHAMMAD E. KHAMSEH, *Amman, Jordan, Ciudad de Buenos Aires, Argentina, Setif, Algeria, Moscow, Russian Federation, Dubai, United Arab Emirates, Tehran, Islamic Republic of Iran*

A_1chieve is an open-label, non-interventional study evaluating the safety and clinical effectiveness of starting insulin analogs in people with type 2 diabetes (T2DM) (n=66 726) in routine clinical care in 28 countries across four continents. This subgroup analysis investigated effectiveness of insulin aspart (aspart) administered at mealtime(s) as required, together with any basal insulin (insulin detemir, neutral protamine Hagedorn or insulin glargine) ± oral glucose-lowering drugs in younger (≤65 yr) and older (>65 yr) insulin-naïve adults with T2DM.Mean age of the younger and older study participants was 49.6 (SD 10.4) and 71.9 (5.5) years respectively. Baseline glycemic control was very poor, with A1C of 10.2 (2.0) in the former and 10.0 (2.5) % in the latter group (Table). A1C decreased significantly to 7.4 (1.2) and 7.3 (1.1) % (p<0.001) respectively. There were also significant improvements in fasting plasma glucose (PG) and post-breakfast PG (p<0.001) after 24 weeks (Table). As expected, overall hypoglycemia remained low but increased in both groups, significantly so in the younger group (p<0.001) (Table). Quality of life, measured by the EQ-5D 100-point visual analog scale, improved in both age groups (Table) (p<0.001). Thus, starting insulin therapy with a basal plus mealtime aspart regimen is feasible in both younger and older adults, and is associated with improved glycemic control with a low rate of hypoglycemia.

Glycemic control, body weight & quality of life after treatment with aspart plus basal insulin

	Younger participants	Older participants
n	1317	244
A1C (%)		
Baseline	10.2 (2.0)	10.0 (2.5)
Change	-2.8 (2.0)*	-2.8 (2.1)*
FPG (mg/dl)		
Baseline	216.4 (72.8)	202.9 (78.0)
Change	-90.1 (74.1)*	-80.3 (79.7)*
PPPG (mg/dl)		
Baseline	283.9 (88.8)	275.3 (92.4)
Change	-121.0 (89.3)*	-115.2 (95.5)*
Hypoglycemia (overall), event/person-year (% with event)		
Baseline	1.43 (4.9)	2.88 (8.2)
Week 24	2.89 (8.4)*	3.49 (10.6)†
Body weight (kg)		
Baseline	75.5 (17.1)	70.3 (15.1)
Change	-0.1 (4.2)†	0.5 (4.0)†
Quality of life (VAS 0-100)		
Baseline	65.7 (17.3)	65.1 (18.0)
Week 24	77.9 (11.9)*	77.6 (12.3)*
Insulin dose (U/kg/day)		
Day 1	0.60 (0.25)	0.57 (0.24)
Week 24	0.65 (0.29)	0.60 (0.27)

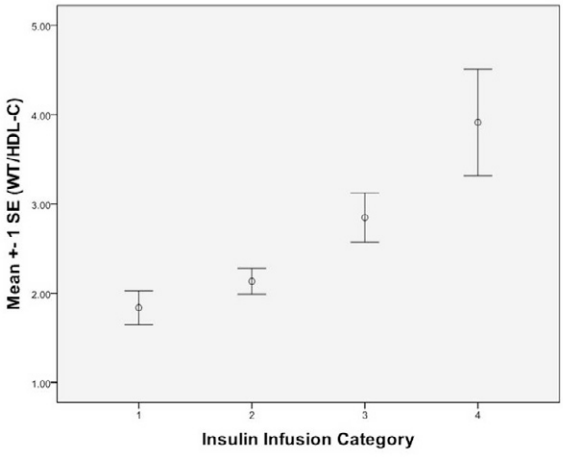
Mean (SD) or as stated; *p<0.001, †p=NS; insulin dose was not analyzed statistically; FPG, fasting plasma glucose; PPPG, postprandial plasma glucose; VAS, visual analog scale

1171-P

Insulin Requirement in Men Following CABG is More Related to Weight and HDL-C than to A1c

MRIDULA WILLIAM, ERA C. MURZAKU, TARAL J. SHAH, STEPHEN H. SCHNEIDER, LOUIS F. AMOROSA, *New Brunswick, NJ*

Hyperglycemia complicates recovery from CABG. Insulin infusion algorithms are routinely employed to improve outcomes following CABG but insulin requirements can vary widely and are difficult to predict. We examined the potential role of routine preoperative clinical variables including age, weight, A1C, and lipids in predicting insulin requirements following surgery. Insulin requirements were defined as the highest insulin infusion rate required for a minimum of two hours to maintain a post operative glucose of less than 150 mg/dL on postoperative day one. Data were obtained on 114 men who underwent CABG between January 2010 and June 2011. Patients receiving insulin or TZDs were excluded. Of patients with a A1C greater than 6.5%, 93% required insulin to maintain a glucose of less than 150 mg/dL. Of 67 men with a A1C of less than 6.5% on no antidiabetic therapy , 88% required insulin infusion. The insulin requirement was categorized into four groups: 1 (zero); 2 (1-5u/h); 3 (6-10u/h); 4 (greater than 10u/h). There was a significant relationship between insulin requirements and HDL-cholesterol and body weight (r= -0.424 and r =0. 403 respectively; P < .01 for both). Combining these readily available parameters as (weight/HDL-C) improved the ability to anticipate post operative insulin requirements (r=0.509, p<.01). These data suggest that preoperative A1C is a poor predictor of post operative insulin requirements. Combining the simple parameters of weight and HDL-cholesterol, two components of the metabolic syndrome, may provide clinically useful insight into the likely post operative insulin requirements following CABG.



1172-P

WITHDRAWN

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

1173-P

Real World Outcomes of Initiating Glargine-Based Insulin Treatment vs. Analog Premix Insulin Among Patients With Type 2 Diabetes Failing Oral Antidiabetes Drugs

ONUR BASER, MURALIKRISHNA TANGIRALA, WENHUI WEI, LIN XIE, *Ann Arbor, MI, Bridgewater, NJ*

In type 2 diabetes (T2DM) patients failing oral antidiabetic drugs (OADs), a previously published randomized clinical trial showed better glycemic control and patient reported outcomes for glargine-based basal-plus insulin treatment vs analog premix insulin.Using IMPACT®, a national managed care database, real world outcomes were compared between patients initiating insulin glargine (GLA) with or without rapid acting insulin (RAI) and those initiating analog premix insulin (PMX).Cohorts were matched at baseline by 1:2 propensity score matching, including 2502 patients (PMX: n= 834, GLA: n=1668; 47.6% women; mean age 55.8 years; A1C 9.55%; # OADs 2.1). During 1-year follow-up, 21.7% (n=363) in GLA added RAI but they were already sicker at baseline than those who stayed on GLA only (baseline Charlson comorbidity index: 0.85 vs 0.66, P=0.01; % hospitalization: 21.7 vs 10.8 %, P<0.001). GLA showed higher treatment persistence than PMX (55.9 vs 45.4%; P<0.0001), but similar adherence rates (adjusted medication possession ratio: 0.66 vs 0.66; P=0.19), lower daily units (29.0 vs 43.9 U/day; P<0.0001; RAI if added: 30 U/day), similar A1C reduction from baseline (-1.26 vs -1.23%; P=0.784), hypoglycemia-related event rates (7.7 vs 8.8%; P=0.349) and total health care costs ($18,108 vs $17,754; P=0.735), but lower diabetes drug costs ($2,041 vs $2,416; P<0.0001). At end of 1 year, 8.5% in GLA were on PMX, but among PMX patients, 10.9% were on GLA and 12.5% were on RAI.This real-world study showed that for T2DM patients failing OADs, initiating insulin with once-daily insulin glargine-based treatment, instead of analog premix, was associated with increased treatment persistence and similar clinical outcomes, but lower pharmacy cost. Most GLA patients stayed on GLA only during 1-year follow-up and those who added RAI were already sicker at baseline. These results may assist in treatment decisions to optimize T2DM management.

Supported by: sanofi-aventis

1174-P

Targeting Inflammation using SALsalate in Patients With Type 2 Diabetes: Effects on Flow Mediated Dilation (TINSAL-FMD)

ALLISON B. GOLDFINE, STEWART BUCK, KATHLEEN A. JABLONSKI, CYRUS DESOUZA, GUILLERMO UMPIERREZ, KIEREN MATHER, LAURA TIPTON, STEVEN E. SHOELSON, MARK A. CREAGER, TINSAL-FMD STUDY TEAM, *Boston, MA, Rockville, MD, Omaha, NE, Atlanta, GA, Indianapolis, IN*

Sub-acute inflammation participates in the pathogenesis of diabetes and cardiovascular disease. Previous studies found the anti-inflammatory drug, salsalate, improves glycemia in patients with T2D. To test the hypothesis that inhibition of inflammation will improve endothelial function in patients with T2D, we conducted an ancillary study to the NIH-sponsored, multicenter, randomized double-masked, placebo controlled trial evaluating safety and efficacy of targeting inflammation using salsalate to improve glycemia in patients with T2D (TINSAL-T2D). Flow mediated, endothelium dependent dilation (FMD) and endothelial independent nitroglycerin mediated dilation (NTG) of the brachial artery were assessed at baseline, and 3 and 6 months following randomization to salsalate, 3.5 g/d or placebo. The primary endpoint was change in FMD at 6 months.88 participants were enrolled, and post randomization data was available in 75. Treatment and control groups were of similar age (56 yr), BMI (33 kg/m2), gender (64% male), ethnicity, current treatment, and baseline HbA1c (7.7%). HbA1c was reduced by 0.32% (*P*=0.003), fasting glucose by 12.5 mg/dl (*P*<0.001), and WBC count by 330 cells/µL (P<0.02) in salsalate vs placebo treated patients. There was no difference in change in FMD (+0.55 vs -0.16%, P=NS, salsalate vs placebo, respectively) or NTG induced dilation (-0.16 vs +0.39%, P=NS) between groups at 6 months. There was no difference in the change in systolic or diastolic blood pressure; while total and LDL cholesterol were respectively 9 mg/dl and 12 mg/dl higher and urinary albumin was 1.6 µg/mg creatinine higher in salsalate vs placebo.Salsalate does not improve FMD in peripheral conduit arteries in T2D despite lowering HbA1c and markers of inflammation. This finding suggests either salicylate targeted inflammatory pathways do not cause endothelial dysfunction in T2D or confounding effects of salsalate mitigate favorable effects on endothelial function.

Supported by: Caraco, Lifescan, Mercodia, NIDDK

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—TREATMENT OF INSULIN RESISTANCE

Guided Audio Tour: Management of Insulin Resistance *(Posters 1175-P to 1182-P), see page 15.*

1175-P

The Effect of CPAP Therapy on Glycemic Excursions and Insulin Sensitivity in Patients With Obstructive Sleep Apnea-Hypopnea Syndrome and Type 2 Diabetes

LIXIN GUO, *Beijing, China*

To investigate the effect of continuous positive airway pressure (CPAP) therapy in patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) and type 2 diabetes mellitus (T2DM). Continuous glucose-monitoring system (CGMS) was used in 40 patients with T2DM and newly diagnosed OSAHS. The measurements were repeated after 30 days of CPAP treatment. Subsequently, insulin sensitivity and glycohemoglobin (HbA_{1c}) were measured and compared to the pre-treatment data. After CPAP therapy, the CGMS indicators showed that the 24 hour mean blood glucose (MBG) and the nighttime MBG were significantly reduced ($p < 0.05$ and $p = 0.03$, respectively). The mean ambulatory glucose excursions (MAGE) and mean of daily differences (MODD) were also significantly reduced ($p < 0.05$ and $p = 0.002$, respectively) compared to pretreatment levels. During the night, MAGE also significantly decreased ($p = 0.049$). The differences between the highest and lowest levels of blood glucose over 24 hours and during the night were significantly lower than prior to CPAP treatment ($p < 0.05$ and $p = 0.024$, respectively). The 24 hour and nighttime durations of high blood glucose (>7.8 mmol/L and >11.1 mmol/L) were decreased ($p < 0.05$ and $p < 0.05$, respectively) after the treatment. In addition, HbA_{1c} levels were also lower than before treatment ($p < 0.05$), and the homeostasis model assessment index of insulin resistance (HOMA-IR) was also significantly lower than before CPAP treatment ($p = 0.034$). CPAP therapy may have a beneficial effect on improving not only blood glucose but also upon insulin sensitivity in T2DM patients with OSAHS. This suggests that CPAP may be an effective treatment for T2DM in addition to intensive diabetes management.

1176-P

The Metabolic Liver Disease of Lipodystrophy: The Effect of Leptin Treatment

ELIKA SAFAR ZADEH, ANDREEA O. LUNGU, ELAINE K. COCHRAN, MARC G. GHANY, THEO HELLER, DAVID E. KLEINER, PHILLIP GORDEN, *Bethesda, MD*

Both inherited and acquired forms of lipodystrophy (LD) present with fat loss, hypoleptinemia, severe insulin resistance, hypertriglyceridemia, and ectopic fat accumulation. A spectrum of nonalcoholic fatty liver disease ranging from steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis seems to be the liver disease of the majority of patients with LD.In an open-labeled prospective study of a cohort of patients with different forms of inherited and acquired LD being treated with leptin, we assessed the liver disease of LD by liver biopsy prior to leptin therapy (n=50) and the effect of leptin replacement in patients who had one or more liver biopsies after institution of therapy (n=28).Forty two females and 8 males with acquired generalized lipodystrophy (26%), congenital generalized lipodystrophy (36%), acquired partial lipodystrophy (10%), and familial partial lipodystrophy (22%) were included in the baseline evaluation of their liver disease. The NASH activity was assessed based on a validated system using the extents of portal and parenchymal inflammation, steatosis, ballooning, presence of Mallory bodies, and fibrosis in the liver biopsy specimens. Fasting blood glucose, triglyceride (TG), hemoglobin A1C and liver enzymes were measured at baseline and at the time of the final liver biopsy.In leptin treated patients, 82% met the scoring criteria for NASH at baseline and only 32% after leptin replacement for mean of 26.5 months (P 0.0003). There was significant improvements in steatosis (P 0.0002), ballooning (P 0.0002) with a significant reduction in NASH activity score by 55.8% (P< 0.0001). Fibrosis was stable. Four patients had autoimmune hepatitis. We observed significant reduction in fasting TG, glucose, hemoglobin A1C, ALT, and AST.In conclusion, the fundamental liver disease of LD is NASH, although other forms of liver disease, i.e. autoimmune hepatitis can also be seen. Leptin appears to be a highly effective therapy for NASH in hypoleptinemic lipodystrophic patients.

1177-P

Effects of Short-Term Intensive Combination Therapy With Insulin and Insulin Sensitizers on Insulin Resistance in Patients With Newly Diagnosed Type 2 Diabetes

XUESI WAN, ZHIMIN HUANG, LING MA, LIEHUA LIU, MINHUA LIANG, JUAN LIU, YANBING LI, *Guangzhou, China*

The aim of this study was to compare the effects and mechanisms of short-term intensive monotherapy (continuous subcutaneous insulin infusion, CSII) with combination therapies (CSII and insulin sensitizers) on insulin resistance in patients with newly diagnosed type 2 diabetes (T2DM). Patients with newly diagnosed T2DM (n=160,103 male, aged 49.8±10.4 ys, HbA1C 11±2.1%) were randomly assigned to four groups: CSII plus rosiglitazone (RSG; 4 mg, QD); CSII with metformin (MET, 500mg, TID); CSII plus α-lipoic acid (ALA, 600 mg, QD) and CSII alone, which were terminated when normoglycaemia had been maintained for 14 days. HOMA IR and intramyocellular lipid (IMCL) were used as indices of insulin resistance.

Patients in the MET groups achieved normal glycaemic control in less time (2.6±1.3days) with less dose of insulin (0.56 ±0.17u/kg/d) than others. HOMA IR improved significantly after intensive interventions in all group. Insulin resistances represented by the IMCL in soleus muscle (SOL) and tibialis anterior muscle (TA) were decreased markedly except those in the MET group. The reduction of IMCL in SOL was more obvious in the RSG group than in the CSII group (4.45±4.15 vs. 1.72±3.26mmol/kg, p=0.022). Whereas, the decline of the IMCL in TA did not remarkably differ among the groups (p=0.24). In the multivariate analysis, the average dose of insulin was an independent predictor of the reductions of IMCL in SOL and TA(R^2=0.075, 0.255 respectively, p<0.01).

Early intensive insulin therapy in patients with newly diagnosed T2DM has favorable outcomes on insulin resistance. The combination therapy with thiazolidinediones is more effective on peripheral insulin resistance for the inimitable pharmacology and sufficient dose of insulin.

1178-P

Endoscopic Duodenal-Jejunal Bypass: Effect on Insulin Sensitivity in Mildly Obese Diabetic Subjects

RICARDO COHEN, CAREL LE ROUX, DIMITRIS PAPAMARGARITIS, JOAO SALLES, TARISSA PETRY, JOSE CORREA, MANOEL GALVAO, BRUNO MARTINS, PAULO SAKAI, CARLOS SCHIAVON, CHRISTOPHER SORLI, *São Paulo, Brazil, London, United Kingdom, Billings, MT*

The duodenal-jejunal bypass liner (DJBL, GI Dynamics, Lexington, MA) is an endoscopic implant that mimics the intestinal bypass part of the Roux en Y. This study investigated the efficacy and potential mechansims of the DJBL in mildly obese subjects. Sixteen T2DM subjects, median duration 6.5 yrs (2-10), BMI 30.5±0.9 kg/m2 were evaluated at baseline and at 1, 12 and 52 weeks post implant. Studies included meal tolerance tests following 12h fast. Glucose, insulin and C peptide were measured. Indices of insulin sensitivity (Matsuda Index), resistance (HOMA IR), secretion (acute & total insulinogenic index) and β cell function (Disposition Index DI) were calculated. At 1y, 62.5% of the subjects had HbA1c below 7% decreasing from 8.6±0.2% to 7.5±0.4% (p<0.05). BMI decreased to 28.1±0.9 kg/m2 (p<0.05) after 1y. Area under the curve (AUC) of postprandial glucose decreased after 1 week and remained lower for 1y (p<0.0001). Matsuda index increased and HOMA IR decreased at 1 week (p<0.0001, p=0.0004 respectively). Insulin and C-peptide AUC, the acute and total insulinogenic index did not change at any time. The DI increased only after week 1 (p=0.01) but returned to baseline levels. Glycemia and insulin sensitivity improved within 1 week after DJBL and remained for the 1y implant duration. β cell function improved immediately after DJBL but returned to baseline levels soon after. The DJBL may form a valuable aid to treat insulin resistance in mildly obese diabetics. In addition to its own benefits, efficacy might be enhanced with the concomitant use of GLP1 analogues, DPPIV inhibitors and/or insulin which may further improve both, insulin sensitivity and secretion deficits.

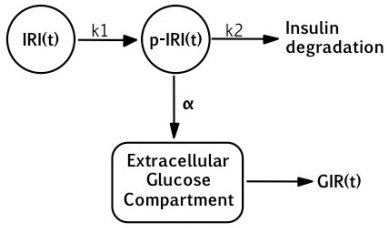
Supported by: GI Dynamics

1179-P

Evaluation of Insulin Sensitivity by Euglycemic Hyperinsulinemic Glucose Clamp Technique Using Two-Compartment Model

KENRO NISHIDA, SEIYA SHIMODA, KAZUO FUJISAWA, SARIE YAMADA, MAIKIKO FUKUNAGA, TOYOKI HIROSE, HIDEKI MARUYAMA, EIICHI ARAKI, *Minamata, Japan, Kumamoto, Japan*

To standardize the method of calculating the whole body glucose disposal (GDR) which is insulin sensitivity index by average glucose infusion rate from 90 min to 120 min during hyperinsulinemic euglycemic glucose clamp, we developed the mathematical model consisted of two compartments representing the plasma insulin pool, peripheral insulin pool which act to insulin target tissue directly as shown in figure. The glucose infusion rate during hyperinsulinemic euglycemic glucose clamp was analyzed using this two-compartment model. Furthermore, by analyzing the relationship between insulin infusion rate (mU/kg/min) and glucose infusion rate (mg/kg/min) using this mathematical model, we developed the new index α which was calculated by pattern of glucose infusion rate during 60 min after hyperinsulinemic euglycemic glucose clamp technique. Hyperinsulinemic euglycemic glucose clamp was done using bedside-type artificial endocrine pancreas STG-55 (Nikkiso Co., Ltd., Japan) in 25 type 2 diabetic patients (Age; 54.1 ± 13.9, BMI; 25.4 ± 4.2 kg/m2). The mean GDR and plasma insulin concentration at 120 min during hyperinsulinemic euglycemic glucose clamp were 5.30 ± 2.92 mg/kg/min and 95.1 ± 33.1μU/mL, respectively. We demonstrated that highly correlation between GDR and α (r=0.872). In conclusion, our results showed that newly developed index α was useful method for evaluating insulin resistance instead of GDR.



$$\frac{d}{dt}p\text{-}IRI(t) = k1 \cdot IRI(t) - k2 \cdot p\text{-}IRI(t) \quad (1)$$

$$GIR(t) = \alpha \cdot p\text{-}IRI(t) \quad (2)$$

$$GIR(t) = \alpha \cdot K1 \cdot e^{-k2 \cdot t} \cdot IRI(t) \quad (3)$$

Figure
Mathematical model for simulating glucose infusion rate during hyperinsulinemic euglycemic glucose clamp

1180-P

KDT501, A Novel Substituted 1,3-Cyclopentadione, Normalizes Glucose Metabolism in Diet-Induced Obesity Mouse and ZDF Rat Models of Diabetes

VEERA R. KONDA, GARY DARLAND, ANURADHA DESAI, NEILE GRAYSON, MATTHEW L. TRIPP, JEFFREY S. BLAND, *Seattle, WA*

Extracts from hops (*Humulus lupulus*) have been widely used as flavoring agents in brewing. Previously, it was reported that mixtures of hop extracts showed anti-inflammatory and anti-diabetic effects. We developed KDT501, a novel, stereo-chemically pure substituted 1,3-cyclopentadione chemically derived from hop extracts, and evaluated it in various *in vitro* and *in vivo* models of diabetes and insulin sensitivity. In a mouse model of diet-induced obesity, oral administration of KDT501 (100 and 200 mg/kg twice/day) for 4 weeks reduced fed blood glucose, and glucose/insulin AUC calculated following an oral glucose bolus. Mice receiving KDT501 at 200 mg/kg exhibited significantly reduced body fat. In ZDF rats, oral administration of KDT501 twice daily for 4 weeks (100, 150 and 200 mg/kg), significantly reduced fed glucose, fasting plasma glucose and glucose AUC after an oral glucose bolus. Similar to metformin (200mg/kg) and pioglitazone (30mg/kg), a significant, dose-dependent reduction of plasma hemoglobin A1c was observed in animals receiving KDT501, when compared to the vehicle control (100mg: -20%, 150mg: -54.6%, 200mg: -54.6%). KDT501 dose-dependently reduced weight gain in ZDF rats, while rats treated with metformin or pioglitazone gained weight compared to vehicle-treated controls. These results suggest that the anti-diabetic mechanism of KDT501 may differ from that of both metformin and pioglitazone and may be a novel therapeutic for the treatment of Type 2 diabetes in humans. Efforts to elucidate the mechanism(s) of cellular pathways will also be discussed. KinDex has initiated a Phase 1 clinical study to determine safety, pharmacokinetics, and preliminary efficacy of KDT501.

Supported by: KinDex Therapeutics, LLC

For author disclosure information, see page 797.

1181-P

The Effect of Early Intensive Insulin Therapy on the Body Fat Distribution and Skeletal Muscle Mass of Individuals With Newly Diagnosed Type 2 Diabetes

JANG WON SON, KWON HEE SUN, HEE KYOUNG JEONG, SEONG SU LEE, SUNGRAE KIM, SOON JIB YOO, *Bucheon, Republic of Korea*

The aim of this study was to evaluate the effects of early intensive insulin therapy on the body fat distribution and skeletal muscle mass of individuals with newly diagnosed type 2 diabetes. A total of 42 subjects with newly diagnosed diabetes participated in a 12 week course of intensive insulin therapy. The patients underwent a 75 g OGTT, measurement of their visceral and subcutaneous fat areas (VFA and SFA) using computed tomography and an assessment of appendicular skeletal muscle mass (ASM) using dual-energy X-ray absorptiometry. After intensive insulin therapy, the fasting plasma glucose, HbA1c levels and the insulin sensitivity index were decreased. Homeostasis model assessment (HOMA-B), the insulinogenic index and the C-peptide to glucose area under the curve (AUC) ratio increased. A body composition analysis revealed that the VFA and the ratio of VFA to SFA decreased, whereas body weight and total fat mass increased insignificantly. The ASM/weight and skeletal muscle mass index increased. The restoration of β-cell function, as identified by HOMA-B, the insulinogenic index and the C-peptide to glucose AUC ratio, correlated with the changes in VFA after controlling for age and gender. In multiple regression analyses, the decrease in the VFA independently contributed to improved HbA1c over the study period after adjusting for confounding factors. These results suggest that a shift in the fat distribution from visceral to subcutaneous fat after early intensive insulin therapy may be associated with improvements in glycemic control and β-cell function in individuals with newly diagnosed type 2 diabetes.

1182-P

Pioglitazone Improves Insulin Sensitivity by Modulating Novel Biomarkers in Impaired Glucose Tolerance

DEVJIT TRIPATHY, WALTER GALL, KLAUS-PETER ADAM, DAWN SCHWENKE, AMALIA GASTALDELLI, NICOLAS MUSI, PETER REAVEN, RALPH DEFRONZO, *San Antonio, TX, Durham, NC, Phoenix, AZ, Pisa, Italy*

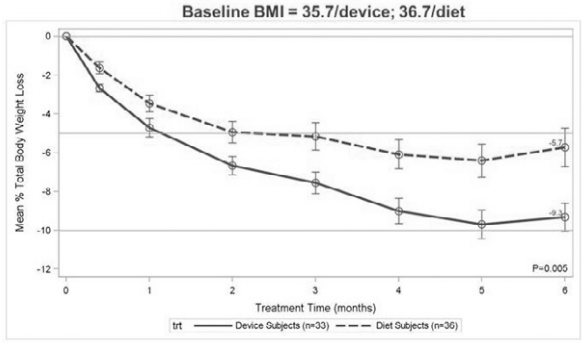
The aim of the study was to examine the effect of insulin sensitizer pioglitazone (PIO) on novel insulin resistance (IR) biomarkers that could reflect the metabolic effects of PIO. 602 IGT subjects were randomized to PIO (45 mg/day) or placebo (PLAC) and followed for 2.4 years. Indices of insulin secretion and insulin sensitivity were derived from the plasma glucose, insulin, and C peptide concentrations during the OGTT and in a subset from IVGTT at baseline and study end. Top-ranking insulin sensitivity metabolites, including plasma alpha-hydroxybutyrate (AHB), linoleoyl-glycerophosphocholine (L-GPC), oleoyl-GPC (O-GPC), glycine, serine, betaine, decanoylcarnitine, and oleate, were measured before and after treatment with PIO/PLAC. 50 PLAC-treated subjects developed type 2 diabetes versus 15 PIO-treated subjects ($p<0.005$). Improvement in Matsuda insulin sensitivity index in PIO-treated subjects was ~2-fold greater than in PLAC-treated. There was no significant difference between treatment groups in plasma metabolite concentrations at baseline. At study end PIO-treated individuals had significantly lower AHB, oleate, and higher glycine, serine, and L-GPC (all $p<0.005$). At baseline Matsuda index of insulin sensitivity correlated most significantly with AHB ($r= -0.178$, $p<0.005$), glycine ($r=0.296$, $p<0.005$), O-GPC ($r=0.267$, $p<0.005$). The improvement in Matsuda index of insulin sensitivity correlated with change in AHB, glycine, and O-GPC. At study end, subjects who reverted to NGT had lower AHB and higher glycine, and L-GPC compared to those who remained IGT or converted to T2DM. Consistent with such analytes tracking with changes in insulin sensitivity and glucose tolerance, AHB also correlated with an index of beta cell function (insulin secretion/IR disposition index, $r= 0.224$, $p<0.005$). PIO modulates novel oxidative stress biomarkers related to amino acid and lipid metabolism which may in part explain the beneficial effects of PIO on insulin sensitivity.

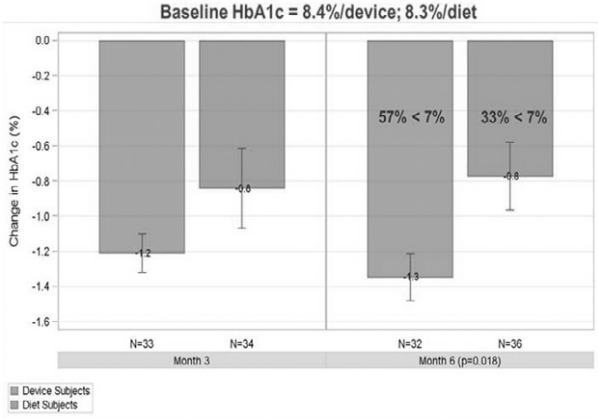
1183-P

Six Month Results of a Multi-Center, Prospective, Randomized Trial of the Endoscopic Duodenal-Jejunal Bypass Liner for the Treatment of Type 2 Diabetes in Obese Subjects

PARWEEZ KOEHESTANIE, BERRY MEESTERS, IGNACE JANSSEN, NICOLE BOUVY, JAN WILLEM GREVE, *Arnhem, The Netherlands, Heerlen, The Netherlands, Maastricht, The Netherlands*

The worldwide increase in obesity results in an exponential increase in type 2 diabetes (T2DM). Surgical treatment has proven to be very effective however with the risk of serious complications. The duodenal-jejunal bypass liner (DJBL, GI Dynamics) is an endoscopic implant that mimics the intestinal bypass portion of the Roux-en-Y. It results in weight loss and improvements in glucose control in obese subjects with T2DM. This is the first report of a large scale 1 year controlled study.In a prospective, randomized, diet controlled, crossover multicentre study, 77 subjects were included, 38 device and 39 diet controls, treatment 6 months with 6 month follow-up. In the device group 34 subjects were implanted (3 failures, 1 withdrawal). The groups were comparable with respect to age, gender, BMI (mean 35.7 vs. 37.3), duration of T2DM (5.2 vs. 5.3 years), HbA1c (8.4 vs 8.3) and T2DM treatment. Study parameters included standardized meal tolerance test and HOMA-IR. There were no serious adverse events. 1 early DJBL removal was required due to obstruction; in the control group 2 subjects withdrew consent.At 6 months there was significantly better weight loss (figure 1) and significantly improved HbA1c (figure 2) in the device group. HOMA-IR was also significantly lower in the device group (8.4 vs 10.3). Medical treatment was reduced in more device subjects than controls. There was a crossover of the control subjects to the device group after 1 year. In conclusion the DJBL is a safe and effective device in the treatment of T2DM in obese subjects.





1184-P

Prediction of Plasma Insulin via Exhaled Breath Analysis in Obesity and Type 2 Diabetes

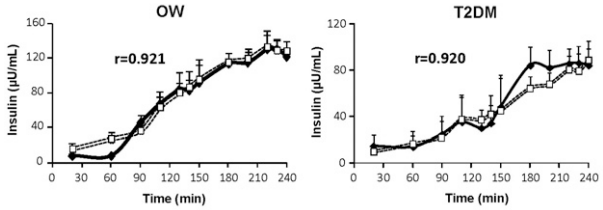
STACY R. OLIVER, MATTHEW K. CARLSON, ROBERT NEWCOMB, SIMONE MEINARDI, REBECCA L. FLORES, DONALD R. BLAKE, PIETRO R. GALASSETTI, *Irvine, CA*

Breath analysis is increasingly considered an alternative methodology to test metabolic variables in obesity (OW), type 1 and type 2 diabetes (T1DM, T2DM). We previously estimated via breath analysis plasma glucose, insulin and lipids in healthy and T1DM adults. Estimating insulin non-invasively may be especially relevant in OW and T2DM, in which insulin resistance is a key feature. As in the past, predictions were stronger when based on condition-specific gas patterns; we hypothesized that accurate breath-based insulin predictions can be obtained with gas clusters specific for each patient group. We therefore studied 10 T2DM (5M, 44±3yrs) and 5 OW subjects (5F, 41±5yrs); in which 12 plasma, room and breath samples were collected over 4 h in basal, hyperglycemic (220 mg/dL) and euglycemic-hyperinsulinemic conditions; ~100 volatile organic compounds (VOCs) were quantified by gas chromatography and matched with plasma ELISA insulin values. Gas-based predictions of plasma insulin were then generated by least squares regression on several VOC clusters. In OW, acetone, BuONO2, i-PrONO2, and in T2DM, m\p xylene, ethylbenzene, n-pentane, 3-methylhexane, CH3Cl, yielded the strongest cor-

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

relations with plasma insulin (0.921 and 0.920). Additional gas combinations were identified allowing broad applicability across both groups.Our data indicate that exhaled VOCs analysis can provide accurate estimates of plasma insulin during glucose and insulin fluctuations in OW and T2DM subjects, and demonstrate the growing potential of breath analysis for non-invasive diagnosis/monitoring of metabolic variables relevant to diabetes.



Plasma insulin measurements (—◆—) and estimates from exhaled gases (—□—) for 5 OW and 10 T2DM subjects at baseline (t = 0-60 min), hyperglycemia (t = 60-150 min), and euglycemic hyperinsulinemia (t = 150-240 min). Data are mean±SEM.

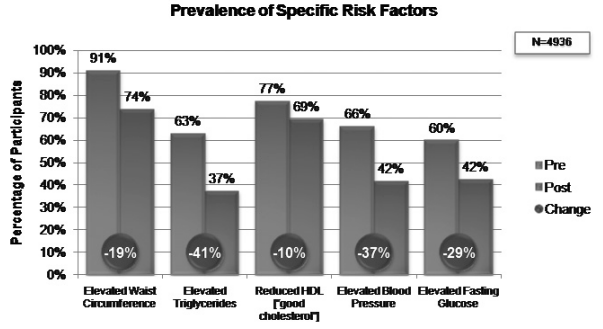
Supported by: NIH (1UL1RR031985, K24 DK085223)

1185-P

Innovative 10 Week Distance Learning Pre-Diabetes Intervention Program: Results on over 4000 Participants

SCOTT E. CONARD, MARCIA UPSON, *Dallas, TX*

Pre-diabetes (MS) suggests an increased risk of developing diabetes.A 10 week web based internet-based curriculum on 4936 individuals for up to 2 years. Based on 35 years of research on food related attitudes and habits of thin individuals, content teaches about naturally slim individuals.Sixty one percent had at least one risk factor for MS resolve after ten weeks, 44% no longer met MS criteria at the conclusion of the program (see graph).Weight loss occurred in 88% of the participants (11.1 pounds average) with 10% of participants losing >25 pounds during the program.Follow-up data up to three years has been followed in a subset who had 43.2% of the individuals go from three or more to less than three risk factors after the initial program. Forty five percent at 12 months, and 55.5% at two years maintained the resolution of MS criteria.ConclusionA 10 week non-local internet based lifestyle program resulted in significant resolution of the criteria for MS in 4936 individuals that was shown to be maintained for over two years. This non-macro-nutrient based curriculum based on over 35 years of research lead to a significant change in the attitude and habits resulting in resolution of MS criteria. Implications for those with pre-diabetes/MS in preventing the further progression toward diabetes is significant. With the proven efficacy and non-local format this program can be made available to those not easily able to access the health care system. Given the cost of prediabetes/MS the potential savings to the healthcare system and individual too are worthy of consideration.



1186-P

The Relationship between Intensive Glucose Control and Prognosis of Patients With Severe Acute Pancreatitis

YAN-YAN ZUO, YAN KANG, BO WANG, WAN-HONG YIN, *Chengdu, China*

To investigate the effects of Intensive Glucose Control (IGC) on Glucose Variability (GV), the clinical outcomes of patients with Severe Acute Pancreatitis (SAP,) and to assess the predictive role of different measurements of GV on Intensive Care Unit (ICU) mortality.This is a prospective, randomized, non-blinded clinical trial, consisting of adult patients with a diagnosis of SAP, and who were admitted into the ICU between July 1, 2010 and July 1, 2011. Eligible patients were randomly assigned to receive either IGC, to maintain glucose at 6.1 - 8.3 mmol/L, or to a control group(no intervention). In the two groups, GV, ICU mortality, the occurrence of infection, duration of mechanical ventilation (DMV), and the ICU stay were compared. The standard deviation of glucose level (SD), the Mean Amplitude of the Glycemic Excursion (MAGE), and the Glycemic Lability Index (GLI), were selected to measure the GV. The above parameters to predict ICU mortality was assessed with the area under a receiver operating characteristic curve (AUC).30 patients with SAP patients were enrolled (IGC 15; Control 15). It was showed that IGC had a reduced trend of GV [SD (mmol/L): 1.81 (0.97, 2.65) vs 2.48 (1.29, 2.87); MAGE (mmol/L): 3.76 (3.67, 5.85) vs 5.30 (4.35, 6.80); GLI [(mmol/L)2·h-1·d-1]: 306.8 (220.6, 613.3) vs 339.5 (218.4, 423.1)], a decrease in ICU mortality (13.3% vs 40.0%), and a shorter DMV [days: 18(14,23) vs 22(15,26)], but of no significant difference (P>0.05). It also shorten ICU stay (days: 11.3±9.9 vs 15.8±7.6, p=0.007), decrease the incidence of infection (6.7% vs 40.0%; 33.3% vs 73.3%, P<0.05). AUC for GLUSD, MAGE, and GLUGLI was 0.594 (95% CI 0.382, 0.805), 0.543 (95% CI 0.287, 0.798) and 0.751 (95% CI 0.548, 0.954) respectively.IGC had a reduced trend of GV, a decrease of ICU mortality, and a shorter DMV, but of no significant difference. It shorted ICU stay and decreased the occurrence of infection. Compared with SD and MAGE, GLI was the best predictor to ICU mortality.

Supported by: America-Asia Diabetes Research Foundation

1187-P

Differences in Response to Subcutaneous Insulin Therapy in General Medical and Surgical Patients With Type 2 Diabetes

DAWN SMILEY, KATHIE HERMAYER, DARIN E. OLSON, AMNA N. KHAN, LIMIN PENG, CHRISTOPHER A. NEWTON, VIVIAN FONSECA, SOL JACOBS, INGRID PINZON, MARIA E. FEREIRA, VICKIE HUNT, ASHWINI GORE, DAVID REYES, MONICA RIZZO, GUILLERMO UMPIERREZ, *Atlanta, GA, Charleston, SC, New Orleans, LA*

We compared differences in glucose control and response to insulin therapy in medicine and surgical patients with T2DM. A total of 375 patients were randomized to 3 regimens: basal bolus (n= 150) started at 0.5 U/kg/day, half as glargine and half as glulisine before meals; basal plus (n=148) started at 0.25 U/kg dose of glargine plus correction doses of glulisine before meals; or sliding scale regular insulin (SSI, n=77) given 4 times/day for BG>140 mg/dl. Medicine patients had higher admission BG, HbA1c, daily BG during treatment, and more treatment failure (>2 consecutive BG readings >240 mg/dl or mean daily BG>240 mg/dl) than surgery patients (Table). There were no differences in hypoglycemia (both 12%, p=0.92) or in the composite of complications including wound infections, pneumonia, respiratory or renal failure and bacteremia (14% vs 11%, p=0.42). For the entire cohort, the mean daily BG was lower in the basal bolus (156±36 mg/dl) and basal plus (163±37 mg/dl) than SSI (172±41 mg/dl, p=0.046). SSI treatment resulted in more treatment failures than basal plus (19% vs 2%, p<0.001), with more failures in medical (7 %) than in surgical (2 %) patients, p=0.026.In summary, patients in the basal bolus and basal plus groups had better glucose control and lower treatment failures than those treated with SSI. Medicine patients with T2DM have higher admission BG and worse inpatient glycemic control than surgery patients. Differences in response insulin treatment may help determine treatment algorithms for the management of medicine and surgery patients with T2DM.

Differences in Glycemia and Response to Insulin Therapy (data are mean ±SD)

	Medicine	Surgery	p-value
Number of patients	198	155	
HbA1c, %	9.0±2.5	7.6±2.0	<0.001
Admission BG, mg/dl	218±88	185±74	<0.001
Mean BG after day 1, mg/dl	166±39	157±36	0.01
Total insulin after day 1, U/day	26.5±18	24.3 ±14	0.61
Length of stay, days	5.3±5	7.0±6	0.003
Treatment failure, n (%)	14 (7)	3 (2)	0.03

Supported by: sanofi-aventis

1188-P

Fasting C-Peptide * Fasting Plasma Glucose is Effective Index of Insulin Resistance in Mildly Obese Japanese Patients With Type 2 Diabetes

TSUYOSHI OHKURA, SHIN-ICHI TANIGUCHI, HIDEKI SHIOCHI, YOUHEI FUJIOKA, KEISUKE SUMI, NAOYA YAMAMOTO, KAZUHIKO MATSUZAWA, SHOICHIRO IZAWA, HIROSHI KINOSHITA, MASAHIKO KATO, KAZUHIRO YAMAMOTO, *Yonago, Japan*

We investigated simple and new insulin resistance index obtained from glucose clamp method and meal tolerance test (MTT) in Japanese type 2 diabetes mellitus patients.Ten type 2 DM patients (average: age 54, male 5/ female 5, fasting plasma glucose 8.0 mmol/L, HbA1c 7.2%, BMI 26.3) were

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

examined and subjected to a MTT and hyperinsulinemic euglycemic glucose clamp. We measured plasma glucose and insulin (0, 30, 60, 120,180 minutes) after a test meal (450kcal), and serum C-peptide immunoreactivity (CPR: 0,120 minutes). We calculated HOMA-R and Insulin Sensitivity Indices (ISI; Matsuda's Index) from the result of MTT. Two days after MTT, we performed hyperinsulinemic euglycemic glucose clamp method and measured glucose infusion rate (GIR).The mean GIR of all patients was 6.0 mg/kg/min. Fasting C-peptide * fasting plasma glucose (F-CPR*FPG) was significantly correlated with GIR (R=0.79, P<0.0001). HOMA-R was also correlated with GIR (R=0.72, P<0.0001), but ISI was not significantly correlated with GIR (R=0.72, P=0.22). In 5 mild insulin resistance patients with GIR 5~8 mg/kg/min, F-CRP*FPG was significantly correlated with GIR (R=0.72, P<0.05), but HOMA-R and ISI were not correlated with GIR (R=0.30, P=0.19; R=0.41, P=0.85, respectively). In conclusion, F-CRP*FPG is simple and effective index of insulin resistance better than HOMA-R and ISI. Especially, F-CPR*FPG is more effective index in patients with mild insulin resistance than HOMA-R. Because the Japanese are not so obese population, we consider our index is effective for Japanese and other Asian population.

Relationship between glucose infusion rate (GIR) and various indexes for insulin resistance

	All patients (n=10)			GIR 5~8 mg/kg/min (n=5)		
Index	F-CPR*FPG	HOMA-R	ISI	F-CPR*FPG	HOMA-R	ISI
R value	0.79	0.72	0.72	0.72	0.30	0.41
P value	<0.0001	<0.0001	0.22	<0.05	0.19	0.85

HEALTH CARE DELIVERY—ECONOMICS

Guided Audio Tour: Innovations in the Delivery of Diabetes Care *(Posters 1189-P to 1196-P), see page 15.*

1189-P

Race/Ethnic Differences in the Diagnosis and Management of Diabetes by Primary Care Physicians: Results of an Experiment

JOHN B. MCKINLAY, REBECCA J. PICCOLO, LISA D. MARCEAU, *Watertown, MA*

One third of diabetes mellitus in the U.S. remains undiagnosed and there are worrisome social disparities when it is eventually diagnosed and managed. Studies of the contribution of healthcare providers to the creation and amplification of healthcare disparities have been encouraged by the IOM and the NIH.The study objectives are: (1) To estimate the effect of patients' race and ethnicity on the initial diagnosis of diabetes; (2) To estimate the contributions of patient, provider and organizational influences to variations in the management of already diagnosed diabetes.An experiment was conducted with 192 primary care physicians. Each viewed two clinically authentic video-based scenarios: the first "patient" had symptoms strongly suggestive of diabetes; the second, with already diagnosed diabetes, had an emerging peripheral neuropathy. Efforts were made to protect external validity. For the first scenario, 60.9 percent of physicians correctly diagnosed diabetes-48 percent when the "patient" was White, 61 percent when Hispanic and 73 percent when Black. Of physicians initially diagnosing diabetes, 23.9 percent would not order confirmatory tests. Competing diagnoses were offered by many physicians even though these conditions were not embedded in the scenario. Physician characteristics and organizational factors had little influence. For the second scenario (diagnosed diabetes with peripheral neuropathy), only 42.2 percent of physicians would do all essential components of a foot exam, 21.9 percent would do none. Males and older "patients", and those of higher SES were more likely to get each component of the foot examination. Female physicians were more likely to do foot examinations.The initial diagnosis of diabetes is significantly influenced by a patient's race/ethnicity, and its subsequent management is influenced by the patient's socioeconomic status, physician gender, and access to clinical guidelines.

Supported by: NIDDK (R01DK066425)

1190-P

A Medical Home Initiative Targeting Diabetes Care: A Positive Deviance Approach to Understanding What Works

ROBERT A. GABBAY, *Hershey, PA*

Despite the plethora of quality improvement efforts aimed at diabetes, it is clear that practice responses to these interventions are diverse. Understanding this heterogeneous response can help better identify target practices, adjust approaches to better suit these practices, and design remedial approaches for lagging practices. Positive deviance examines what enables some practices to improve more than others. This study identifies practices exhibiting the greatest and least improvement in diabetes care in a Patient Centered Medical Home (PCMH) demonstration involving 25 primary care practices as part of a statewide multi-payer statewide initiative in PA.Practices were ranked according to degree of improvement on key diabetes measures: (A1C<7, BP<130/80, LDL<100) from baseline to 18 months, and those in the top and bottom improvement quintiles were selected for mixed method analyses, using surveys, site interviews, and focus groups.On the aggregate, practices had a statistically significant improvement in key diabetes outcomes with heterogeneity in performance improvement with absolute percentage changes as follows: A1C<7 (+15 to -18%), BP<130/80 (+35 to -11 %), LDL<100 (+20 to -15%). Practices that had the greatest improvement made specific changes sooner than others. These included implementing team based care, delegating work to medical assistants, regularly reviewing performance data to drive change, adopting evidence-based guidelines, and holding regular clinical improvement meetings. Barriers commonly reported by practices that exhibited lower degrees of improvement included high staff turnover, ineffective leadership, and lack of a shared vision.Lessons from primary care practices that have displayed the greatest benefits from participation in a PCMH pilot may help guide current and future efforts to improve the quality of diabetes care.

Supported by: R18HS019150 Grant from the Agency for Healthcare Research

1191-P

Simulated Diabetes Training Helps Providers Bring Patients to Goals—A Cluster Randomized Trial

JOANN SPERL-HILLEN, PATRICK O'CONNOR, WILLIAM RUSH, STEPHEN ASCHE, DEEPA APPANA, ANDREW RUDGE, JERRY AMUNDSON, PAUL JOHNSON, HEIDI EKSTROM, OMAR FERNANDES, *Minneapolis, MN*

The purpose of this study was to evaluate a simulated training program on resident physician ability to manage patients with diabetes mellitus (DM). 341 consented primary care residents from 19 residency programs were trained to use a web-based simulated diabetes management interface. They were then randomized by program to receive (n=177) or not receive (n=164) an intervention using 18 simulated learning cases with DM of varying severity and complexity (average time 15 minutes per case). Providers treated patients through an interactive electronic health record interface and were challenged to use any desired number of encounters to bring patients to care goals for A1c, blood pressure (BP), and LDL within 6 months of simulated time. Physiologic modeling simulated outcomes of provider actions over any follow-up time interval. Between encounters, providers received feedback to critique and guide actions. After the intervention period, control and intervention subjects were assigned 4 simulated assessment cases involving type 1 and 2 DM. Generalized linear mixed models were used to test for study arm differences in the proportion of residents bringing each simulated case to composite goal for A1c, BP, and LDL. 232 residents completed at least one assessment case (intervention (I) n=97, control (C) n=135). Residents were 52% female, 53% white, mean age 30, 44% family medicine, 53% internal medicine, and in post graduate years 1 (34%), 2 (35%), 3 (28.5%), and 4 (3%). The proportion of residents bringing patients to composite goal was significantly higher in the intervention group for all cases: case 1 - I 74.5%, C 21.3%, p < .001; case 2 - I 95.8%, C 61.1%, p < .001; Case 3 - I 82.6%, C 33.9%, P < .001; case 4 - I 96.7%, C 83.4%, p = .015. These results, in addition to previous studies showing improved outcomes of actual patients of primary care providers who completed similar learning programs, provide strong evidence to support integration of simulated diabetes training into medical residency curriculums.

Supported by: NIDDK 1R18DK079861

1192-P

Insulin Degludec Reduces Hypoglycemia and Improves Health Status vs. Insulin Glargine in Insulin-Naïve Type 2 Diabetes

HELENA W. RODBARD, YEHUDA HANDELSMAN, BERTRAND CARIOU, THUE JOHANSEN, TORSTEN E. CHRISTENSEN, CHANTAL MATHIEU, *Rockville, MD, Tarzana, CA, Nantes, France, Bagsvaerd, Denmark, Søborg, Denmark, Leuven, Belgium*

Insulin degludec (IDeg) has an ultra-long and flat action profile exceeding 24 hours recently demonstrated to be associated with reduced risk of hypoglycemia. Health status - an important measure of treatment efficacy and satisfaction - was evaluated in insulin-naïve patients with type 2 diabetes receiving once-daily IDeg (n=773) or insulin glargine (IGlar; n=257) in combination with oral antidiabetic drugs in a 52-week, open-label, random-

ized trial. Health status was assessed at baseline and 52 weeks using the validated Short Form 36 (SF-36 v.2) questionnaire. Scores were analyzed using ANOVA, with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and relevant baseline values as covariates. The intent-to-treat population was analyzed. The long study duration was considered sufficient to ensure that any possible initial patient reporting bias was minimal. At baseline, mean age was 59.1 yr, BMI 31.1 kg/m^2 HbA_{1c} 8.2% (66 mmol/mol) and fasting plasma glucose (FPG) 172.8 mg/dL. At 52 weeks, FPG was significantly lower with IDeg vs IGlar (-7.75 mg/dL [95% CI: -13.33; -2.34]) while HbA_{1c} was statistically comparable (IDeg non-inferior to IGlar). Confirmed nocturnal hypoglycemia (midnight to 6 AM) was significantly lower (relative rate [RR] 0.64 [95% CI: 0.42; 0.98]) and overall confirmed hypoglycemia (plasma glucose <56 mg/dL or requiring assistance) was 18% less frequent (RR 0.82 [95% CI: 0.64; 1.04]) for IDeg vs IGlar. At 52 weeks, overall physical health status was 1.03 [95% CI: 0.08; 1.97] (p<0.05) points higher with IDeg vs IGlar, primarily due to improvement in the physical functioning sub-domain: 1.35 [95% CI: 0.26; 2.44] (p<0.05) points. Other SF-36 sub-domains showed no significant differences between IDeg and IGlar.Thus, improvement in overall SF-36 physical health and functioning is observed after 52 weeks of IDeg treatment, with a reduced risk of hypoglycemic events and improved FPG levels for IDeg vs IGlar.

1193-P

Improving Diabetes Outcomes Through Web-Based Registry and Interactive Education

ROBERT W. MORROW, JASON FLETCHER, KIM F. KELLY, LAURA A. SHEA, MAUREEN M. SPENCE, JANET N. SULLIVAN, JOAN R. CERNIGLIA, YOONJUNG YANG, *Bronx, NY, Albany, NY, Tarrytown, NY, Garrison, NY*

Through an annual consensus process the New York Diabetes Coalition (NYDC) brings together health care professionals and other stakeholders to adopt, endorse, and distribute a guideline for the management of adult diabetes. To support guideline adoption by primary care practices, the NYDC promoted use of an electronic diabetes registry and developed an interactive educational module on using the registry and improving patient communication. The NYDC hypothesized that use of a prompting registry would achieve clinically meaningful improvement in the proportion of patients at goal for diabetes health metrics. The NYDC project included seven small to mid-sized primary care practices. To be included in the diabetes cohort, a patient had to have had two or more visits with a diagnosis of diabetes spanning a 12 month period. For each patient, health measure status (at goal, above goal, not recorded) was assessed for A1C, LDL, and blood pressure, and average A1C values for each quarter were calculated. A cohort analysis was performed using random effects regression models to assess the impact of the registry over time for each diabetes health metric. Interactive education was provided to the practice teams. After controlling for variability between sites, a significant improvement in the proportion of patients at goal for A1C, LDL and blood pressure was observed. However, improvement in average A1C did not reach statistical significance.Utilizing a Web-based registry and interactive education, the project demonstrated the feasibility of collecting aggregate data from unrelated, independent practices and improved patient outcomes.

Odds Ratios For time effects from compliance regression models

	OR	95%CI (OR)	95% CI (OR)	P
HbA1c <=9	1.43	1.05	1.31	<0.001
LDL<100	1.83	1.63	2.07	<0.001
BP <130/80	0.93	0.89	0.98	0.003
BP <140/90	1.31	1.25	1.37	<0.001

Supported by: NYSDOH, Merck, Inc., Hudson Health Plan

1194-P

Effectiveness of Adding a Pharmacist to the Primary Care Team Compared to Usual Care: Clinical Markers and Long-Term Cardiovascular Risk

ERIC J. IP, BIJAL M. SHAH, JUNHUA YU, JAMES CHAN, LYNDA T. NGUYEN, DEEMPAL C. BHATT, *Vallejo, CA, Mountain View, CA, Oakland, CA*

To determine the effects of adding a clinical pharmacist to the primary care team (enhanced care group) compared to usual care with a primary care physician (control group) on 1) clinical markers [hemoglobin A1C (A1C), LDL cholesterol (LDL-C), and blood pressure (BP)], 2) attainment of the American Diabetes Association A1C, LDL-C, and BP goals, and 3) long-term cardiovascular outcomes [United Kingdom Prospective Diabetes Study (UKPDS) 10-year risk of coronary heart disease (CHD), fatal CHD, stroke, and fatal stroke] in adult type 2 diabetes (T2DM) patients over 12 months. Patients with T2DM ≥ 18 years who had been under pharmacist care at Kaiser Permanente (KP) were in the enhanced care group. T2DM patients who met study criteria and never received additional care from a pharmacist at KP were included in the control group. Electronic patient charts from the period of June 2007 to February 2010 were reviewed. Patient characteristics (age, gender, A1C, and Charlson co-morbidity score) were matched at baseline. The sample consisted of 147 patients in each group. After 12 months, the mean A1C decreased from 9.5 to 6.9% in the enhanced care group compared to 9.3 to 8.4% in the control group (p<0.001). The enhanced care group was more likely to obtain A1C levels <7% (62.6% vs. 28.6%, p<0.001), LDL-C <100 mg/dL (85.0% vs. 57.5%, p<0.001), BP <130/80 mmHg (61.9 vs. 43.5%, p<0.002), and all three goals simultaneously (36.7% vs. 9.5%, p<0.001) than the control group. The 10-year CHD risk decreased from 16.4 to 9.3% in the enhanced care group compared to 17.4 to 14.8% in the control group (p<0.001), and fatal CHD risk decreased from 11.3 to 5.7% in the enhanced care group compared to 11.9 to 10.3% in the control group (p<0.001). Adding a pharmacist to the primary care team is effective in improving short-term clinical markers as well as decreasing long-term cardiovascular risk in T2DM patients.

Supported by: AACP

1195-P

Ten-Year Trends in Controlling the ABCs of Diabetes and the Incidence of Coronary Heart Disease in a Community Based Endocrinology Practice

SWARNA VARMA, LAURA L. BOYLES, GRETCHEN A. PIATT, *Bridgeville, PA, Ann Arbor, MI*

Evidence demonstrates that prevention of diabetes complications, including coronary heart disease (CHD), is achievable through glucose (A1c), blood pressure (BP), and cholesterol (LDL) control (ABCs). Despite the 2-3 fold increased risk of CHD in people with diabetes, national data demonstrate that only a small fraction of adults in the US meet the established guidelines for the ABCs. We therefore aimed to determine whether ABC control was associated with incident CHD in a community-based endocrinology practice (CBEP) over 10 years. 395 consecutive patients seen in consultation for diabetes management in a CBEP comprised the analysis cohort. To be included, a patient had ≥ 2 A1C, BP, and LDL measurements respectively without prevalent CHD. All patients were 18 years or older with a diagnosis of diabetes before or during calendar year 2000 (100% identified using ICD-9 codes, problem lists, medication, or labs). Average age was 61.9 years, 92.8% were Non-Hispanic white, and 60% were female. At baseline, 60.1% had A1c < 7%, 44.9% had BP < 130/80 mmHg, and 73.3% had LDL < 100 mg/dL. 22.1% had all ABCs in control. 17.6% of patients developed incident CHD over 10 years. After controlling for age, gender, and time, patients who improved their A1c to < 7% during the time they were treated in the CBEP had a 27% reduction in incident CHD (HR=0.73, p=0.06). Similar trends were observed for LDL (31% reduction, HR=0.69, p=0.03) and BP (32% reduction, HR=0.68, p=0.02) control. Additionally, a 30% reduction in incident CHD occurred in patients who improved all ABCs to goal levels during the time they were seen in the practice (HR=0.7, p=0.05). These results highlight the feasibility of achieving ABC goals above the national average and demonstrate the significant impact that ABC control has on incident CHD in a CBEP. Models of care that focus on secondary prevention of complications may lead to decreased morbidity and mortality.

1196-P

Point-of-Care Hemoglobin A1c Testing in a Community Diabetes Prevention Program

MARIE E. MCDONNELL, KATIE JAHREIS, WAHEED KHAN, ASHLEY C. BOURLAND, DIANA CULLUM-DUGAN, PATRICIA HANRAHAN, CAROLINE M. APOVIAN, *Boston, MA*

We evaluated the feasibility of employing point-of-care hemoglobin A1c (A1c) testing performed by non-clinical/non-technical personnel within a community health program designed to prevent or improve Type 2 Diabetes (T2DM). The Exercise and Nutrition to Decrease Diabetes program or END Diabetes, is a community program intended to improve cardiovascular health by reducing the risks of diabetes and obesity in people diagnosed with T2DM or pre-diabetes. Four Boston-area neighborhoods known to have higher rates of diabetes (6-9% of population) and the highest rates of hospitalization due to heart disease were selected for enrollment. Enrolled community members participated in an intensive 12-week nutrition and exercise

For author disclosure information, see page 797.

program at their local YMCA followed by a 6-month free YMCA membership. Point-of-care A1c testing was performed by a non-clinical community project coordinator at baseline and 12 weeks. A total of 116 out of the 135 participants from the 5 YMCA sites had testing at baseline and 45 out of the 116 at 12 weeks. Following the program's lifestyle intervention, the average % A1c was reduced from 7.03% ± 1.55 (n=114) to 6.63% ± 1.48 (n=45), an absolute reduction of 0.39% (P<0.05). Sixty percent of participants had a reduction in A1c and 26.09% had an A1c level change from diabetes range (≥6.5%) to non-diabetes range (<6.5%), (P<0.05). The A1c testing was an important motivating factor for participants who completed the program as well as the prime indicator used for program success. The test represented 2.11% of the total budget for the program. Body mass index (BMI) also decreased in 25 of 30 participants with 12-week data; overall the average BMI decreased significantly by 0.95 kg/m^2 (P<0.05), which is roughly equivalent to 6 lbs per participant. In conclusion, point-of-care A1c testing could be feasibly and cost-effectively added to the standard metrics (e.g. scale to measure weight) that individuals can access at fitness centers and other community programs that strive to prevent or improve diabetes.

Supported by: AstraZeneca

Guided Audio Tour: Measuring the Costs of Diabetes for Patients and the Health System *(Posters 1197-P to 1204-P), see page 13.*

1197-P

Changes in Health Care Related Out-of-Pocket Financial Burden in Working Age Persons With Diabetes, 2001–02 and 2007–08

RUI LI, *Atlanta, GA*

High out-of-pocket payments (OOP) can have a direct negative effect on patient utilization of necessary services, appropriate drug use, and health outcomes. The impact of the past decade's changing economic conditions and health care coverage on OPP for diabetes patients has not been evaluated. We examined the OOP for working age (18-64 years) persons with diabetes by insurance status, income level, and health status (2001-02 and 2007-08). A nationally representative Medical Expenditure Panel Survey was used to calculate percentage of persons with diabetes residing in families with high OOP financial burden, defined as all family OOP spending on health insurance premium and on health services exceeding 10% of family income. All OOP spending were converted to 2008 dollars. In 2007-08, 26% of adults with diabetes at working age were living in families with high OOP financial burden, a 7.1% decrease from 28% in 2001-02 (P=0.23). Between 2001 and 2008, the proportion of adults with a high OOP financial burden increased 24% among those with private insurance (from 21% to 26%, P=0.02). We found no evidence that OOP burden changed among those with high family income (defined as 4 times the poverty level) (8% in 2001, 10% in 2008, P=0.80). However, the proportion with a high OOP financial burden decreased 39% among those receiving public insurance (from 44% to 26%, P<=0.001), decreased 29% among those below the poverty level (from 59% to 42%, P<=0.001), and decreased 13% among those with poor health status (from 38% to 33%, P<=0.04). Income and health status related disparities in OOP burden for adults with diabetes have decreased during the past decade.

1198-P

A Discrete Choice Experiment to Evaluate Diabetes Patients Preferences and Willingness-to-Pay for A New Basal Insulin

MIN YANG, PEGGY LIN, NEIL WINTFELD, CHRISTIAN FROIS, *Boston, MA, Princeton, NJ*

Despite the gains made with the introduction of basal insulin, many diabetes patients achieve inadequate control on these therapies. This study evaluated willingness to pay (WTP) for key attributes of a new hypothetical basal insulin among patients with type 2 diabetes mellitus (T2DM) including: hypoglycemia events risk, diabetes control, injection frequency and timing flexibility, blood glucose monitoring frequency, copayment and health insurance contribution.A discrete choice experiment survey was designed to assess these patient preferences. The survey was administered online to a US-representative sample of 600 adult patients with T2DM. Random effects probit models were used to analyze the data. WTPs were expressed either in terms of monthly copayment or increased health insurance contribution. On a copayment basis, total WTP for a new basal insulin was estimated as much as $90.10 per month. Patients with T2DM valued the following basal insulin attributes the most: injection timing flexibility, diabetes control, a 25% reduction in overall hypoglycemia events, and a 40% reduction in nighttime hypoglycemia reduction. Similar results were found for WTP based on a health insurance contribution, although patients were willing to pay more in this case.Our study suggests that in addition to A1C control and hypoglycemia, considerations such as injection timing flexibility are important for patients with T2DM, when considering a new insulin therapy.

Attribute	WTP ($ per month)	
	Financing through copayment*	Financing through contribution*
Overall hypoglycemia events reduced by 25%	17.02	25.78
Night-time hypoglycemia events reduced by 40%	15.57	23.59
Improvement in diabetes control	20.86	31.60
Insulin injection from twice to once daily	5.13	7.77
Injection timing flexibility†	21.25	32.19
Blood glucose monitoring and strip use, once a week vs. once daily	10.27	15.56
Total WTP	**90.10**	**136.49**

† e.g. up to 2 days gap between consecutive injections* All p < 0.001

Supported by: Novo Nordisk, Inc.

1199-P

Cost-Effectiveness of Vildagliptin Compared to Generic Sulphonylureas Added on to Metformin from a Portuguese Healthcare System Perspective

FREDERICO J. CALADO, JEAN-BERNARD GRUENBERGER, ENRICO DE NIGRIS, JOSÉ SILVA-NUNES, DAVIDE CARVALHO, *Sintra, Portugal, Basel, Switzerland, London, United Kingdom, Lisbon, Portugal, Porto, Portugal*

Vildagliptin has demonstrated efficacy on HbA1c comparable to glimepiride after 2 years of add-on treatment to metformin with markedly reduced hypoglycemia risk. The current analysis aims to assess the add-on of vildagliptin versus generic sulphonylureas (SU's) to metformin using a cost effectiveness analysis (CEA) framework from a Portuguese healthcare system perspective. Whilst generic SU's have a lower acquisition price, severe hypoglycaemic events represent a significant economic burden and therefore the CEA framework can contribute to better decision-making. The CEA utilized a patient level simulation model building on the UKPDS risk equations to estimate micro/macro-vascular complications and mortality over a lifetime horizon. Clinical parameters in the current model include: HbA1c levels, weight gain, systolic blood pressure, total cholesterol, HDL and incidence of severe hypoglycaemic events. Patient distribution on demographic and clinical variables was based on Portuguese epidemiological data. The treatment algorithm allows for treatment switch when: HbA1c goal is not met; drug intolerance; poor compliance. Drug parameters and quality of life decrements were derived from literature. Drug costs were based on Portuguese list prices, while the unit cost of each complication was obtained from the Diagnosis Related Groups tariff. On average, the add-on of vildagliptin was estimated to result in a per patient gain of 0.31 QALY and an increase of €1'537 on total cost when compared to the add-on of SU to metformin resulting in a Incremental Cost-Effectiveness Ratio of €4'875/QALY. For the Portuguese health care system, adding vildagliptin is projected to be likely cost-effective for patients with type 2 diabetes who are not at HbA1c goal on metformin compared with adding generic SU's.

1200-P

Insulin Degludec Improves Health-related Quality of Life (Utility) vs. Insulin Glargine

NICK FREEMANTLE, MARC EVANS, TORSTEN E. CHRISTENSEN, MICHAEL L. WOLDEN, JAKOB B. BJORNER, *London, United Kingdom, Cardiff, United Kingdom, Søborg, Denmark, Copenhagen, Denmark*

An important parameter when assessing the cost-effectiveness of new treatments is health-related quality of life (HRQoL). HRQoL may be expressed as a single value (health utility) with 0 (equivalent to death) and 1 (perfect health). Utility may be derived from the Short Form 36 (SF-36) questionnaire, based on a subset of the SF-36 items (SF6D), or using algorithms that map SF-36 scores to those of the utility instrument, EQ5D. This study evaluated utility in 4001 patients with diabetes receiving insulin glargine (IGlar) or insulin degludec (IDeg), a new-generation basal insulin with an ultra-long action profile.SF-36 data were collected in six open-label, randomized trials comparing IDeg with IGlar (one in type 1 basal/bolus, one in type 2 basal/bolus and four basal/oral therapy trials). SF-36 scores were converted to EQ5D and

a generalized linear model was used to estimate utility differences between IDeg and IGlar. Non-significant variables (including an interaction term between trial and treatment effect) were removed via backwards elimination. In all trials IDeg glycated hemoglobin (HbA_{1c}) achieved non-inferiority over IGlar, IDeg fasting plasma glucose and nocturnal hypoglycemic events were numerically or significantly reduced and IDeg overall hypoglycemic events were equal to or fewer than IGlar. The final model contained six independent variables (Table 1). A significant treatment-specific utility difference in favor of IDeg vs IGlar of 0.005 (SE ± 0.002; p=0.024) was found.As assessed through a global utility score, IDeg is associated with a modest, but statistically significant, improvement in HRQoL vs IGlar.

Table 1. Regression model with significant variables predicting the utility value

Variable	Parameter	Estimate ± SE	p-value
Intercept		0.315 ± 0.016	
Treatment			0.024
	Degludec	0.005 ± 0.002	
	Glargine	0	
Sex			0.003
	Female	-0.006 ± 0.002	
	Male	0	
Region			0.017
	Asia	-0.023 ± 0.010	
	Europe	-0.015 ± 0.009	
	Japan	-0.024 ± 0.012	
	North America	-0.021 ± 0.009	
	South Africa	-0.013 ± 0.010	
	South America	0	
Trial			<0.0001
	NN1250-3579	-0.007 ± 0.003	
	NN1250-3582	-0.015 ± 0.003	
	NN1250-3583	-0.005 ± 0.004	
	NN1250-3586	0.010 ± 0.008	
	NN1250-3668	-0.004 ± 0.005	
	NN1250-3672	0	
Age		-0.001 ± 0.000	<0.0001
Baseline utility		0.712 ± 0.012	<0.0001

1201-P

One-Year Time Analysis of Time Utilization in an Academic Diabetes Clinic

MARCEL BUDICA, BRYAN A. COMSTOCK, ALISON B. EVERT, MARY M. JANCI, DORI KHAKPOUR, RHEA C. SMITH, PAM THOMSON, SARA TORBET, DACE L. TRENCE, IRL B. HIRSCH, *Seattle, WA*

Non-reimbursed time affects allpractices yet detailed analysis has not been reported. We collected time data for 4 months and extrapolated to 1 year to estimate annual time spent on all non-reimbursed encounters in our clinic for 2224 patients with 82% requiring insulin.Meter, pump, and sensor analyses were collectedseparately as download and printing times. 2025 downloads were analyzed (table 1).There were 2814 triage interactions (telephone, fax, oremail). Medication issues (questions, refills, prior authorizations) accounted for 51%. Times for common triage interactions (table 2) were estimated with a linear regression model. For telephone calls alone, mean time per call was 13 min, or 804 clinic hours/year averaging 22 min/patient/year.In conclusion, non-reimbursed time is significant in our diabetesclinic serving mostly insulin-requiring patients. The substantial time required for downloads and triage disincentivizes optimal care. Medication issues prompting the majority of triage interactions reflect our difficult insurance environment. Understanding the details of the time expended to care for this population should promote more realistic reimbursement, incentive to provide such care, and better outcomes.

Time Required for Most Common Devices		
Device	Total Time (min)	Range (min)
Bayer	3.1	0.6-36
Lifescan	3.0	0.5-45
Accucheck	2.8	0.4-17
Freestyle	2.0	0.5-32
Animas	10.7	5.8-23
Medtronic	6.1	1.6-44
Dexcom	13.0	2.9-23

Most Time Consuming Triage Interactions		
Problem	Mean Time (min)	95% CI
Prior Authorization	11.8	1.0-110
Glucose Management	8.2	7.0-9.3
Hypoglycemia	8.1	2.0-14
Nutrition	7.6	4.9-10
"Health Challenges"	7.1	6.0-8.3
Surgery Questions	6.9	3.4-10
Steroid Questions	6.9	2.0-12

1202-P

Non-Reimbursed Time Use in an Academic Diabetes Clinic

DACE L. TRENCE, BRYAN A. COMSTOCK, ALISON B. EVERT, PETER HUYNH, MARY M. JANCI, LORI SAMESHIMA, BARBARA J. SMIT, PAM THOMSON, IRL B. HIRSCH, *Seattle, WA*

Providing diabetes care is time-intensive with reimbursementmostly related to face-to-face time interaction. To determine how much effort is required to provide non-reimbursed care, we captured all non-billed interactions at the University of WA Diabetes Care Center between Sept 1 and Dec 31, 2011. Our clinic volume is over 9400 visits/yearconsisting of 2224 patients, approximately half with type 1 diabetes, 82% using insulin, and 26% on insulin pumps. We have 4.8 FTE of non-MD/ARNP clinical personnel. Glucose meter, pump, and sensor (Dexcom) downloading andprinting took on average 2.9, 6.6, and 13.0 min respectively. There was little variability in the time of meter downloads, while for the pumps, the Medtronic required 6.1 min while the Animas required 10.7 min.Of the 2713 triage encounters, phone calls and faxing were45 and 57% respectively. The greatest time spent were for walk-ins andcompleting pre-authorizations for medications at 13.6 and 11.8 min.Multivariate linear regression analysis revealed the next most common problems were prescription management, medication questions, and pump questions, with the mean time for 17 categories at 7.6 min. Phone time ranged from 1 to 120 min with an average of 13.4 min per call and 2.9 hours of phone time per day (21 min/patient/year). We averaged 31 separate triage events/day (3.8/patient/year) with 64% resulting in complete resolution while 37% required some assistance from an MD or nurse practitioner.In conclusion, non-reimbursed time for management and care for a mostly insulin-treated population is substantial and significantly underappreciatedby payers. To our knowledge this is the first survey capturing the actual time required to care for this population and likely contributes to the lack ofenthusiasm of both providers and hospital systems to care for these patients. Due to the rising prevalence of diabetes, future efforts need to be focused on appropriate incentives for the non-face-to-face interactions required to care for this population.

1203-P

Long-Term Validation of the IMS CORE Diabetes Model in Type 1 and Type 2 Diabetes

DAVID GRANT, VOLKER FOOS, JAMES PALMER, ADAM LLOYD, MARC EVANS, PHIL MCEWAN, *London, United Kingdom, Basel, Switzerland, Cardiff, United Kingdom, Swansea, United Kingdom*

The IMS CORE Diabetes Model (CDM) is an extensively validated simulation model designed for use in both for type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) studies. Validation to external studies is an important part of demonstrating model credibility, however, many studies are conducted over a relatively short period. As the CDM is widely used to estimate long-term clinical outcomes in diabetes patients the objective of this study was to validate the CDM to contemporary outcomes data; including those with a 20-30 year time horizon.A total of 81 validation simulations

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

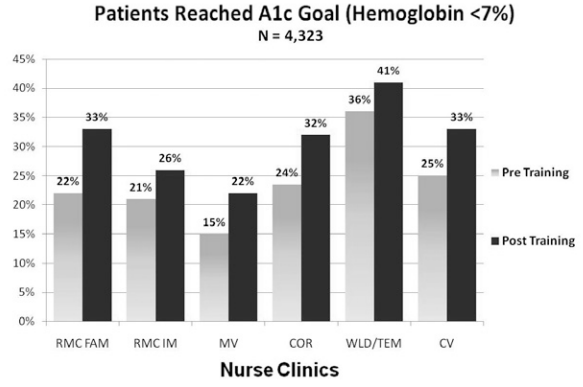
were performed stratified by duration of study follow-up (long-term defined as > 15 years follow-up); for long-term results simulation cohorts representing baseline DCCT and UKPDS cohorts were generated and intensive and conventional treatment arms were defined in the CDM. Predicted versus observed macrovascular and microvascular complications and all cause mortality were assessed using the coefficient of determination (R2) goodness of fit measure.Across all validation studies the CDM simulations produced an R2 goodness of fit statistic of 0.90. For validation studies with duration of follow-up <= 15 years the CDM achieved R2 values of 0.9 and 0.88 for T1DM and T2DM respectively. In T1DM, validating to 30-year outcomes data resulted in an R2 of 0.67; for long-term 20-year validation to UKPDS in T2DM an R2 of 0.92 was obtained.This study supports the CDM as a credible tool for predicting the absolute number of clinical events in DCCT and UKPDS like populations. With increasing incidence of diabetes worldwide this is of particular importance for healthcare decision-makers for whom the robust evaluation of alternative healthcare policies and therapeutic options is essential.

1204-P

Diabetes Nurse Training Program: A Cost Effective and Efficacious Method for Enhancing Diabetes Care in Nurse Clinics in a Patient-Centered Medical Home at Kaiser Permanente Riverside

LUAN K. TRUONG, ANANDA D. NIMALASURIYA, MARIA D. DIESTRA, KANDY M. MERICA, YVONNE E. BARILLAS, RICHARD G. RAJARATNAM, *Riverside, CA*

Kaiser Permanente at Riverside has previously demonstrated the effectiveness of the Nurse Clinic model in improving diabetes care. To further improve the effectiveness we developed an internal specialized diabetes training program using the American Association of Diabetes Educators and the American Diabetes Association guidelines. The training was delivered to registered nurses in five nurse clinics consisting of 10 three hour sessions over a 10 month period.Components of the Nurse Clinic included a face-to-face initial visit and phone follow-up for up to eight weeks or until the patient reached glycemic goal. The nurse addressed: Medication adherence and titration, self-management skills, lipid and hypertension management including depression and preventative screening.Outcomes after the training demonstrated an improvement in glycemic control rate (A1C < 7%) in all five clinics from five to eleven percent (N=4,323). A1C sustainability (six to nine months) also increased by 10% from pre to post training (56% vs 66%). The financial impact of the enhanced training proved to be cost effective. The usual care cost per patient is estimated to be $202/physician visit compared to the RN visit at $30 per face-to-face visit and $20 for follow up phone calls. Furthermore, a department survey reflected at 92% provider satisfaction with training provided. The specialized diabetes training program further enhanced the value of clinical outcomes in a patient-centered medical home.



1205-P

Deleterious Changes In Cardiovascular Risk Factors Following Initiation Of Dual Oral Glucose-Lowering Therapy In Clinical Practice

PHIL MCEWAN, JASON GORDON, MARC EVANS, KLAS BERGENHEIM, *Swansea, United Kingdom, Adelaide, Australia, Cardiff, United Kingdom, Molndal, Sweden*

Successful glucose control in patients with type 2 diabetes (T2DM) nearly always requires therapy escalation. Consensus algorithms advocate adding agents such as sulphonylurea (SU) or thiazolidinedione (TZD) to metformin (MET) monotherapy based on their glucose-lowering properties. These agents have differing cardiovascular (CV) risk factor profiles. This study aimed to assess changes in composite CV risk factors in UK patients escalating from first-line monotherapy.This retrospective cohort study using data from The Health Improvement Network included T2DM patients with a first prescription for an oral antidiabetes agent (OAD) from 1 Jan 2005 to 31 Dec 2009. Patients escalating from mono to dual therapy were selected and pre and post treatment change in HbA1c, weight, systolic blood pressure (SBP) and total cholesterol evaluated.A total of 7,230 patients (mean age, 62.91 yrs [SD=11.80]) were included; 60.4% were men; 55%, 21%, 21% of add-on treatment was SU, TZD, MET, respectively. Adjusted annual mean (SD) change in HbA1c after therapy escalation was -0.61 (3.90), -1.07 (3.54), -1.20 (3.55) for SU, TZD, MET, respectively. Change in adjusted annual mean (SD) weight (kg) in moving from mono to dual therapy was 0.77 (1.99), 0.009 (1.95), -0.98 (1.07) for SU, TZD, MET. 44% of patients had HbA1c ≥7.5% post therapy escalation (last recorded measurement). A deleterious change in CV risk factor profile, defined as an increase in either HbA1c, SBP, weight or total cholesterol after therapy escalation was observed in 93% of patients; individually, 43% HbA1c, 49% SBP, 59% weight, 57% total cholesterol. 10% of patients had a deleterious change in all 4 CV risk factors.This observational study demonstrated inadequate control of T2DM and CV risk factors in routine clinical practice. The differential impact upon composite CV risk factors associated with OADs should be considered in prescribing strategies for managing glycemic control in T2DM.

1206-P

Clinical and Economic Outcomes, According to Adherence to Medication, of Patients With Type 2 Diabetes Mellitus in the Republic of Korea: A 3-Year Follow-Up Study

MIN SUK LEE, SO-YEON AN, HAE JIN KIM, KI HONG CHUN, SEUNG JIN HAN, DAE JUNG KIM, YOUNG SEOL KIM, JEONG TAEK WOO, KYU JEUNG AHN, YONG-SOO PARK, MOON SUK NAM, SEI HYUN BAIK, TAE HO KIM, KWAN-WOO LEE, *Suwon, Republic of Korea, Seoul, Republic of Korea, Incheon, Republic of Korea, Goyang, Republic of Korea*

The prevalence of diabetes mellitus (DM) is increasing worldwide. This trend is notable because the social burden associated with DM is increasing. Adherence to medication is important in improving clinical outcomes and reducing burden in patients with DM. This study was designed to evaluate the association between adherence to medication and clinical and economic outcomes in patients with type 2 DM (T2DM) in the Republic of Korea during the 3 years.This study used cohort data from the Korean National Diabetes Program, performed at 13 university hospitals. Data from 608 patients who used oral hypoglycemic agents (OHAs) were analyzed. During the 3 years, medication possession ratios of ≥90% and <90% were used to define adherent and non-adherent groups, respectively. Degree of glycemic control, changes in blood pressure, lipid profiles, and healthcare costs were compared according to adherence to medication.Of the 608 patients, 472 were in the adherent group and 136 in the non-adherent group. Adherent patients were older and fasting blood glucose, HbA1c, total cholesterol, and LDL-cholesterol values improved from the moment of enrollment in the cohort. Adherent patients showed better glycemic control during the 3 years. The total cholesterol level was lower in the adherent group at baseline and at 36 months. At baseline and at 24 months, LDL-cholesterol levels were lower in the adherent group. During the last year, hospitalization costs did not differ between the two groups. The adherent group spent more money on outpatient clinic services than the non-adherent group because of expenses relating to drug purchases.During the 3 years of our study, OHA-adherent patients showed better glycemic control and beneficial trends in lipid profiles. Drug costs were higher for adherent patients, but overall healthcare costs, including costs of hospitalization, were similar in adherent and non-adherent patients.

1207-P

Gender Differences in Lipid Levels Persist Despite Similar Treatment With Statins in Diabetes

VARSHA G. VIMALANANDA, DONALD R. MILLER, TIMOTHY P. HOFER, ROB HOLLEMAN, MANDI L. KLAMERUS, EVE A. KERR, *Boston, MA, Bedford, MA, Ann Arbor, MI*

Among those with diabetes, women are less likely than men to have an LDL < 100mg/dL. We examined whether this might be due to differences in treatment with statins. Using July 2009-June 2010 data from the VA Corporate Data Warehouse, we examined the proportion of 18,052 women and 583,855 men with diabetes, aged 50-75, who met each of three quality measures: 1) LDL < 100mg/dL; OR 2) use of at least a moderate dose statin; OR 3) LDL ≥ 100mg/dL with appropriate clinical action within 90 days (start, change, or use of moderate dose statin, or repeat LDL < 100mg/dL). Two-level logistic regression models included age, care in a community-based clinic vs. medical center, number of primary care visits, presence of ischemic heart disease (IHD), and VA facility. We examined the interactions between

gender and both age (< or ≥ 65 yrs) and IHD. Women were less likely to have LDL < 100mg/dL (52% vs. 65%, p < 0.0001), but were treated similarly with at least a moderate dose statin (47% vs. 51%, p < 0.001) and received comparable clinical action within 90 days of an elevated LDL (9% vs. 6%, p < 0.001) Adjustment for confounders did not change the results. There were no interactions with age or IHD. We conclude that, despite similar treatment with statins, LDL levels in women with diabetes are higher than levels in men with diabetes. The reasons for this are unknown, but may include gender differences in medication adherence.

Mean LDL values and distribution of statin dose level by gender

	Female (n=18,052)		Male (n=583,855)	
	Mean LDL values (mg/dl)	% at statin dose	Mean LDL values (mg/dl)	% at statin dose
No statin	108	32	94	28
Low dose	94	21	82	21
Moderate dose	94	20	84	23
High dose	97	27	87	28

Supported by: VA QUERI RRP 09-111

Clinical Diabetes/ Therapeutics POSTERS

1208-P

Targeted Cost Saving Strategies in Diabetes Prevention Using Risk Stratification

LOUIS P. GARRISON, EDWARD J. MOLER, SEAN D. SULLIVAN, *Seattle, WA, Emeryville, CA*

We sought to evaluate the impact of diabetes prevention costs and effectiveness on the projected return on investment (ROI) from the perspectives of a U.S. healthcare payer and a large, self-insured employer.A model comprised of a closed cohort with four Markov health-states was developed to project diabetes-specific costs and offsets due to incident diabetes and utilization of prevention resources. Subjects identified as "at-risk" for diabetes in an annual health risk appraisal would be tested and stratified into high or moderate-to-low risk groups. High risk subjects optionally enter a diabetes prevention program. Cost inputs included direct and indirect medical costs of diabetes and pre-diabetes, cost of testing, and cost of interventions. Model outputs included projected costs, savings, and number of life years and diabetes-free years saved. Projected costs were adjusted for inflation and discounting.At an annual program cost of $850 and intervention effectiveness of 58%, employers would see a positive ROI by year 2 that increased through year 5. Savings at year 5 represented a return of $1.71 for every $1 spent on diabetes prevention, with 167 diabetes cases prevented, 547 diabetes-free years and 6.3 life years saved per 10,000 employees. Payers could achieve cost savings at lower program costs and/or increased effectiveness. The ROI depends strongly dependent on intervention effectiveness in the range examined (31%-72%) and is moderately sensitive to cost variations.Cost savings for employers and payers are possible using risk stratification in conjunction with an effective prevention program to reduce diabetes incidence.

1209-P

Indirect Costs Associated With Diabetes Mellitus: A Systematic Review

SUNDAR SHRESTHA, PING ZHANG, XUANPING ZHANG, *Atlanta, GA*

Numerous studies have assessed the indirect cost of diabetes and its complications during last two decades. We conducted a systematic review of studies published from 1990 through 2011 following the procedure specified in the Cochrane review. We grouped the studies first by country setting (USA and other developed countries), then by diabetes or diabetes complication status and by the type of indirect costs due to morbidity and premature mortality. For the cost due to morbidity, we also separated studies by estimation method: aggregate approach estimating the earning loss and segment approach estimating the costs due to absenteeism, presenteeism, and long term disability. We summarized costs as annual median, minimum and maximum per patient or per life lost. Costs were converted to 2010 US dollars.Of the124 articles reviewed for abstract, 16 met the study criteria, thus were included in the review (Table). In the table all are annual costs except for mortality. The cost estimates appeared greater in the US than in other developed counties. The aggregate approach appeared to yield a larger cost estimates due to morbidity than the segment approach. In terms of magnitudes, the cost associated with mortality was greater than the cost due to morbidity. Among the three cost components due to morbidity, long term disability was the greatest, followed by presenteeism and then by absenteeism. The indirect cost associated with diabetes and its complications were substantial underpinning the importance of further improvement in diabetes care and management.

Table: Indirect costs ($) (Median, Minimum-Maximum) attributable to diabetes and its complications

Excess cost due to	Earning loss/ person	Absenteeism/ person	Presenteeism/ person	Long term disability/ person	Mortality/ life lost
USA:					
Diabetes	17160 7999-23313	696 308-887	1432 1432-1432	2984 779-5879	142384 99617-186812
Diabetes Retinopathy	—	471 471- 471	—	850 850-850	—
Macrovascular complication	—	1931 1931-1931	—	—	—
Other Developed Countries:					
Diabetes	—	217 217-217	—	2209 1257-2331	40926 33636-48215

1210-P

Rates of Type 1 Diabetes (T1D) Complications in Rwandan Youth

SARA L. MARSHALL, DEBORAH EDIDIN, GRAHAM OGLE, TREVOR ORCHARD, *Pittsburgh, PA, Chicago, IL, Sydney, Australia*

The Life For a Child (LFAC) program is managed by the International Diabetes Federation with the Australian Diabetes Council and HOPE*worldwide*. LFAC's mission is to help alleviate the burden of diabetes by providing insulin and glucose monitoring supplies to children and young adults with diabetes in developing countries. This program works with the Association Rwandaise des Diabetiques (ARD) in Rwanda to locally address their emerging diabetes problem. Children supported by this program have an annual visit, which documents clinical status.From June 2009 - November 2010, 301 youth aged 25 yrs or less had their first HbA1c test, of whom 286 (95%) were regularly taking insulin. Mean age, duration and age at diagnosis of this cohort was 18.64.6 yrs, 3.33.1 yrs and 15.34.9 yrs respectively. The mean HbA1c was 11.12.8% with only 52 patients (17.3%) having HbA1c under 8%, while 89 (29.6%) had HbA1c over 14%. Five (2.1%) had either abnormal tuning fork vibratory sensation or monofilament response (DIAMOND Protocol, 1996); 31 (21%) had microalbuminuria (A/C Ratio >30 and <300 mg/dL, DCA Vantage) and 7 (5%) had nephropathy (A/C Ratio >300 mg/dL, DCA Vantage). Five of these 7 had diabetes duration <10 yrs.In comparison to a prior T1D international study (DiaComp) with centers in Asia, Caribbean/South Am, and Europe comprised of participants aged ≤ 18 years and duration ≤ 15 years (n=380) (Walsh et al, 2004), similarly aged Rwandans (n=126) had older age at diagnosis (12.0±4.2 yrs v 6.0±3.2 yrs, p<0.001) and higher mean HbA1c% (11.3±2.8 v 9.1±1.7, p<0.001). Significantly fewer Rwandan patients monitored their glucose once or more per week (21% v 87%, p<0.001). Microalbuminuria prevalence in Rwanda, however, was not greatly increased (21% v 16%, p=0.28), likely reflecting a shorter duration (2.5±2.6 yrs v 7.6±2.9 yrs, p<0.001).The older age at diabetes onset raises concerns about missed fatal causes at a younger age, while the development of nephropathy, at such short duration, underscores the need for improved, and earlier, treatment.

1211-P

Diabetes Specific Outcomes in 402 Patients Facilitated by an Inter-Office Visit Call Centre Based Intervention for 1 Year

RAMAKRISHNAN SANTOSH, S.G. MOAZAM, RAJITHA KAMSHATTI, ABHILASH PILLAI, RABINDRA N. MEHROTHRA, *Hyderabad, India*

Background: The number of patients who reach the ADA recommended goals for diabetes specific outcomes are dismal in most countries. In a recent study conducted in India, the percentage of people who had HbA1c values less than 7 percent, BP less than 130/80 mm Hg , HDL >50mg/dl , LDL< 100 mg/dl and Triglycerides less than 150 mg/dl were 20.7%, 15.5%, 20.8 %, 33.2%, and 39.4% respectively.Aim of the study: This was a pilot study to see whether a multifactorial intervention approach plus an innovative call centre support mechanism would improve diabetes specific outcomes.Methods: A total of 980 patients were enrolled in the Apollo hospitals SUGAR clinic between October 2009 to October 2010. All patients underwent a multifactorial check up. After the patients left the clinic, they were followed up by a call centre. An average of 21 calls over a period of one year was made to each enrolled patient. At each call, patients were enquired about their health (SMBG values, compliance, adverse events). Continuing diabetes specific education, reminders about appointments for cliic visits and group

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

sessions were also a part of the agenda.Results: A total of 402 patients completed one year and reviewed on time successfully in this program. The mean HbA1c, Fasting Plasma Glucose, LDL cholesterol, SBP and DBP dropped from 9.13 to 7.75 %, (p<0.001), 158 mg/dl to 131 mg/dl (p<0.0001), 106 mg/dl to 94mg /dl, (p <0.03), 127 to 119 mm of Hg (NS) and 88 mm of Hg to 84mm Hg (NS) respectively. The number of patients who reached target HbA1c, Fasting plasma glucose values and LDL improved from 26% at baseline to 40%, 58% to 37% and 45.6% to 61% respectively. There was no significant increase or decrease in the BMI, microalbuminuria values, serum creatinine, HDL cholesterol and serum triglyceride levels.Conclusions: A multifactorial approach helped by a call centre intervention improved many of the diabetes specific outcomes in a cohort of 502 patients. A randomised control trial will help us validate the pilot study.

1212-P

Health Status in People With Type 2 Diabetes on Basal-Oral Therapy is Significantly Improved With Insulin Degludec vs. Insulin Glargine

NICK FREEMANTLE, LUIGI MENEGHINI, TORSTEN E. CHRISTENSEN, MICHAEL WOLDEN, JOHAN JENDLE, ROBERT E. RATNER, *London, United Kingdom, Miami, FL, Søborg, Denmark, Karlstad, Sweden, Hyattsville, MD*

Insulin degludec (IDeg) is a new-generation ultra-long acting basal insulin, forming soluble multi-hexamers following subcutaneous injection, achieving a stable time-action profile >24 hrs. An individual patient data meta-analysis from three open-label, randomized trials of 26 or 52 weeks duration compared the efficacy of IDeg and insulin glargine (IGlar) in basal-oral therapy in people with type 2 diabetes. We assessed glycemic control via HbA_{1c} and fasting plasma glucose (FPG) concentrations, hypoglycemia, defined as plasma glucose <56 mg/dL (<3.1 mmol/L), and health-related quality of life, using the MOS SF-36.Insulin-naïve patients received IDeg (n=1290) or IGlar (n=632) once daily, in combination with oral antidiabetic drugs. Statistical analysis was performed using a generalized linear model with treatment, trial, antidiabetic therapy at baseline, gender, region, age and relevant baseline values as explanatory variables.At baseline, mean age was 58.6 yrs, HbA_{1c} 8.3 % (67 mmol/mol), FPG 169.4 mg/dL (9.4 mmol/L) and BMI 30.0 kg/m^2. In all three trials IDeg was confirmed as non-inferior to IGlar based on HbA_{1c}. In each of the trials comprising the meta-analysis, FPG and confirmed overall and nocturnal (00:01-05:59 hrs) hypoglycemia were all numerically or significantly lower with IDeg vs IGlar. At study end overall physical component score was significantly higher (better) with IDeg vs IGlar (+0.66 [95% CI: 0.04; 1.28]), largely due to a difference (+1.10 [95% CI: 0.22; 1.98]) in the bodily pain domain score. In the mental domains, vitality was significantly higher with IDeg vs IGlar (+0.81 [95% CI: 0.01; 1.59]). The remaining SF-36 domains had scores in favor of IDeg, but were not significantly different between insulins. Compared with IGlar, IDeg leads to improvements in both mental and physical health status for people with type 2 diabetes on basal-oral therapy.

1213-P

Inaccuracy of In-Patient Mealtime Insulin Administration: An Investigation of Frequency and Causes

MATTHEW J. MEYERS, SAMANTHA A. CONROY, ANTHONY M. PERRY, *Scranton, PA*

The timing of mealtime insulin administration in hospitalized patients is often inaccurate. In an attempt to quantify this inaccuracy and identify possible reasons for its occurrence, a two-phase observational study was conducted at a 200 bed community hospital. In the first phase, administration of mealtime insulin lispro, a drug with well defined recommendations for timing of administration, was tracked relative to onset of meal ingestion using the electronic medication administration record and hospital food service reports respectively. Of the 68 non-critical care patient mealtimes measured, insulin was administered within the target time range only 44% of the time, with 39% administered before and 17% after the recommended time frame. The second phase of the study consisted of the distribution of an anonymous multiple-choice questionnaire to house nursing staff designed to assess both their knowledge of proper mealtime insulin timing and their estimation of its importance. An additional comments section asked each nurse to provide an evaluation of the factors contributing to inaccurate insulin administration and suggest methods for improvement. 56 surveys were completed.The survey results showed the nurses to have a high degree of basic knowledge regarding mealtime insulin timing under normal circumstances, as well as a strong positive opinion of the importance of proper timing. However, surveys indicated a significant knowledge deficit regarding insulin timing in unusual circumstances such as a hypoglycemic event, lack of patient appetite or concurrent patient care.The written responses indicated that the other important factors were predominantly logistical. Examples cited included nurse workload, requirement for backup observers of insulin administration, summons to emergencies, inconsistent timing of meal delivery, pharmacy delays due to dosage changes, as well as insufficient access to computers, medication dispensing areas, and glucose meters.

Supported by: The Commonwealth Medical College

1214-P

Improving Diabetes Care in Cap Haitian, Haiti

JOHN T. DEVLIN, NANCY CHARLES-LARCO, PHILIPPE LARCO, MICHEL PIERRE, NIJNIE JASMIN, NATE NICKERSON, *Portland, ME, Port-au-Prince, Haiti, Cap Haitian, Haiti*

Haiti is the most challenging environment in the Western Hemisphere in which to improve diabetes-related outcomes. We represent a collaborative effort between the Hôpital Universitaire Justinien (HUJ), Konbit Sante, and FHADIMAC. We report 6-months follow-up data from a two-year translational (RE-AIM framework) effort to improve outcomes.Enrollees are adults of either sex, attending the HUJ Diabetes Clinic, residing within greater Cap Haïtien area, who have *either* HbA1c >9%, *or* BP >160/95. Foot risk classification is based on the International Working Group on the Diabetic Foot. Research RN records whether medical residents follow stepped-care algorithms for glycemic (BG) and BP control using generic medications, and patient attendance at educational sessions.82 individuals have been enrolled and followed for ≥ 6 months. Of these, 66 completed follow-up evaluation ("completers"), 7 died, 8 dropped out for various reasons, 1 moved from the area, and 1 was not evaluable while hospitalized. Six patients were hospitalized during this period.

Table: "Completers" (age 54 ± 12 yr; 83% female; 94% type 2 DM)

	BG protocol adherence	BP protocol adherence	Fasting BG (mg/dL)	HbA1c* (%)	BP Syst (mm Hg)	BP Diast (mm Hg)
Baseline	95%	98%	266±95	10.7±2.1	143±26	89±15
6 mos	43%	89%	228±115	9.9±3.3	142±29	86±15
p (t test)			0.013	0.67	0.42	0.07

*A1c Now® (Bayer)

We observed high mortality rates (8.5%) over 6 months in this high-risk cohort. Significant (ANOVA) predictors of mortality include male sex (OR 3.9), failure to prescribe aspirin (OR 10.9) and HCTZ (OR 2.6), and hospitalization during follow-up (OR 21). Adoption of glycemic protocol was poor due to failure to initiate insulin therapy. Lack of effectiveness in improving glycemic and BP control can be explained by inability and/or unwillingness to purchase prescribed medications, and omission of antidiabetic agents when unable to purchase food.

Supported by: BRIDGES, IDF

1215-P

Simulated Training Improves Provider Knowledge and Confidence in Managing Diabetes

JOANN SPERL-HILLEN, PATRICK O'CONNOR, WILLIAM RUSH, STEPHEN ASCHE, HEIDI EKSTROM, OMAR FERNANDES, ANDREW RUDGE, DEEPA APPANA, JERRY AMUNDSON, PAUL JOHNSON, *Minneapolis, MN*

Simulation is a commonly used training tool in non-medical industries, but efficacy remains unproven in most health applications. Our objective was to evaluate satisfaction, knowledge, and self-confidence outcomes from a simulated diabetes training intervention consisting of: (a) 18 complex diabetes cases, (b) a web-based interactive interface, (c) a physiologic model to simulate outcomes of provider actions across a series of patient encounters, and (d) a library of feedback messages to critique and guide provider actions. 341 consented primary care residents in 19 residency programs were randomized to receive (n=177) or not receive (n=164) the intervention. Following the intervention, a satisfaction survey was completed by 94 (53%) intervention subjects, and results analyzed using mixed quantitative and qualitative methods. A knowledge and confidence questionnaire was completed by 220 (65%) of subjects and mean (95%CI) scores were compared by group, adjusting for program clustering. Responses were favorably higher than neutral for general satisfaction (93%), recommending to colleagues (91%), training adequacy (90%), navigation ease (95%), blood sugar displays (86%), drug & help links (76%), goal graphs (49%), and feedback (81%). The most valuable learning pertained to insulin use, general management, and goal achievement. The mean knowledge score (95% CI) was 5.31 (4.87-5.75) for intervention and 4.1 (3.69-4.50) for control subjects (p<.001). Self-confidence measures were higher for intervention compared to control subjects for: use

of all drug classes (3.64 vs 3.09, p<.001), insulin use (4.12 vs. 3.36, p<.001), blood sugar interpretation (4.21 vs. 3.58, p< .001), individualizing goals (4.06 vs. 3.42, p< .001), and overall confidence (3.97 vs. 3.28, p< .001). In conclusion, the simulated learning program improved knowledge and confidence for diabetes management in primary care residents. Satisfaction was high, indicating good potential for broader dissemination.

Supported by: NIDDK (1R18DK079861)

1216-P

Clinical Differences between Patients Prescribed Saxagliptin and Other Non-Insulin Antidiabetic Medications in a U.S. Health Plan

SARAH W. THAYER, SETAREH A. WILLIAMS, YING FAN, SHREEKANT PARASURAMAN, *San Francisco, CA, Wilmington, DE, Eden Prairie, MN*

In retrospective database studies, reasons for treatment initiation and choice of therapy are generally unobservable. Baseline characteristics may play a role in choice of therapy. This study was conducted to compare baseline demographics and clinical characteristics in patients initiating saxagliptin (SAXA), a DPPIV inhibitor, following its US approval compared with those initiating other non-insulin antidiabetic (AD) therapy during the same period.Data were from a large US insurance claims database and included commercial and Medicare Advantage members with evidence of T2DM and use of SAXA, other oral AD medications or GLP-1 analogs. Patients were placed in a SAXA or "Other" cohort based on medication use between 01 August 2009 and 31 December 2010. The first prescription fill for SAXA or another study drug was identified as the index date. Inclusion criteria were age ≥18, ≥12 months continuous enrollment in the health plan, and new to SAXA or other index therapy regimen. Patients with evidence of insulin or pramlintide, T1DM, or gestational diabetes were excluded. Patients were observed for 12 months prior to therapy start.Patients initiating SAXA (N=4,763) were older than the other (N=75,943) patients (57.4 vs. 56.3 years; p<0.001) and had significantly higher baseline Charlson-Quan comorbidity scores. Prior to therapy start, patients initiating SAXA had higher rates of renal insufficiency, ischemic heart disease, peripheral vascular disease, retinopathy and other eye complications, erectile dysfunction or impotence, and neuropathy (all differences p<0.001). Pre-index A1C was higher in patients subsequently treated with SAXA (8.2% vs. 7.8%; p<0.001) and fewer had pre-index glycemic control (i.e., A1C<7%) than the other patients (23.4% vs. 40.2%; p<0.001).In a managed health care setting, patients initiating SAXA appeared to have generally worse health status prior to therapy start than those initiating other non-insulin AD therapy.

1217-P

Patterns of Acute and Non-Acute Health Care Utilization Associated With a 30-Month Diabetes Self-Management Intervention

ROSEANNE O. YEUNG, TRICIA S. TANG, *Vancouver, BC, Canada*

This investigation was part of a larger study examining the impact of a 30-month diabetes self-management intervention on health outcomes in 60 African-American adults with type 2 diabetes. Specifically, we explored health care utilization prior to and over the course of the intervention. The intervention started with 6 months of mailed weekly diabetes education newsletters and was followed by 24 months of weekly drop-in diabetes self-management support (DSMS) group sessions. The DSMS groups, led by two health care professionals, used empowerment principles and focused on experiential learning, emotional coping, problem solving, and goal setting. Health care utilization was assessed every 3 months over the study duration, and included disability associated with having diabetes (defined as days lost due to diabetes) and frequency of acute (composite of emergency room visits, urgent care visits, and hospitalizations) and non-acute (out-patient visits) health care utilization. For statistical analysis, we calculated utilization patterns in 6-month intervals: 6 months of usual care (period just prior to study enrollment), the first 6 months of the intervention, and the last 6 months of the intervention.Mean age was 62± 10.2 years, 30% (n=18) were men, and average A1C was 8.0 ±2.2%. Mean acute health care utilization was 0.93±2.69 visits for the 6-month usual care period; 1.27±3.50 visits for the first 6-months of intervention and 0.98±2.65 visits during the last 6-months of intervention. Mean non-acute utilization was 3.02±2.66 for the usual care period; 3.36±2.97 visits for the first 6-months of the intervention and 3.88±2.88 during the last 6-months of the intervention. Days lost from disability were reduced by -0.66±5.65 days/month in the last month of intervention compared to a month of usual care. Health care utilization did not significantly change over the course of the intervention, however, there was a trend in reduction of days lost from disability.

Supported by: The British Columbia Endocrine Research Foundation

1218-P

A Hyperglycaemia Management Pathway Safely Reduces Hospital Admissions

ROSELLE HERRING, CLAIRE PENGILLEY, HELEN HOPKINS, BEVERLY TUTHILL, SUE DAVIDSON, DAVID RUSSELL-JONES, *Guildford, United Kingdom*

Up to one fifth of inpatients in the United Kingdom have diabetes. In most cases patients are admitted under the care of non-specialist teams. Patients may be admitted unnecessarily or have their discharge delayed if the admitting team do not feel sufficiently confident to make decisions on diabetes care. We have developed a hyperglycaemia management pathway for use by medical physicians as an admission avoidance initiative.This was an interventional study design. Clinical practice was evaluated during phase 1. All patients assessed by an acute medical physician with a blood glucose meter reading >11.1mmol/L (200mg/dl) were identified. 11.1mmol/L was based on the World Health Organisation diagnostic criteria for diabetes. Data was collected on acute assessment, diagnosis and management. The hyperglycaemia management pathway was then introduced and its impact assessed during phase 2. Key assessment requirements included plasma glucose, plasma ketones and urea and electrolytes. Patients who did not require admission were commenced on the recommended treatment, provided with a patient information leaflet and contacted by a member of the diabetes team the next working day.Phase 1. 72 patients were identified over a period of 156 days. 100% were admitted. 63% were started on an intravenous insulin infusion. Hyperglycaemia was the primary admitting diagnosis in 32 patients, of which 15 patients had new or known type 1 diabetes and 17 had type 2 diabetes. The term hyperglycaemia included patients presenting in a hyperglycaemia hyperosmolar state and diabetic ketoacidosis.Phase 2. The pathway has been used for 97 patients. Hyperglycaemia was the primary diagnosis in 47 patients. Admission was avoided in 19 of the 47 patients (40%). Patients with Type 2 diabetes had the greatest potential for admission avoidanceWidespread application of the hyperglycaemia management pathway could enable safe discharge, improve patient experience, patient safety and reduce inpatient care costs.

1219-P

Adherence to GLP-1 Agonist Therapy in U.S. Managed Care

ENGELS CHOU, HONGWEI WANG, WENFENG MIAO, MAEVA GERME, MARIE FOURNIER, STANLEY SCHWARTZ, *Bridgewater, NJ, Paris, France, Wynnewood, PA*

Non-adherence is a major obstacle for outcomes improvement in diabetes care. This study evaluated medication adherence with GLP-1 Agonist (GLP1) therapy. Patients who initiated a GLP-1 therapy during Apr 2005 to Dec 2010 with 1 year follow-up were identified from the Impact™ Database. Adherence to GLP1 was approximated by medication possession ratio (MPR) as the ratio of days a patient had GLP1 drug in possession relative to the calendar days in the year after the drug initiation. Yearly adherence was defined as MPR ≥80%. Mean age of exenatide (EXEN: n=52,898) and liraglutide (LIRA: n=1,587) initiators was 53 years. Yearly adherence rate for EXEN decreased from 34% in 2005 to 20% in 2010, and was 31% in 2010 for LIRA. In A1C responders (<7%), adherence rate to both GLP-1 therapies was higher than in non-responders (OR=2.21; 1.98-2.46). The yearly rate of medical claims for nausea or vomiting was 4.5-5.2% for EXEN and 6.5% in 2010 for LIRA. Specifically for EXEN, nausea or vomiting were related with non-adherence in 2009 (Odds ratio [OR]=0.59; 95% CI: 0.40-0.85) and 2010 (OR=0.28, 0.13-0.59). EXEN adherence was associated with metformin use (OR=1.37; 1.27-1.48), endocrinologist care (OR=1.20; 1.14-1.26), or microvascular event (OR=1.20; 1.13-1.26) and hospitalization (OR=0.70; 0.64-0.76). Adherence to EXEN or LIRA therapy is suboptimal and non-adherence to EXEN increased between 2005 and 2010. Adherence rate to these GLP-1 therapies is higher in patients who achieve A1C goal than those who do not. Medically treated nausea or vomiting and hospital admissions are contributing factors to non-adherence to EXEN therapy while endocrinologist care appears a mitigating factor. A new therapy with better tolerability may improve adherence hence patient outcomes.

Supported by: sanofi-aventis

For author disclosure information, see page 797.

1220-P

The Influence of Household Income on Therapeutic Goal Achievement in Diabetic Patients in the Canadian Healthcare System

PENDAR FARAHANI, MITCHELL LEVINE, ABRAHAM THOMAS, *Detroit, MI, Hamilton, ON, Canada*

Objective: To assess the association of household income strata with therapeutic goal achievement rates for blood glucose, blood pressure and LDL-C in diabetic patients in a Canadian population.Method: Data (household income, CV risk factors, drugs profile, clinical and laboratory variables) from a cross-sectional study of diabetic patients filling a prescription for a lipid-lowering drug in selected pharmacies across Canada were obtained. The therapeutic goal achievement for blood glucose, blood pressure and LDL-C were assessed according to Canadian diabetes guidelines and incorporated into regression models corresponding to household income strata.Results: Seven household income strata were defined in the cohort (from less than 20,000 CDN$, up to 70,000 CDN$ by increments of 10,000 CDN$). Number of patients in each incremental ascending strata. Aggregate CV risk factors as Mean (SD) were 4.0 (1.1), 4.0 (0.9), 4.0 (1.0), 4.0 (1.0), 3.7 (0.9), 3.8 (0.8), 4.1 (1.1), 3.9 (0.9) [P-value =0.86]. Number of subjects who achieved diabetes goals (and rates) as N (%) were, for BLOOD GLUCOSE: 24 (50%), 23 (41%), 16 (35%), 28 (49%), 16 (59%), 2 (15%), 16 (51%), 125 (45%) [P-value=0.09]; for BLOOD PRESSURE: 16 (33%), 34 (60%), 24 (53%), 34 (59%), 19 (70%), 7 (53%), 19 (61%), 153 (55%) [P-value=0.03]; for LDL-C: 17 (35%), 19 (34%), 13 (29%), 20 (35%), 8 (29%), 6 (46%), 13 (42%), 96 (34%) [P-value=0.87]; for global goal (all three goals achieved) 2 (4%), 5 (9%), 2 (4%), 8 (14%), 3 (11%), 0 (0%), 3 (9%), 23 (8%) [P-value=0.30].Conclusions: This study demonstrated that diabetic patients in this Canadian population achieved therapeutic goals for blood glucose, blood pressure and LDL-C regardless of their household income. This finding may reflect that household income is not a determinant of therapeutic goal achievement in the Canadian healthcare system where healthcare delivery is reimbursed by government for all patients who seek therapeutic interventions.

1221-P

Implementation of a Standardized Glucose Management Program Across a Large Hospital System: 1 Year Results

ROBIN MORRISEY, STEPHANIE DECKER, TAMARA FINGER, SOULING CHOU, JAMES KOZIOL, BRIEN ACKERLY, KEITH JOHNSON, KATHY BRENNER, BRUCE COVNER, ATHENA PHILIS-TSIMIKAS, *La Jolla, CA*

Specific glucose targets and medication guidelines within a hospital environment are currently advocated by national clinical guidelines. Standardizing approaches for treatment of hyperglycemia in the hospital may reduce variation in practice and lead to improved quality outcomes.Scripps is a 4 hospital health system in San Diego, CA with 20,000 DM patient visits per year. From May 2010 to May 2011, a standardized glucose management program (GMP) was undertaken on the med/surg units at its largest hospital. Baseline approaches to care and changes that resulted from implementation of the intervention (POST) were evaluated and compared to a 12 month period prior to the intervention (PRE).Intervention consisted of 1) Creation of systemwide glucometric reports to identify glucose outliers and to track progress of glucose control over time 2) CME and CEU programs on DM management and protocols conducted for all clinical staff 3) Standardized sub Q insulin order sets created for the management of med/surg patients identified 4) An expert team of advanced practice RNs provided support to the hospital staff.Over the 1 year intervention period 3083 patients met the criteria for a diagnosis of DM by ADA criteria or ICD9 code. Interestingly, only 1854 (60%) received any POC glucose testing; similar in the PRE group (59%). Excursion rates for hypo and hyperglycemia were calculated based on counts of excursions (per patient basis, numbers of excursions (exc) to glucose levels <70 or >180, with normalization by length of observation). Multivariable negative binomial regressions, looking simultaneously at phase (PRE/POST) and intervention, along with other covariates, were conducted. For exc>180, no phase or intervention effect; for exc<70, both factors achieved statistical significance: phase, p<.001; and intervention, p=.045.Undertaking a hospital wide GMP required substantial planning and infrastructure support. In year 1 there was a significant effect on reducing hypoglycemia.

Supported by: Woltman Family Foundation, Novo Nordisk, Inc., sanofi-aventis, NCRR-1U54RR025204

1222-P

Costs of Diabetes Care Over Time: Changes and Components

SEAN SIMPSON, THOMAS J. HOERGER, *Research Triangle Park, NC*

With millions of Americans living with diabetes, the increased level of medical care required to treat diabetes means a higher level of related expenditures. To identify just how much higher expenditures are for persons with diabetes, and how this excess expenditure has changed over time, we evaluated nine years of MEPS Household Component data. We find that the total expenditures have increased more for persons with diabetes than for persons without diabetes, by roughly 17% over the nine years of data, with an estimated excess effect of $4,121 (2010 USD) in 2000 to $5,140 in 2003; the excess remained close to $5,000 throughout the remaining years of data. Prescription medication expenditures appear to be the largest driver of this increase in costs (the effect of diabetes on annual medication expenditures increased from $1,604 in 2000 to $2,318 in 2005, remaining well over $2,000 through 2008); although the effect of diabetes on prescriptions filled has increased slightly over this time period, this increase is not nearly as dramatic (20 additional prescriptions in 2000, compared to 23 in 2008). Among other evaluated categories, the effect of diabetes has remained relatively stable over time. The marginal effect on office-based provider visits remained between 3.4 and 3.9 additional visits per year, with the effect on related expenditures increasing from $658 in 2000 to a high of $861 in 2007, but generally remaining around $800 from 2004 onward. The effect of diabetes on the number of hospital events is rather muted, with slight effects upon inpatient stays and emergency department visits (both under 0.1 additional per year) and a somewhat greater effect on outpatient visits (.7 - 1 additional per year). Overall, diabetes leads to about 1 additional hospital event per year, and expenditures on hospital events for persons with diabetes are about $2,000 per year greater than for persons without diabetes; these marginal effects are roughly proportionate.

Supported by: CDC

1223-P

Frequency of Missed Clinic Visits and Family Member Visit Attendance by Provider in a Pediatric, Adolescent, and Young Adult Diabetes Clinic

JESSICA T. MARKOWITZ, LORI M. LAFFEL, *Boston, MA*

Pediatric diabetes care requires quarterly visits that may add burden to families from missed school and lost work revenue. In a pediatric clinic composed of MDs, NPs, RNs, and RDs, we examined rates of missed (cancelled/no-show) appointments and assessed family member in attendance at visit by provider type over 2 years (11/1/09-11/1/11).For 2,208 individual patients <30 years old, there were 23,102 scheduled appointments with a 36% cancellation/no-show rate. Visits were scheduled with an MD (34%), NP (29%), RN (27%), and RD (10%). Missed visit rate differed across disciplines (p<.001) with RDs having the highest (39%) and RNs the lowest (35%); rates for MDs and NPs were intermediate.Notably, 88% of patients had at least 1 missed appointment; 15% missed 1, 13% missed 2, 13% missed 3, and 46% missed ≥4 appointments over 2 years. Those with ≥4 missed appointments had higher mean A1c than those with <4 (8.9±1.5 vs 8.4±1.4%, p<.0001). Females were more likely to miss ≥4 appointments than males (50% vs 42%, p<.001). Youth with type 2 diabetes were more likely to miss ≥4 appointments than youth with type 1 diabetes (60% vs 37%, p<.04). There was no difference in missed visit rate by age.Mothers attended most visits (47%) with their children; fathers attended 9%, both parents attended 15%, and neither attended 21% of visits. Regarding parent attendance across disciplines, fathers (alone or with a 2nd parent) were more likely to attend MD visits than other visits (p<.0001).Over one third of scheduled visits yielded a cancellation or no-show. Given the limited pediatric diabetes expertise nationwide and higher missed visit rate in patients with higher A1c's who likely need additional support, it is important to explore reasons for missed visits with families and to find approaches to maximize attendance. One might consider extending clinic hours to evenings/weekends to accommodate the schedules of working families with the aim to encourage parents to attend visits.

1224-P

Less Distress = More Productivity

SARAH G. IMERSHEIN, CAROLE MENSING, JAY MEYER, RICHARD A. JACKSON, *Boston, MA, Minneapolis, MN*

Diabetes is an important factor in the workplace, and is associated with loss of productivity due to a variety of factors. Part of this loss can be due to the psychological burden of diabetes. The many self-care tasks required by diabetes are associated with diabetes specific frustrations, or "distress." In addition, people with diabetes are more likely to suffer depression.We exam-

ined the association of workplace productivity with depression and diabetes distress in a large employer that provided their employees and dependents with a diabetes disease management program. Depression screening was performed with the PHQ-2, and the Diabetes Distress Scale (DDS) was used to measure distress. We report here on the results of 537 participants who were employed from baseline through year 2 of the program.We trained telephonic disease managers to use these scores to identify people with high levels of diabetes distress and depression, and to incorporate this information into their coaching.Observations made when people were segmented by depression and distress (Table 1): (1) loss of productivity is most pronounced in people with both depression and distress, or distress alone at Baseline; (2) mean A1C is significantly higher in people with diabetes distress regardless of their depression scores, versus those people with depression alone ($p<.05$ for each group comparison each year); (3) mean A1C and productivity improve Baseline to Year 2 ($p<0.05$ for each), partly due to the decreasing numbers of employees with diabetes distress.A telephonic disease management program guided by diabetes distress and depression scores can lower diabetes distress and improve workplace productivity.

Table 1. Diabetes Distress, Depression, Work Productivity and A1C

Employed Participants	Baseline			Year 2		
	% of Total Population	% with Some Loss of Productivity	Mean A1C	% of Total Population	% with Some Loss of Productivity	Mean A1C
Low PHQ-2 and Low DDS	76.5%	21.7%	7.28	87.9%	17.1%	7.14
High PHQ-2 Only	5.2%	21.4%	7.25	2.3%	41.7%	6.94
High PHQ-2 and High DDS	4.9%	73.1%	8.40	2.9%	60.0%	8.85
High DDS Only	13.4%	47.2%	8.24	6.9%	41.7%	8.18
Total Population	100.0%	27.6%	7.46	100.0%	20.7%	7.28

1225-P

Patient and Educator Attitudes Toward Biosimilar Insulin

JOSEPH P. SHIVERS, ADAM S. BROWN, MARK YARCHOAN, ERIC M. CHANG, BENJAMIN M. KOZAK, VINCENT L. WU, LISA S. ROTENSTEIN, IRL B. HIRSCH, RICHARD WOOD, KELLY L. CLOSE, *San Francisco, CA, Philadelphia, PA, Seattle, WA*

Only 26% of people with diabetes in the US use insulin, even though 44% have A1c levels over 7%. Cost may be a barrier to insulin use, and, thus biosimilar insulin (BI) offers potential savings.. A regulatory pathway for biosimilar drugs was created in 2010, and several preparations are in development. This study's purpose was to assess the openness of diabetes patients and certified diabetes educators (CDEs) to BI.In mid-2011 we surveyed a panel of subscribers to a diabetes patient newsletter (diaTribe) and a panel of US CDEs about their willingness to use or recommend BI, respectively. A total of 1,637 insulin users (65% type 1, median age 49 yrs, 62% female, median household income $25,000-$49,999, 67% bachelor's degree or higher, 81% private health insurance) and 415 educators (52% outpatient hospital setting, 28% private office, mean 21 patients per week) responded to the survey. Both surveys specified that BI would be priced favorably relative to current insulins; patients were to assume healthcare provider approval.Most patients said they would "definitely" (30%) or "likely" (37%) use BI, while only 17% said "unlikely" or "definitely not." Answers of "definitely" were more common among patients currently using NPH (46%, n=26) or premixed insulin (41%, n=36) than rapid-acting analogs (28%, n=341); "definitely" answers were also more common among those with type 2 diabetes (38%, n=213) than adults (29%, n=256) or children (13%, n=26) with type 1 diabetes. Most CDEs said they would "definitely" (41%) or "likely" (42%) recommend BI, with only 5% saying "unlikely" or "definitely not." In open-ended follow-up questions, vast majorities of both groups stressed that BI must be identical to current insulin in safety, efficacy, action profile, and/or quality. Thus the study's results are contingent on these factors.Nevertheless, we conclude there is great interest in the future use of BI among patients and CDEs which could result in major transformation in insulin usage in the US.

PEDIATRICS—OBESITY

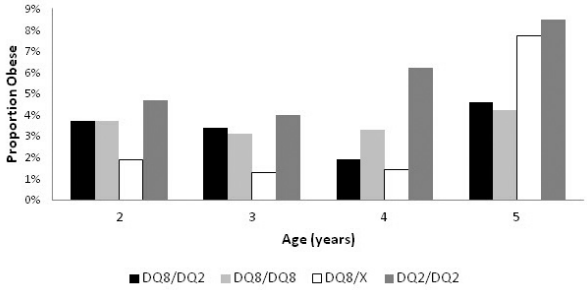
Guided Audio Tour: Genetic and Environmental Risk Factors and Determinants of Pediatric Obesity *(Posters 1226-P to 1232-P), see page 17.*

1226-P

Prevalence of Obesity in Young Children Genetically At-Risk for Type 1 Diabetes

JIMIN YANG, ULLA UUSITALO, KRISTIAN LYNCH, JEFFREY KRISCHER, KENDRA VEHIK, TEDDY STUDY GROUP, *Tampa, FL*

Body size is postulated to modulate the onset of type 1 diabetes (T1D) as either a trigger or an accelerator. As the prevalence of overweight and obesity continues to rise, it is of great interest to understand the role human leukocyte antigen (HLA) genes play in growth and obesity in children genetically at risk for T1D. The prospective study Environmental Determinants of Diabetes in the Young (TEDDY) enrolled children with T1D high risk genotypes in the US, Finland, Germany and Sweden. Weight and height measured at study clinics were available in 5,440 subjects followed for 2 or more years, of whom the majority (57%) had 3 or more measurements collected. Relative obesity rate (ROR) was evaluated by comparing the obesity rate in DQ 8/8 subjects against that in subjects with DQ2/8, DQ2/2, and DQ8/X genotype. According to the criteria set by the International Obesity Task Force, the proportion of overweight subjects was high (20-25%) but not significantly different by HLA genotypes. The ROR in DQ2/8 subjects were similar between age 2 and 5. The DQ2/2 subjects showed an increase in ROR at ages 4 and 5 compared to younger counterparts. The DQ8/X children showed an increase in ROR at age 5. Compared to the homozygous DQ8/8 genotype, children with lower T1D risk genotypes DQ8/X and DQ2/2 showed ROR increasing with age, while no trend noted in those with the highest T1D risk genotype DQ2/8. Preliminary results suggest T1D DQ genotype rather than a specific DQ gene may influence obesity rate.



Supported by: NIDDK, NIAID, NICHD, NIEHS, JDRF, and CDC

1227-P

Improvements in Insulin Sensitivity and Metabolic Syndrome During an Adolescent Weight Loss Trial

PAMELA ABRAMS, LORRAINE LEVITT KATZ, RENEE H. MOORE, MELISSA S. XANTHOPOULOS, JUDITH LAU, ROBERT I. BERKOWITZ, *Philadelphia, PA, Beverly Hills, CA*

Our objective was to assess the association of weight loss with insulin sensitivity and metabolic syndrome (MS) in obese adolescents following weight loss treatment, and to determine if there is a threshold amount of weight loss that is required in order to see an improvement in these measures.A randomized, controlled behavioral weight loss trial was conducted with 113 obese adolescents. In this analysis, changes in fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), whole body insulin sensitivity index (WBISI), body-mass index (BMI), and MS criteria were assessed at baseline and at month 4.There was significant improvement in all measures of insulin sensitivity at month 4. Average fasting insulin dropped to normal levels of less than 17 μU/mL from 22.3 μU/mL ($p<0.0001$). HOMA-IR decreased significantly from 4.9 to 3.7 ($p=0.001$) and WBISI increased significantly from 2.87 to 3.98 ($p<0.0001$). An 8% decrease in BMI led to a significant improvement in WBISI ($p=0.03$) and was the optimal threshold (See Figure 1). Fewer individuals met criteria for MS after weight loss ($p=0.0038$), and the average percent decrease in BMI for those subjects whose MS resolved was 7.28%.An approximate decrease in BMI of 8% was the threshold level at which insulin sensitivity and MS improved at month 4. As more weight loss programs are designed for obese adolescents, it will be of use to have reasonable weight loss goals that will yield metabolic improvements.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

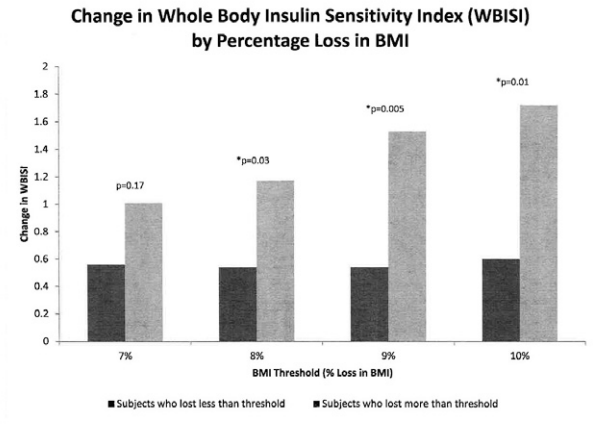


Figure 1
Each BMI threshold represents the entire population (N=72), divided between those who lost less than that percent of their BMI and those who lost more than that percent of their BMI.
* represents a significant difference in change in WBISI between the two groups (p<0.05)

1228-P

Depressive Symptoms are Associated With Risk Markers for Type 2 Diabetes in Obese Adolescents

TAMARA S. HANNON, DANA L. ROFEY, SOJUNG LEE, SILVA A. ARSLANIAN, *Indianapolis, IN, Pittsburgh, PA*

Although studies have found higher rates of depression among individuals with type 2 diabetes (T2D), few studies in pediatrics have examined associations between depressive symptoms and risk markers for T2D. The objective of this study was to determine relationships between depressive symptoms and measures of glucose homeostasis in obese non-diabetic adolescents. Participants (n=56, age 15.0±1.6 y, 68% female) completed the Child Depression Inventory (CDI) indicating depressive symptomatology. Indices of insulin sensitivity and secretion were calculated from oral glucose tolerance tests. Participant characteristics by depressive symptom status are shown.

Variable	Lower depressive symptoms CDI T-score <50N = 39	Higher depressive symptoms CDI T-Score >50N = 17	*P*
Age	15.0 ± 1.7	14.8 ± 1.5	0.600
Sex (% female) *	61.5	76.5	0.436
Race (%)*			0.604
Non-Hispanic Black	35.9	23.5	
Non-Hispanic White	56.4	70.6	
More than one race	7.7	5.9	
BMI (kg/m^2)	38.0 ± 7.5	37.9 ± 8.3	0.977
BMI Z-score	3.3 ± 0.3	3.3 ± 0.4	0.924
Waist circumference (cm)	109.9 ± 18.3	109.3 ± 17.9	0.916
Visceral adipose tissue (cm^2)	80.6 ± 40.4 (n=32)	83.1 ± 27.4 (n=10)	0.855
HbA1C (%)	5.4 ± 0.4	5.5 ± 0.4	0.118
Fasting glucose (mg/dL)	88 ± 7	92 ± 7	0.078
2-hr glucose (mg/dL)	121 ± 15	138 ± 21	0.045
AUC_{glc}	14,920 ± 1,522	16,599 ± 1,991	0.001
Fasting insulin (μU/mL)	30.9 ± 18.7	39.0 ± 17.6	0.126
AUC_{ins}	20,094 ± 10,757	26,970 ± 18,028	0.209
HOMA-IR	6.68 ± 3.88	8.92 ± 4.45	0.019
Whole body insulin sensitivity index (WBISI)	1.82 ± 0.78	1.33 ± 0.69	0.028
Insulinogenic index (IGI; ins_{30}-ins_0/glc_{30}-glc_0)	4.36 ± 2.90	3.08 ± 2.77	0.140
Oral (oDI; IGI × WBISI)	6.82 ± 3.52	3.66 ± 1.63	<0.001
Impaired fasting glucose (IFG; % presence)	5.1	11.8	0.577
Impaired glucose tolerance (IGT; % presence)	15.4	35.3	0.158
Either IFG or IGT (% presence)	20.5	41.2	0.188

Non-Hispanic whites had lower median oDI compared with the other race groups (4.24 vs 6.28 in non-Hispanic black and 6.51 in bi-racial participants, p=0.01). There was no difference in median CDI T-scores across race groups. After controlling for race and BMI there was a negative partial correlation between CDI T-score and oDI (r =-0.49, p<0.001), and positive partial correlations between CDI T-score and fasting glucose (r =0.27, p=0.04), 2-hr glucose (r =0.35, p =0.007), and AUC_{glc} (r =0.38, p=0.005). In this cross-section of obese non-diabetic adolescents, depressive symptoms were associated with higher fasting and stimulated glucose levels, lower insulin sensitivity and lower insulin secretion relative to insulin sensitivity (oDI). The relationship between depressive symptoms and glucose tolerance in obese adolescents should be investigated further to determine if early recognition and treatment of depressive symptoms could lessen the risk of T2D.

Supported by: NIH R03HD057532 (T.H.), K23KD061598 (D.R.), K12DK063704 (S.A.), UL1RR024153-CTSA

1229-P

Genetic Architecture of Bone Mass Related Traits and Their Correlation With Metabolic Syndrome Components in Mexican American Children

GEETHA CHITTOOR, SOBHA PUPPALA, SHARON P. FOWLER, VIDYA S. FAROOK, JENNIFER SCHNEIDER, ROY G. RESENDEZ, KELLY J. HUNT, BENJAMIN S. BRADSHAW, EUGENIO CERSOSIMO, RECTOR ARYA, LAURA ALMASY, JOANNE E. CURRAN, ANTHONY G. COMUZZIE, DONNA M. LEHMAN, CHRISTOPHER P. JENKINSON, JANE L. LYNCH, RALPH A. DEFRONZO, JOHN BLANGERO, DANIEL E. HALE, RAVINDRANATH DUGGIRALA, *San Antonio, TX, Charleston, SC, Houston, TX*

The relationship between fat mass and bone mass has been controversial. In addition, the association between metabolic syndrome (MS) and bone mass is not extensively studied, particularly in children. Hence, this study examined the genetics of DXA-based bone mass related traits including bone mineral content (BMC), bone mineral density (BMD), and bone area (BA) and their correlation with selected MS-related traits such as body mass index (BMI), waist circumference (WC), fat mass (FM), lean mass (LM), percent body fat (%BF), systolic and diastolic blood pressure measures (SBP, DBP), fasting measures of triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), glucose (FG), insulin (FI), Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), and hsC-reactive protein (hsCRP), using data from our San Antonio Family Assessment of Metabolic Risk Indicators in Youth (SAFARI) Study (N = 670, aged 6-17 years [mean age = 12 yrs], girls = 49%, obesity = 34%, pre-diabetes = 13%, and MS = 19%). All analyses were conducted using SOLAR program, and a given trait was adjusted for the covariate effects of age, sex and pubertal status. We determined that the bone measures were significantly (P < 0.05) heritable (h2 = BMC: 0.53, BMD: 0.47, and BA: 0.46) and that they shared significant genetic influences (i.e., pleiotropy) with certain MS-related traits. Both BMC and BMD were under strong common genetic influences (genetic correlation [ρG] = 0.74, P = 0.0001). BMC exhibited significant ρGs with BMI (0.42), WC (0.45), FM (0.44), LM (0.47), %BF (0.39), SBP (0.33), FI (0.47), and HOMA-IR (0.45). BA also exhibited similar patterns of ρGs [e.g., FM (0.61), LM (0.88), FI (0.55), and HOMA-IR (0.52)]. However, BMD failed to be significantly genetically correlated with MS-related traits. In summary, we found that BMC, BMD, and BA were under strong additive genetic influences, which also exhibited complex common genetic influences with certain MS-related traits.

1230-P

Traditional and Emerging Cardiovascular Risk Factors at 1 Year of Life in Infants Born to Women With and Without Gestational Diabetes

RAVI RETNAKARAN, CHANG YE, ANTHONY J. HANLEY, MATHEW SERMER, PHILIP W. CONNELLY, BERNARD ZINMAN, JILL HAMILTON, *Toronto, ON, Canada*

Compared to their peers, the offspring of women with gestational diabetes (GDM) exhibit an enhanced cardiovascular (CV) risk factor profile by as early as 6 years of age. It is not known, however, whether these risk factors are present in infancy or arise subsequently. Thus, in this prospective cohort study, we evaluated traditional (glucose, LDL, HDL, triglycerides) and emerging (CRP, adiponectin) CV risk factors at age 1 year in 104 term singleton infants of women with (n=36) and without GDM (n=68). At age 1 year, there were no differences between the GDM and non-GDM groups with respect to infant sex, ethnicity, breastfeeding, sum of skinfolds, BMI Z-score, and each of the traditional and emerging risk factors. On Spearman correlation analysis adjusted for infant age (Panel B), area-under-the-glucose-curve on the maternal antepartum oral glucose tolerance test was not correlated with any of these risk factors (with r values ~0). Furthermore, after adjustment for age, sex, ethnicity, and breastfeeding, there were no differences

in mean adjusted levels of any of the traditional or emerging risk factors between infants of women with GDM and their peers (Panel A). Indeed, in most cases, the mean adjusted values were almost identical in the 2 groups. In summary, differences in CV risk factor profile were not evident at 1 year of life between infants of women with and without GDM. These data support a model in which the offspring of women with GDM have a propensity for the early accrual of CV risk factors that begins to manifest between infancy and early childhood.

A:				B:	
	no GDM	GDM	p	r	p
Glucose	4.5	4.5	0.80	-0.13	0.19
LDL	2.67	2.59	0.55	0.01	0.95
HDL	1.12	1.17	0.30	0.03	0.74
Trig	1.16	0.96	0.07	-0.08	0.41
CRP	0.34	0.35	0.90	0.04	0.70
Adiponectin	21.0	20.1	0.52	-0.07	0.49

Supported by: CIHR

Clinical Diabetes/ Therapeutics
POSTERS

1231-P

Longitudinal Changes in Infant Body Composition and Childhood Obesity

MICHAELA B. KOONTZ, LARRAINE PRESLEY, PATRICK M. CATALANO, *Cleveland, OH*

Rapid infant weight gain has been associated with increased risk for obesity in later childhood and adulthood. However, the time frame during which rapid weight gain is most detrimental is unclear, and the contribution of fat mass (FM) vs lean mass (LM) accrual is unknown. We aimed to determine which time period during infancy is most predictive of later obesity, and to assess the roles of infant FM and LM accrual on developing later overweight/obesity (O/O). Sixty-four term infants were evaluated at birth, throughout infancy (4, 8, and 12 months), and in mid-childhood (age 8.8 ± 1.8 years). Infant FM and LM were assessed via total body electrical conductivity. Logistic regression was used to determine associations between rates of total weight gain, FM, and LM accrual for each time period and later O/O, adjusted for sex, race, age, parent education, birth fat mass, and birth lean mass (Table 1). At follow-up, 35% of children were O/O (defined as CDC BMI percentile ≥ 85%). More rapid total weight gain from 0-4 months (p=0.025) and 0-8 months (p=0.041), but not 0-12 months, was associated with higher odds of childhood O/O. Faster FM accrual from 0-8 months was significantly associated (p=0.035) with later O/O. In conclusion, the results suggest that rapid weight gain in earlier infancy, rather than over the entire first year, predicts mid-childhood O/O. FM accrual seems to contribute to this association more than LM accrual. Preventing childhood obesity requires further research to determine optimal infant feeding and growth patterns.

Table 1. Associations between total, fat, and lean mass accrual (expressed as 100 grams per month) during each infancy time period and overweight/obesity status in childhood. Adjusted for sex, race, age, parent education, birth fat mass, and birth lean mass.

	Odds Ratio	95% CI	p-value
0-4 months (n=37)			
Total weight gain (100 g/month)	2.79	1.14-6.83	0.025
Fat mass gain (100 g/month)	2.72	0.867-8.57	0.086
Lean mass gain (100 g/month)	3.47	0.752-160.24	0.111
0-8 months (n=30)			
Total weight gain (100 g/month)	23.72	1.13-505.48	0.042
Fat mass gain (100 g/month)	19.73	1.23-316.44	0.035
Lean mass gain (100 g/month)	14.51	0.816-258.19	0.069
0-12 months (n=28)			
Total weight gain (100 g/month)	3.90	0.681-22.28	0.126
Fat mass gain (100 g/month)	3.65	0.38-35.09	0.262
Lean mass gain (100 g/month)	20.04	0.66-613.66	0.086

Supported by: NICHD 22965

1232-P

A Locus on Chromosome 3 near CCNL1 is Associated With Newborn Adiposity

JEAN MORRISON, M. GEOFF HAYES, DOUGLAS SCHEFTNER, DAVID LEVINE, CAITLIN MCHUGH, LYNN LOWE, ANNA PLUZHNIKOV, MARGRIT URBANEK, LOREN ARMSTRONG, CHRISTINE ACKERMAN, DANIEL B. MIREL, KIM DOHENY, ALAN DYER, BOYD E. METZGER, NANCY COX, WILLIAM L. LOWE, JR., *Chicago, IL, Seattle, WA, Cambridge, MA, Baltimore, MD*

Higher levels of newborn fat may be associated with a later risk of childhood obesity and adult metabolic disease. Both maternal fuelsand genetic factors impact newborn adiposity. To begin to define the genetic architecture underlying newborn body fat and provide insight into the association between newborn adiposity and later risk of metabolic disease, we performed a genome wide association study using DNA and newborn sum of skinfolds (ssf), fat mass and birth weight of newborns inthe Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. DNA from 4,167 Thai, Afro-Caribbean, Northern European ancestry, and Mexican-American newborns was genotyped on Illumina 610 Quad and 1M platforms, and the four cohorts were imputed separately to a panelof 2.2 million SNPs using all HapMap II reference populations and BEAGLE software. Cohort-specific analyses were performed using linear regression with SNPTEST against an additive genotype variable followed by meta-analysis using METAL, weighting each cohort by samplesize. Three models which adjusted for an increasing number of clinical variables were used. The most stringent model, model 3, includedmaternal glucose and C-peptide levels during an OGTT at ~28 weeks gestation. A locus on chromosome 3 intergenic between *CCNL1* and *LEKR1* demonstrated association with sum of skinfolds. The major T allele of the lead SNP, rs17451107, was associated with higher ssf (p-values 1.49×10^{-11}, 2.24×10^{-11}, and 1.55×10^{-9} in models 1, 2 and 3,respectively). The magnitude of the association varied somewhat across the 4 populations (0.07 to 0.19 mm higher ssf per T allele). This same locus also showed marginal association with birth weight and fat mass ($p = 1.03 \times 10^{-6}$ and 5.44×10^{-7}, respectively) and was previously shown to be associated with birth weight in a large meta-analysis of Northern European ancestry populations. These data suggest that association of thelocus on chromosome 3 with birth weight may occur through an effect on newborn fat independent of maternal glucose levels.

1233-P

Gene Expression Changes following a Diabetes Prevention Program for Obese Latino Youth

DANIELLE N. MIRANDA, DAWN K. COLETTA, VALENTIN DINU, DARWIN TSINAJINNIE, ROCIO ORTEGA, JUSTIN RYDER, LAWRENCE J. MANDARINO, GABRIEL Q. SHAIBI, *Scottsdale, AZ, Tempe, AZ*

Obesity and type 2 diabetes disproportionately affect Latino youth. Although lifestyle interventions can improve obesity-related health risk factors, few studies have examined the biological mechanisms contributing to these health improvements. Therefore, the purpose of this study was to explore biological pathways associated with intervention-induced improvements in whole body insulin sensitivity. Fifteen (7M/8F) overweight/obese (BMI percentile = 96.4±4.5) Latino adolescents (15.0±1.0 years) completed a 12-week lifestyle intervention that included weekly nutrition education classes and 180 minutes of moderate to vigorous exercise per week. Insulin sensitivity, estimated by OGTT using the Matsuda Index, increased 29.2% post intervention (2.4±0.3 to 3.1±0.4, p=0.01). Global microarray analysis profiling using mRNA from whole blood was performed to examine the gene expression response. Fasting blood samples were collected in PAXgene blood RNA tubes for RNA isolation. Gene expression profiles were generated using Agilent whole human genome 44K Microarrays. Expression values were analyzed using GeneSpring to identify genes, and Ingenuity Pathway Analysis was used to explore biological pathways that were significantly changed in response to the intervention. A total of 1,408 probes were differentially expressed (fold change >1.5, P <0.05). Among the genes identified were AKT1, G6PC3, NFATC2, PNPLA3, and TUB. There were 18 pathways identified that met the criteria for significance, including linoleic acid metabolism, starch and sucrose metabolism, actin cytoskeleton signaling, and FXR/RXR activation. Improvements in insulin sensitivity following a lifestyle intervention are associated with changes in individual genes. These pathways may offer insight into the mechanisms underlying type 2 diabetes among high-risk Latino youth.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

1234-P

Correlations of Advanced Glycation End Products and their Receptors With Adiposity and Adiposity-Related Co-Morbidity Risk are Different in Children than in Adults

SIHAM ACCACHA, LISA ALTSHULER, CLAUDIA BOUCHER-BERRY, DENIS CAREY, RUSHIKA CONROY, DEBORAH DESANTIS, ILENE FENNOY, MICHELLE KLEIN, ALAN JACOBSON, BARBARA LOWEL, LESLY MICHEL, SHAHID MALIK, ROBERT RAPAPORT, WARREN ROSENFELD, STEVEN SHELOV, PHYLLIS SPEISER, SVETLANA TEN, MICHAEL ROSENBAUM, *Mineola, NY, Brooklyn, NY, New Hyde Park, NY, New York, NY*

Advanced glycation end-products (AGE) and their receptors (RAGE) play important roles in the development of adiposity-related co-morbidities in adults. However their role has not been clarified in children. We compared concentrations of the AGE carboxymethyllysine (CML), soluble RAGE (sRAGE), and endogenous secretory RAGE (esRAGE) with adiposity, waist circumference, inflammatory markers (IL-6, CRP, and TNF-alpha), the anti-inflammatory cytokine ACRP30, lipids (cholesterol, triglycerides, HDL, LDL), insulin sensitivity, (Quantitative Insulin Sensitivity Check Index, QUICKI), insulin secretory capacity [acute insulin response (AIR, mean rise in insulin 3 and 5 minutes after iv dextrose) and glucose disposal index (GDI, AIR corrected for insulin sensitivity)] in 87 children age11-15 yrs (37 F, 50 M) enrolled in the Reduced Obesity and Diabetes (ROAD) study . CML correlated positively with age and insulin sensitivity (QUICKI) and negatively with adiposity (% fat and fat mass), dyslipidemia (LDL-cholesterol) and inflammation (IL-6). sRAGE correlated positively with esRAGE and negatively with adiposity (weight, BMI, fat mass), and inflammation (IL-6). Both sRAGE and esRAGE correlated negatively with AIR even when corrected for adiposity. All correlations were reported as significant at $p < 0.05$. No significant gender differences were detected in CML, sRAGE, or esRAGE levels. Our findings suggest that unlike adults, CML in children is negatively associated with adiposity and adiposity-related co-morbidity risk. As in adults, sRAGE and esRAGE were, to varying degrees, negatively correlated with body fatness and risk factors for adiposity-related co-morbidities (dyslipidemia, inflammation, and type 2 diabetes). CML levels in these students (mean±sem = 423±16 ng/ml) were ~20% below average adult levels ($p<0.001$) which may account for the age-related differences in correlational analyses.

Supported by: Academy for Medical Development and Collaboration (AMDeC)

1235-P

Expression Analyses of the Genes Harbored by the Type 2 Diabetes and Pediatric BMI Associated Locus on 10q23

JIANHUA ZHAO, SANDRA DELIARD, ALI R. AZIZ, STRUAN F. GRANT, *Philadelphia, PA*

There is evidence that one of the key type 2 diabetes (T2D) loci identified by genome wide association studies (GWAS) exerts its influence early on in life through its impact on pediatric BMI. This locus on 10q23 harbors three genes, namely HHEX, IDE and KIF11. We analyzed the impact of adipogeneis on the mRNA and protein expression levels of these genes in the human adipocyte cell line, SGBS, in order to investigate which could be the culprit gene(s) in this region of linkage disequilibrium. Following activation of differentiation with a PPARγ ligand, we observed ~20% decrease in IDE, ~40% decrease in HHEX and in excess of 80% decrease in KIF11 mRNA levels when comparing the adipocyte and pre-adipocyte states. We also observed decreases in KIF11 and IDE protein levels, but conversely we observed a dramatic increase in HHEX protein levels. Subsequent time course experiments revealed marked changes in expression as early as three hours after activation of differentiation. Our data suggest that the expression of all three genes at this locus are impacted during SGBS adipogenesis and provides insights in to the possible mechanisms of how the genes at this 10q23 locus could influence both adipocyte differentiation and susceptibility to T2D through insulin resistance.

Supported by: NIH (R01 HD056465)

1236-P

High Rate of Dyslipidemia Without Obesity in Indigenous Argentinian Children Living at High Altitude

VALERIA HIRSCHLER, GUSTAVO MACCALLINI, CLAUDIO ARANDA, CLAUDIA MOLINARI, SAN ANTONIO DE LOS COBRES STUDY GROUP, *Buenos Aires, Argentina*

Background: Pima Indians are a population in the USA with a high prevalence of T2DM. However, Koya Indians, a South-American Indian population, have never been studied.Objectives: (1) to compare the prevalence of cardiovascular diseases (CVD) risk factors in Koya Indian children from San Antonio de los Cobres (SAC) and children from Buenos Aires (BA) and (2) to examine body mass index (BMI), waist circumference (WC) and WC/height as predictors of dyslipidemia in both groups.Methods: Data were collected cross-sectionally from BMI, WC, blood pressure, Tanner, glucose, lipids, and insulin. Dyslipidemia was defined by the NCEP (National Cholesterol Education Program) and AHA (American Heart Association).Results: The mean ages were 10.6 ± 3.0 years and 9.5 ± 2.0 years of SAC and BA children respectively. Of the 603 BA children, 97 (16.1%) were overweight (OW) and 82 (13.6%) obese (OB), and of the 330 SAC children, 15 (4.5%) were OW and 12 (3.6%) OB, per CDC norms ($p<0.01$). There was a significantly higher prevalence of high triglycerides (28.8 vs. 3.5% $p<0.01$) and low HDL-C (30.0% vs. 5.5%;$p<0.01$) in SAC vs. BA children. The areas under the receiver operator characteristic curves (AUROC) in predicting high triglycerides were BMI = 0.65 (95% CI 0.52-0.77; $p=0.02$) in BA, and BMI = 0.55 (95% CI 0.48-0.62; $p=0.15$) in SAC children. Similar results from the AUROC were obtained when low HDL-C (<35 mg/dL), was used as the dichotomous variable, indicating that BMI was not a significant predictor for dyslipidemia in SAC children. When BMI was replaced by WC and WC/height, results were similar.Conclusions: We found that SAC children had a lower prevalence of obesity and a higher prevalence of dyslipidemia than BA children. Anthropometric markers were not an acceptable predictor for NCEP cutoffs for dyslipidemia in SAC children. Future longitudinal studies should determine if SAC children are at high risk for CVD due to genetic background or if the cutoffs proposed by the NCEP do not apply for this community.

1237-P

Insulin Resistance Does Not Have a Negative Impact on the Growing Bones of Healthy Children—A 6y Longitudinal Study

ADAM J. STREETER, BRAD S. METCALF, JOANNE HOSKING, ALISON N. JEFFERY, MOHAMMOD B. MOSTAZIR, LINDA D. VOSS, TERENCE J. WILKIN, *Plymouth, United Kingdom*

Osteoporosis and obesity share a common progenitor cell and osteoporosis has been dubbed 'obesity of the bone'. Indeed osteoporosis is a well-recognised co-morbidity of diabetes, itself largely attributable to obesity. Low peak bone mass is an important determinant of osteoporosis, but there is little information on the impact of body composition and metabolic health on bone growth in children. We hypothesised insulin resistance (IR) would be associated with lower BMD.The relationships between bone mineral density (BMD by DEXA), body mass index (BMI sds) and insulin resistance (by HOMA2), log transformed (lnIR), were investigated annually from 9-14y in a cohort of 307 healthy children.BMD rose with age in both genders ($r=0.79$, $p<0.001$). Age-related trends for BMI ($r=0.36$,$p<0.001$) and lnIR ($r=0.25$,$p<0.001$) were weaker, but clear. In boys the rise in lnIR was monotonic, but in girls it appeared to flatten after 11y. 5% of children were obese at 14y.The effect of BMIsd and lnIR on BMD was explored through response-profile modelling, controlling for age-related growth and age-standardised height (see table). There was a positive association between BMD and BMIsd, which remained after controlling for lnIR. A positive association between BMD and lnIR in boys disappeared after adjustment in the model for BMIsd. There was still no effect of lnIR on BMD in either gender, even after standardising lnIR for BMI to mitigate multicolinearity.

Modelled variables, adjusting for age-related growth & age-adjusted height		Girls		Boys	
		Coefficient	p-value	Coefficient	p-value
BMIsd		0.013	<0.001***	0.009	<0.001***
lnIR		-0.0004	0.82 (n/s)	0.004	0.003**
BMIsd +lnIR	BMIsd	0.012	<0.001***	0.009	<0.001***
	lnIR	-0.003	0.12(n/s)	0.003	0.07 (n/s)
BMIsd + lnIR(BMIadj)	BMIsd	0.012	<0.001***	0.009	<0.001***
	lnIR (BMIadj)	-0.003	0.12(n/s)	0.003	0.07 (n/s)

In conclusion, BMD is higher in fatter children but, once fatness has been accounted for, insulin resistance has no adverse effect on their bone density.

1238-P

Thyroid Stimulating Hormone Within the Normal Range is Associated With Metabolic Abnormalities in Obese Children and Adolescents

NALINI N. RADHAKISHUN, MARISKA VAN VLIET, INES A. VON ROSENSTIEL, OLIVIER WEIJER, JOS H. BEIJNEN, DEES P. BRANDJES, MICHAELA DIAMANT, *Amsterdam, The Netherlands*

The relationship between thyroid function and obesity-related risk factors has been previously reported in adults. However, only few data are available

for pediatric populations. In the present study we investigated the association between normal-range variables of thyroid function and cardiometabolic risk factors in obese children and adolescents. A retrospective analysis of patient records was performed from 703 obese (Z-BMI>2.3) euthyroid children and adolescents from multi-ethnic origin (48% boys; 24.6% of Turkish, 25.0% of Moroccan, 15.5% of Dutch and 8.0% of African descent; mean age 10.7±3.3 years, mean Z-BMI 3.3±0.6), who visited the obesity-outpatient clinic in an urban general hospital in Amsterdam. We performed anthropometric measurements, an oral glucose tolerance test, and measured serum thyroid stimulating hormone (TSH), lipid levels and alanine aminotransferase (ALT), a marker of hepatic steatosis.TSH levels in the upper limit of normal (4.0-6.5 mU/L) were present in 10.7%. All individuals with TSH in the normal range (0.4-6.5 mU/L) were included in the current analysis. In linear regression analysis, a positive association between TSH (beta 0.134, *P*= 0.05) and Z-BMI was observed. Logistic regression analysis showed a significant association between TSH and glucometabolic disorders (OR 1.28, 95% CI 1.09-1.50), high total cholesterol (OR 1.23, 95% CI 1.01-1.48) and high triglycerides (OR 1.25, 95% CI 1.07-1.47). No significant results were found for the association between TSH and elevated ALT, low high-density lipoprotein-cholesterol or hypertension. These results were independent of ethnic background.In this multi-ethnic cohort of obese children and adolescents, TSH in the normal range was associated with Z-BMI and several metabolic abnormalities. Additional studies are needed to determine the prognostic value of childhood thyroid function and its course on cardiometabolic health in adult life.

1239-P

Gender-Assortative Waist Gain and its Metabolic Impact in Mother-Daughter and Father-Son pairs: A 10-Year Longitudinal Study of Trios

MOHAMMOD B. MOSTAZIR, BRAD S. METCALF, JOANNE HOSKING, ADAM J. STREETER, ALISON N. JEFFERY, LINDA D. VOSS, TERENCE J. WILKIN, *Plymouth, United Kingdom*

Previous studies suggest that contemporary weight (BMI) gain in children is largely gender assortative (mother-daughter, father-son). However, abdominal adiposity, measured as waist circumference (WC) appears to be a better marker for metabolic risk than BMI, so we explored WC and its impact on metabolic risk over time in a cohort of 224 trios - mother (M), father (F) and child, from 5-15y.Childhood WC was expressed as sds relative to the 1990 UK standards. Parents' WC, measured at baseline, was categorised according to the 1998 WHO standards as Normal Risk (NR) <94cm (female <80cm), Increased Risk 94cm~<102cm (Female 80cm~=102cm (Female >=88cm). A height-adjusted WC index (WCi, cm/m2) was derived in the children, and one-way ANOVA used to compare group means of WCi for each time point. Linear mixed model was used to assess the change in WCi, controlling for the random effects of age and height. Fixed effects included age, height, birth weight, gestational period and parents' WC.Mean WC sds was significantly higher at all time points in the daughters of SR mothers (p<.01) and sons of SR fathers (p<0.05). In a fully adjusted model, and compared with NR parents, 1cm increase in WC of SR M was associated with 3.1 WCi units (p1.2 WCi units (p<.05) among the sons (but not daughters). Mixed models confirmed that the sons (but not daughters) of SR F and the daughters (but not sons) of SR mothers have higher waist- hip ratio, leptin, and lower SHBG (all p<.05).The findings suggest that childhood WC is gender assortative, and associated with metabolic risk. Early parental behaviour (role-modelling) may be an explanation. Given that obesity is commoner in adults than children, and that parental obesity precedes that of their children, there may be more metabolic benefit in targeting the WC of parents-to-be than the WC of children.

PEDIATRICS—TYPE 1 DIABETES

Guided Audio Tour: Pediatric Type 1 Diabetes—Blood, Brains, and Guts *(Posters 1240-P to 1247-P), see page 13.*

1240-P

Counterregulatory Hormone Responses in Youth With Short Duration of Type 1 Diabetes

ANA MARIA ARBELAEZ, EVA TSALIKIAN, NELLY MAURAS, DARRELL M. WILSON, WILLIAM TAMBORLANE, JENNIFER SHERR, DONGYUAN XING, CRAIG KOLLMAN, KATRINA RUEDY, PHILIP E. CRYER, NEIL H. WHITE, DIABETES RESEARCH IN CHILDREN NETWORK (DIRECNET), *St. Louis, MO, Iowa City, IA, Jacksonville, FL, Stanford, CA, New Haven, CT, Tampa, FL*

Hypoglycemia is a limiting factor in achieving optimal glycemic control of type 1 diabetes (T1D). Prevention and recognition of hypoglycemia depend on counterregulatory (CR) hormone (glucagon [GON] and epinephrine (EPI]) responses as well as sympathoadrenal-mediated awareness of hypoglycemia. Those with blunted responses to hypoglycemia are at an increased risk for severe hypoglycemia. We studied CR hormone responses to hypoglycemia during hyperinsulinemic (2.0 mU.kg^{-1}·min.$^{-1}$) euglycemic (5.2 mM) followed by hypoglycemic (3.0 mM) clamps in 15 adolescents (9-17 yrs old, mean±SD 13.0±3.1 yrs) at baseline (BL; 7-51 weeks after diagnosis), and 1 yr later, and in 16 older nondiabetic controls (CONT, 23.3±1.8 yrs). Median, quartiles and range of peak (p) and increases (Δ) of plasma GON (n=12) and EPI (n=16) during hypoglycemia at BL and 1 yr in T1D and in CONT were:

	pGON (pg/mL)	ΔGON (pg/mL)	pEPI (pg/mL)	ΔEPI (pg/mL)
	Median (quartiles) [Range]			
T1D-BL	50 (39, 72)*[26-85]	20 (14, 27][0-39]	747 (248, 948][28-1485]	719 (228, 915][17-1451]
T1D-1 yr	49 (42, 66)* [30-85]	12 (8, 18]*[1-35]	529 (305, 656) [29-1302]	462 (292, 621) [9-1255]
CONT	93(60, 111][47-189]	38(19, 66][11-122]	383 (329,493) [186-669]	336(298, 471][166-656]

* p<0.01 T1D vs CONT; BL and 1 yr not significicantly different for any of these values

In 2 T1D subjects, ΔGON could not be determined at BL since the starting value was <20 pg/mL. Three (23%) and 6 (40%) had ΔGON of <11 (the lowest value in CONT) at BL and 1 yr, respectively. Three (20%) and 1 (7%) had a ΔEPI <166 (the lowest value in CONT), respectively. Two subjects at BL and 1 at 1 yr had low ΔGON *and* low ΔEPI suggestive of defective glucose counterregulation. Early in T1D in youth, during the "honeymoon" period when hypoglycemia is relatively infrequent, glucagon responses to hypoglycemia are blunted but epinephrine responses are not. Avoidance of hypoglycemia, which would reduce sympathoadrenal responses to subsequent hypoglycemia and thus cause defective glucose counterregulation and hypoglycemia unawareness, is an important target even early in T1D.

1241-P

Transient False Positive Elevations of Antibody Markers of Celiac Disease at the Onset of Diabetes

SATYA SHANMUGHAM, BRUCE BUCKINGHAM, *Stanford, CA*

As part of the Pediatric Diabetes Consortium, patients with T1DM were enrolled in a database that included information on whether a celiac disease screen was obtained at onset of diabetes. At Stanford, 10 of 142 patients had positive antibodies at diagnosis (7%), all had IgA tissue transglutaminase antibodies (TTG) and 8 also had deamidated gliadin peptide (DGP) IgA measurements. All of these 10 patients had normal IgA levels and minimal acidosis at diagnosis (mean HCO_3= 21 mEq/L (range: 18 to 29). Three patients were confirmed to have celiac disease with positive small bowel biopsies (SBB). Two of these patients were tested for DGP antibodies, and 1 was strongly positive. One patient with a positive TTG (46 u/mL) was lost to follow-up. Six patients with positive IgA TTG antibodies were subsequently found to have negative repeat antibody tests, and 3 had SBB that were normal. DGP antibodies were negative in 4 of these 5 patients. Patients with transient IgA TTG antibodies had low titers (≤ 35 u/mL), and the one positive DGP antibody was also a low titer (22 u/mL).

	n	TTG Mean u/mL (range)	DGP u/mL	SBB n
Transient Positive Celiac Screen	6	32 (28-35) N=6	4 negative 1 positive = 22	3 (all negative)
Biopsy-proven Celiac	3	104 (46-192) N=3	1 negative 1 positive = 221	3 (all positive)

There is a high incidence of false positive celiac screening tests at the time of diagnosis of diabetes using a TTG antibody assay, and these patients have low levels of antibody positivity. The presence of these low titer antibodies does not appear to be related to severity of ketoacidosis. We would recommend initial screening for celiac disease is delayed until the 3-month visit unless there are clinical symptoms to warrant earlier screening.

1242-P

White Matter Microstructural Integrity in Youth With T1DM

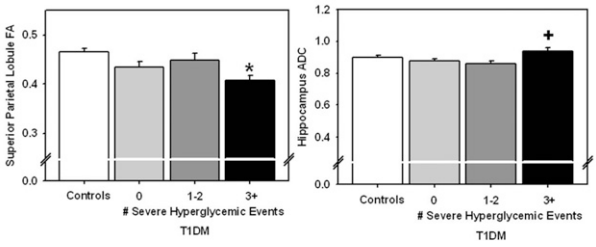
JO ANN ANTENOR-DORSEY, ERIN MEYER, JERREL RUTLIN, DANA C. PERANTIE, NEIL H. WHITE, JOSHUA SHIMONY, TAMARA HERSHEY, *St. Louis, MO*

Hyperglycemia is hypothesized to affect white matter (WM) integrity in the developing brain. We and others have seen decreased white and gray matter volumes in the occipital-parietal cortex in T1DM and this appear to be related to hyperglycemia exposure. Based on human and animal work,

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

we hypothesized that WM in the superior parietal lobule (SPL) and the hippocampus is altered in T1DM. We examined the microstructural integrity of WM in these *a priori* brain regions, as well as ten other exploratory regions, in a large sample of youth with T1DM (n=73; mean age=16.8±2.9) and their non-diabetic sibling controls (n=30; mean age=15.9±3.4) using diffusion-weighted magnetic resonance images. Lifetime median HbA1c weighted for T1DM duration was calculated (hyperglycemia exposure) and the numbers of severe hyperglycemia- and hypoglycemia-related episodes were obtained from patients' medical records and by interviews. Univariate analyses or hierarchical linear regressions were performed controlling for the effects of age and gender. The T1DM group had lower Fractional Anisotropy (FA; indicates directionality of water molecule movement) in the SPL and reduced Apparent Diffusion Coefficient (ADC; indicates mean degree of water molecule movement) in the thalamus compared to controls. A history of 3+ severe hyperglycemic episodes was associated with reduced FA in the SPL and increased ADC in the hippocampus (Fig 1). These results add microstructural integrity of WM to the types of alterations seen in the SPL in T1DM. Longitudinal analyses will be necessary to determine how these alterations change with additional diabetes exposure or age.

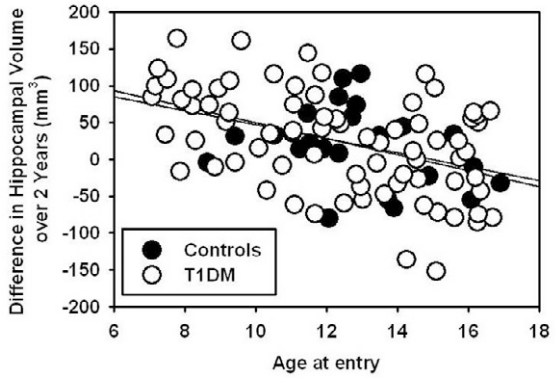


1243-P

Hippocampal Development in Youth With Type 1 Diabetes Mellitus (T1DM)

HEATHER LUGAR, MICHAEL MURRAY, JONATHAN KOLLER, NEIL H. WHITE, TAMARA HERSHEY, *St. Louis, MO*

Hippocampal gray matter may be vulnerable to both severe hypoglycemia and hyperglycemia, and may be more sensitive to during the brain development. However, there are no longitudinal, prospective data on hippocampal volume in youth with T1DM. The goal of this analysis was to determine if hippocampal volumes follow the typical developmental trajectory over childhood in T1DM, and whether they are affected by severe hypoglycemia or chronic hyperglycemia. T1-weighted magnetic resonance images were acquired in 77 youth with T1DM and 24 healthy sibling controls at entry to the study (ages 6-17; T1DM mean age=12.3, SD=2.9; Control mean age=12.7, SD=2.3) and two years later. T1DM youth were categorized as having had either 0 (n=58) or >0 (n=19) severe hypoglycemic episodes during follow-up; HbA1c values were averaged over follow-up. Freesurfer-generated hippocampal volumes were generated from scans at both time points and validated against gold-standard stereologic measurements from scans at entry. We found a strong effect of age at study entry on change in hippocampal volumes over the subsequent two years (p=.005; Fig 1). Diagnosis of T1DM (vs controls), prospectively ascertained episodes of severe hypoglycemia and chronic hyperglycemia did not alter hippocampal development over the follow-up period. We conclude that hippocampal volume develops normally in T1DM over the age range, time interval and degree of glycemic exposure we studied.



Supported by: R01 DK064832

1244-P

Structural MRI Shows Neuroanatomical Differences In Very Young Children With T1 Diabetes (T1D)

NELLY MAURAS, MATT MARZELLI, NAAMA BARNEA-GORALY, PAUL K. MAZAIKA, TAMARA HERSHEY, NEIL H. WHITE, EVA TSALIKIAN, TANDY AYE, STUART WEINZIMER, ROY BECK, KATRINA RUEDY, ALLAN REISS, DIABETES RESEARCH IN CHILDREN NETWORK (DIRECNET), *Jacksonville, FL, Stanford, CA, St. Louis, MO, Iowa City, IA, New Haven, CT, Tampa, FL*

Deleterious effects of hypoglycemia on the brain (e.g. hippocampus) have been demonstrated in animal models and humans, and hyperglycemia can also adversely affect neurodevelopment, particularly white matter. We sought to characterize neuroanatomical differences in very young (4- 9 y/o) children with T1D vs healthy controls. Unsedated high resolution brain MRIs were performed using 3T Siemens TimTrio scanners at 5 clinical centers. Volumetric and voxel-based morphometric (VBM) analyses were performed using *Freesurfer* 5.1 and *SPM8* software, respectively. ANCOVA models were utilized with group and sex as main effects, total cerebral gray, white or tissue volume and age as covariates. From 178 children scanned volumetric data were available on n=162 (98 T1D), and n=135 (85 T1D) for whole brain VBM. Mean ages were: 6.9 ± 1.5 yrs- T1D, 7.1 ± 1.7 yrs -controls, A1c: 7.8% ± 0.8 and 5.1 ± 0.2 respectively. There were no significant differences comparing T1D subjects vs controls in total cerebral grey matter volume (GMV), white matter volume (WMV), or left and right hippocampal volumes. However, VBM, which permits more granular analysis, showed significantly increased GMV in T1D subjects bilaterally in superior, middle and orbital-frontal gyri (p=0.003), and decreased GMV most prominently bilaterally in parietal and occipital cortices (p=0.004), including cuneus, precuneus, calcarine, lingual gyrus, cingulate and cerebellum. Similarly, decreased WMV was observed bilaterally in T1D subjects relative to controls (p=0.002) in subcortical regions including the putamen-pallidum, internal capsule, thalamus, pons, midbrain and cerebellum.These preliminary results demonstrate significant neuroanatomical differences in multiple specific brain regions in very young children with T1D. Ongoing analysis of the association of these structural changes with chronic dysglycemia and glucose variability will better allow us to understand possible mechanisms underlying these observations.

1245-P

Pilot Study of Autologous Umbilical Cord Blood (UCB) Transfusion Followed by Docosahexanoic Acid (DHA) and Vitamin D (VitD) Supplementation in Children With Type 1 Diabetes (T1D)

MICHAEL J. HALLER, CLIVE H. WASSERFALL, KIERAN MCGRAIL, MIRIAM CINTRON, TODD M. BRUSKO, WILLIAM SLAYTON, MICHAEL J. CLARE-SALZLER, JOHN R. WINGARD, MARK A. ATKINSON, DESMOND A. SCHATZ, *Gainesville, FL*

Autologous UCB infusion fails to preserve C-peptide in children with T1D. We conducted a randomized open label pilot study to determine if UCB infusion combined with one year's supplementation of daily DHA(38mg/kg) and VitD(2,000IU) would synergistically restore adaptive immune regulation, prevent innate inflammation, and preserve C-peptide. Ten children with T1D received autologous UCB, DHA, and VitD and 5 children were controls. No adverse events were observed. Primary analysis was 1 year post-infusion. Results are provided in the table.

	Treated			Controls			P Value comparison of changes: 1 year minus screen between groups
	Screen	1 year	P Value for Δ at 1 year	Screen	1 year	P Value for Δ at 1 year	
Age (yrs)	7.2	—	—	6.6	—	—	—
HbA1c (%)	7.4	7.3	0.4	6.9	7.3	0.4	0.31
Insulin Dose (units/kg/d)	0.37	0.65	0.001	0.3	0.7	0.001	0.18
AUC C Peptide (pmol/ml/120min)	0.38	0.13	0.01	0.51	0.18	0.002	0.29
Vitamin D (ng/mL)	31	39	0.16	40	24	0.05	0.01
Regulatory T Cells (%)	4.05	4.05	0.99	4.18	2.74	0.3	0.3
CD4:CD8	2.3	2.3	0.96	2.5	1.9	.02	0.03

While the absolute rate of C-peptide decline was slower in treated vs control subjects, intergroup comparisons failed to reach significance (P=0.29). As expected, AUC C-peptide declined and insulin use increased in both groups

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

(P= <0.01). VitD levels remained stable in treated subjects but declined in controls (P=0.01 between treatments). Similarly, CD4:CD8 ratio remained stable in treated subjects but declined in controls (P=0.03 between treatments). No changes were seen in regulatory T cell number, total CD4 count, or autoantibody titers at 1 year. DHA and cytokine measurements of innate inflammation are pending.UCB based pilot studies have yet to demonstrate efficacy but continue to support the feasibility and safety of autologous UCB therapy. Future efforts to demonstrate efficacy require larger patient cohorts, isolation and expansion of specific immunoregulatory cell subsets, and optimization of the immunoregulatory and anti-inflammatory effects of VitD and DHA.

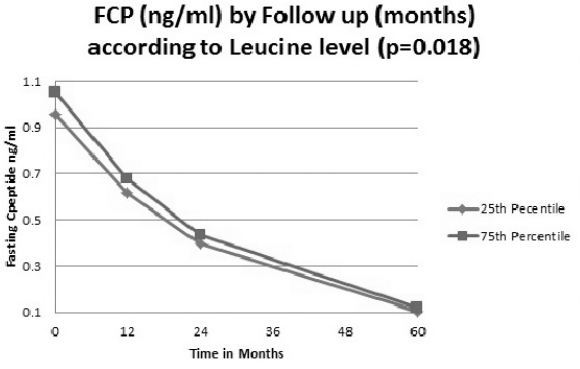
Supported by: JDRF

1246-P

The Branched Chain Amino Acid Leucine is Associated With Insulin Secretion Among Youth With Type 1 Diabetes (T1D): SEARCH for Diabetes in Youth

ELIZABETH MAYER-DAVIS, RALPH B. D'AGOSTINO, JR., DANA DABELEA, LAWRENCE M. DOLAN, JEAN M. LAWRENCE, CATHERINE PIHOKER, *Chapel Hill, NC, Winston-Salem, NC, Aurora, CO, Cincinnati, OH, Pasadena, CA, Seattle, WA*

Preservation of insulin secretion following a T1D diagnosis predicts better health outcomes. Leucine has been shown to stimulate insulin secretion. We evaluated leucine intake (measured by food frequency questionnaire) and fasting c-peptide (FCP) in SEARCH participants using data from baseline, 12-, and 60-mo visits. Participants were 367 youth [baseline: mean age, 13.6 yr (SD 2.4); mean duration, 8.3 mo (SD 5.8)] who had a diagnosis of T1D, ≥ 1 diabetes autoantibody present, age ≥ 10yrs, and baseline FCP≥0.23 at baseline, which is the Diabetes Control and Complications Trial (DCCT) cut-point for preserved beta cell function.Adjusted for total energy, baseline leucine was positively associated (r=0.33) with FCP at baseline (p<0.0001). In mixed effects regression models to account for repeated measures, with additional adjustment for demographics, duration, HLA-risk, insulin regimen, BMI-z score, insulin sensitivity score and saturated fat intake, baseline leucine was significantly positively associated with time-varying FCP (p=0.018; Figure). Time-varying leucine was added to the model and baseline leucine remained significant in relation to time-varying FCP (p=0.003). Likely due to the very minimal change in leucine intake over time (mean 1.28% kcal at baseline, 1.27% kcal at 60 mo), time-varying leucine was not significant in the fully adjusted model.In summary, higher intake of leucine is associated with higher insulin secretion following diagnosis of T1D in youth. Further research is needed to evaluate whether supplemental leucine would be beneficial.



Supported by: The CDC with support from the NIDDK

1247-P

Persistence of Prolonged C-Peptide Production in Type I Diabetes in Patients With Advanced Disease

DENISE L. FAUSTMAN, LIMEI WANG, NICHOLAS F. LOVEJOY, *Charlestown, MA*

Current evidence suggests that even modest levels of beta-cell function are associated with lower rates of hypoglycemia and lower incidence of retinopathy and nephropathy in patients with longstanding disease. Using an ultrasensitive assay, we examined the persistence of C-peptide production years after type 1 diabetes onset and factors associated with preservation of beta-cell function. Serum C-peptide level, a marker of insulin production and surviving beta-cells, was measured in human subjects (n = 182) by ultrasensitive assay (lower detection limit: 1.5 pmol/L). Disease duration, age at onset, age, sex, and autoantibody titers were analyzed by regression analysis to determine their relationship to C-peptide production. A separate patient group (n=4) was serially studied for up to 20 weeks to examine C-peptide levels and beta-cell functioning. The ultrasensitive assay detected C-peptide in 10% of individuals 31-40 years after disease onset. Those with levels as low as 2.8+/-1.1 pmol/L responded to hyperglycemia with increased C-peptide production, indicating intact beta-cell functioning. Disease duration and level of zinc transporter 8 autoantibodies were significantly associated with C-peptide production. Unexpectedly, disease onset after age 40 was associated with low C-peptide production, despite shorter disease duration. The ultrasensitive assay, 22x more sensitive than current standard assays, revealed that C-peptide production persists for decades after disease onset and remains functionally responsive. These findings suggest that patients with advanced disease, whose beta-cell function was thought to have long ceased, may benefit from interventions that preserve or stimulate beta-cell function.

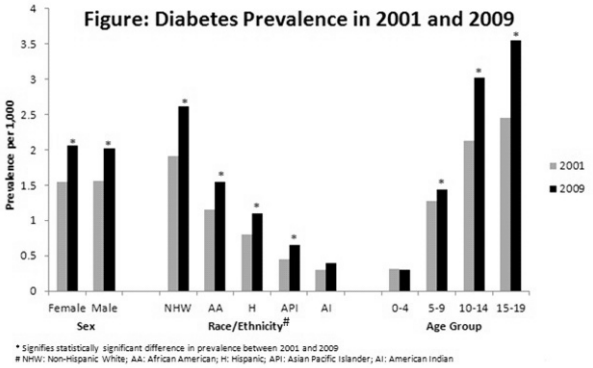
Guided Audio Tour: Pediatric Type 1 Diabetes—Complications and Health Care Delivery *(Posters 1248-P to 1255-P), see page 13.*

1248-P

Increase in Prevalence of Type 1 Diabetes from the SEARCH for Diabetes in Youth Study: 2001 to 2009

ELIZABETH MAYER-DAVIS, DANA DABELEA, JENNIFER W. TALTON, RICHARD F. HAMMAN, JASMIN DIVERS, ANGELA BADARU, TESSA L. CRUME, LAWRENCE M. DOLAN, GIUSEPPINA IMPERATORE, JEAN M. LAWRENCE, ANGELA D. LIESE, BARBARA LINDER, SHARON SAYDAH, FOR THE SEARCH FOR DIABETES IN YOUTH STUDY GROUP, *Chapel Hill, NC, Denver, CO, Winston-Salem, NC, Aurora, CO, Seattle, WA, Cincinnati, OH, Atlanta, GA, Pasadena, CA, Columbia, SC, Bethesda, MD*

Evidence of an increase in the incidence of type 1 diabetes (T1D) has emerged from around the world, suggesting that prevalence may also have increased. To estimate prevalence, SEARCH identified and validated reports of physician-diagnosed T1D cases among youth age < 20 years, with cases ascertained from a network of providers in defined geographic regions in Ohio, Colorado, Washington and South Carolina. Denominators were projected from age-, race- and gender-specific population counts for youth < 20 yrs old using vintage 2000 US census data. Methods were the same for 2001 and 2009 estimates, including a 22 month case ascertainment period for each year. Race/ethnicity was based primarily on self-report, with data from medical records or geocoding used when self-report was not available. In 2001, 3925 cases were identified from a population of over 2.5 million; in 2009, 5392 cases were identified from a population of over 2.6 million. From capture-recapture analyses, case ascertainment completeness was estimated to be 93% in 2001 and 99% in 2009. Prevalence (cases/1000) was 1.55 (95% CI, 1.5, 1.6) in 2001 and was 2.04 (95% CI 1.99, 2.1). After adjustment for completeness of ascertainment, prevalence for 2001 and 2009 respectively was 1.67 (95% CI, 1.62, 1.72) and 2.06 (95% CI, 2.01, 2.12). Prevalence increased in all gender, age and race/ethnicity subgroups except for the two subgroups with the lowest prevalence (youth age 0-4 yrs, and American Indians; see Figure). These results show a striking 23% increase in the burden of T1D among youth in the US, which likely reflects increases in disease incidence over recent years.



Supported by: SEARCH is funded by the CDC with support from the NIDDK

For author disclosure information, see page 797.

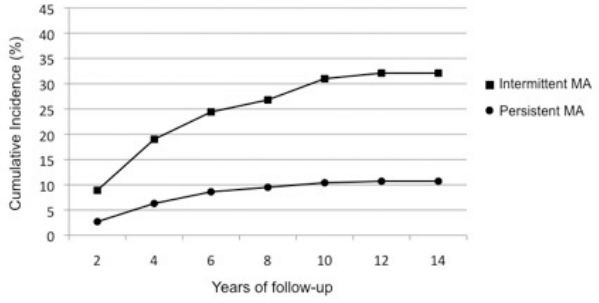
Guided Audio Tour poster ADA-Funded Research

1249-P

Cumulative Incidence (CI) of Microalbuminuria (MA) in Youth-Onset Type 1 Diabetes (T1D) Remains High in Current Era

CIELO R. ALLEYN, LISA K. VOLKENING, MICHELLE L. KATZ, LORI M. LAFFEL, *Boston, MA*

With modern intensive therapy, glycemic control has improved and rates of microvascular complications have declined. In order to assess development of early renal disease in contemporary patients with T1D, we determined CI of MA in 336 youth previously classified as normoalbuminuric (NL) during a 2 year baseline period. Spot urines were analyzed for albumin/creatinine (Alb/Cr). BP and A1c were averaged over the 2 year baseline and during follow-up (F/U). MA, based on Alb/Cr ≥20 µg/mg, was defined as persistent (PMA) with ≥2 elevations or intermittent (IMA) with 1 elevation over a 2 year F/U period.During baseline, youth (47% male) had a mean (±SD) age of 14.3±2.4 years, T1D duration of 7.1±3.1 years, BP of 108±8/67±5, and A1c of 8.6±1.1%. Youth, providing 2091 urine samples, were followed for 7.5±3.1 years (range 0.2-12.6) until age 21.8±3.3 and T1D duration of 14.6±4.1. During F/U, mean BP was 121±8/73±5 and A1c was 8.7±1.1%.During F/U, most youth (68%) remained NL while 11% developed PMA and 21% had IMA (see figure). The PMA group had longer T1D duration (15.9±4.4) than the NL group (14.3±4.1) (p<.03); IMA group was intermediate. During F/U, A1c was higher in PMA (9.5±1.2%) and IMA (8.9±1.1%) groups vs NL (8.5±1.0%) (p<.004 for all comparisons). Baseline A1c was also higher in PMA group vs NL (p<.0001). Those with or without MA did not differ regarding age or BP. Only 30 patients received ACE-inhibitors; Rx was related to MA (31% Rx in PMA, 13% in IMA, 4% in NL group, p<.0001).MA continues to develop in youth with uncontrolled diabetes; ongoing efforts are needed to improve A1c in order to reduce kidney disease risk.



Supported by: DERC #3P30DK03683624S2

1250-P

Apolipoprotein B Reclassifies Cardiovascular Risk in Adolescents With Type 1 Diabetes

SCOTT A. CLEMENTS, FRANZISKA K. BISHOP, NICOLE E. PRENTICE, JANET K. SNELL-BERGEON, DAVID M. MAAHS, R.P. WADWA, *Aurora, CO*

LDL cholesterol (LDL-c) is used as the primary lipid marker of cardiovascular disease (CVD) risk in adults and adolescents with type 1 diabetes (T1D). Apolipoprotein B (apoB) has been proposed as an additional predictor of CVD risk with LDL-c. We hypothesized that apoB would help to reclassify CVD risk in adolescents with T1D.Fasting lipids, including apoB, were assessed in 289 subjects, age 12-19 years with T1D duration >5 years and mean A1c 9.0% ± 1.6%, and 92 similar age and sex non-diabetic (non-DM) controls. Per ADA guidelines for T1D youth, we defined elevated LDL-c as ≥130 mg/dl, borderline LDL-c as 100-129 mg/dl, and normal LDL-c as <100 mg/dl. We defined elevated apoB as ≥90 mg/dl, and normal apoB as <90 mg/dl.Distribution of LDL-c in T1D subjects was similar to that of non-DM controls (LDL-c <100 mg/dl: 73% vs. 81%, LDL-c 100-129 mg/dl: 22% vs. 16%, LDL-c ≥130 mg/dl: 5% vs. 3%, respectively; p=0.32). ApoB levels were significantly higher in T1D subjects versus non-DM controls (77 ± 24 mg/dl vs. 68 ± 18 mg/dl, p<0.001) and more T1D subjects had elevated apoB compared to non-DM controls (24% vs. 8%, p<0.001). All 15 T1D subjects with elevated LDL-c, but only 16 of the 210 T1D subjects with normal LDL-c, had elevated apoB. Of the 64 T1D subjects with borderline LDL-c, 37 (58%) had elevated apoB, compared to only 4 of the 15 non-DM controls with LDL-c 100-129 mg/dl (p=0.03).Measurement of apoB in addition to LDL-c identified a group of T1D subjects who may have increased CVD risk. Thus, apoB may be helpful in stratifying CVD risk in T1D adolescents with borderline LDL-c.

ApoB distribution for T1D and non-DM adolescents by LDL-c category

			LDL cholesterol		
			<130 mg/dl	100-129 mg/dl	≥130 mg/dl
T1D	ApoB	<90 mg/dl	194 (92%)	**27 (42%)***	0 (0%)
		≥90 mg/dl	16 (8%)	**37 (58%)**	15 (100%)
Non-DM	ApoB	<90 mg/dl	73 (99%)	11 (73%)	1 (33%)
		≥90 mg/dl	1 (1%)	4 (27%)	2 (67%)

* p=0.03 for apoB category by T1D status for LDL-c 100-129 mg/dl

Supported by: JDRF 11-2007-694; NIDDK DK075360; University of Colorado CTRC: NIH M01 RR000051

1251-P

Emergency Healthcare Utilization for Young Adults (YA) With Type 1 Diabetes (T1D) Who Have Aged Out of Pediatric Healthcare

PAOLA A. SEQUEIRA, MARC WEIGENSBERG, BETH PYATAK, LUCY MONTOYA, JAMIE WOOD, SUSAN CLARK, VALERIE RUELAS, ANNE PETERS, *Los Angeles, CA, Orange, CA*

Transitional care for YA with T1D is understudied and particularly important because of the change from family-focused care to independent disease management leaving the emerging adult without familiar resources and care. Our objective was to examine differences in emergency healthcare utilization among YA who had on-going care versus those lost to follow-up. Nonpregnant YA with T1D age 19-25yrs were recruited into 2 groups for a transition care program: 1)Continuity Group (CG), currently receiving routine diabetes care by pediatrics providers (n=81) and 2)Rescue Group (RG), finished pediatric care and were lost to medical follow-up for >3 mo (n=22). Baseline assessment for both groups included emergency department (ED) visits, hospitalizations, and paramedic utilization for the previous 6 mo and A1C. RG group was older and more predominantly Latino (Table). Within the 6 mo prior to enrollment, about 5 times as many people in RG used paramedics (p=0.02), more than 3 times as many had ED visits (p=<0.01), and ~3 times more were hospitalized (p=0.04) than in CG. RG also had significantly higher A1C values, adjusting for age and ethnicity (p< 0.05). Our results demonstrate that YA with T1D who experience absent or poor health care transition demonstrate increased emergency healthcare utilization and poorer glycemic control. Programs to improve transitional care for emerging adults with T1D may be useful in reducing excess emergency healthcare use and acute complications of diabetes.

Subject Characteristics and Healthcare Utilization

	CG(n=81)	RG(n=22)	p value
Age (yrs)	**19.6 ±0.9**	**21.1 ± 1.1**	**<0.001**
Sex (% F)	**43.8%**	**45.5%**	**0.93**
Age of Diagnosis(yrs)	**10.2±3.6**	**9.3±4.6**	**0.41**
Ethnicity (% Latino)	**53.1%**	**68.2%**	**<0.01**
Paramedic Usen (%)	**3 (3.7%)**	**4 (18.2%)**	**0.02**
ED Visits n (%)	**10 (12.3%)**	**9 (40.9%)**	**<0.01**
Hospitalizations n (%)	**8 (9.9%)**	**6 (27.3%)**	**0.04**
A1C (%)	**9.3±2.0**	**10.9±2.3**	**<0.01**

*Statistical analysis: Chi square for categorical variables; ANOVA, adjusting age/ethnicity, for A1C.

Supported by: The Leona M. and Harry B. Helmsley Charitable Trust

1252-P

Pediatric Diabetes and Deprivation: Association of Material and Social Deprivation With Glycemic Control

CAROLINE ZUIJDWIJK, FARID H. MAHMUD, *Toronto, ON, Canada*

Discrepancies in the social determinants of health help to explain the health inequities between individuals in a society, including those with universal access to medical care. The Hospital for Sick Children (SickKids) is the primary pediatric hospital in Toronto, Canada, caring for a large and diverse urban and suburban patient population.This evaluation sought to characterize the pediatric T1D clinic population through measurement of social determinants of health (socioeconomic status, family structure and ethnicity) and to describe how these relate to diabetes metabolic outcome (A1C).De-identified patient postal code information was used to determine dissemination areas, which were then linked to the data sets of the INSPQ Deprivation Index (material and social deprivation) and to the ON-Marginalization Index (ethnic concentration), providing robust census based,

population-level measures of socioeconomic status, family structure, and ethnicity for T1D patients regularly followed at SickKids. Quintile scores for each of the indices were then related to our primary outcome measure of mean patient A1C.Our patient population (N=890) was most concentrated in the least deprived (31%) and most deprived (33%) quintiles for material deprivation. While this mirrors the trend for the background population, a greater proportion of deprivation was observed in our clinic. A1C levels correlated significantly with all three measures of social determinants of health (1st vs. 5th quintile), including material deprivation (8.3% vs. 9.2%, p<0.001), social deprivation (8.3% vs. 9.1%, p<0.001) and ethnic concentration (8.0% vs. 8.9%, p=0.02). This novel population-level analysis describes the significant impact of social determinants of health in the pediatric diabetes patient population. Despite universal access to care, we observed a significant effect of material and social deprivation on metabolic control.

Supported by: CPEG Fellowship Grant

1253-P

Race and Socioeconomic Status Independently Predict Whether Youth Receive Insulin Pump Therapy in the First Year of Type 1 Diabetes (T1D) Treatment

MARIA H. LIN, JAMIE R. WOOD, SIEW WONG-JACOBSON, PEDIATRIC DIABETES CONSORTIUM, *Los Angeles, CA, Tampa, FL*

Socioeconomic factors have been shown to influence the use of insulin pump therapy in patients with type 1 diabetes. The aim of this study is to determine predictors of insulin pump therapy use within the first year of T1D diagnosis in youth participating in the Pediatric Diabetes Consortium (PDC). The PDC began enrollment in July 2009 and includes 7 centers throughout the U.S. with longitudinal data collected from the time of diabetes diagnosis. The analysis included 787 participants with T1D duration of more than 1 year. Mean age at diagnosis was 9.1 years; 50% were females and 65% were non-Hispanic Caucasians. Logistic regression was used to determine factors associated with insulin pump use within the first year of diagnosis. Of the 787 participants, 26% (N=204) were placed on insulin pump therapy within the first year of T1D diagnosis, although this varied by center (range 16-57%, p<0.001). Median T1D duration at pump start was 8.6 months (IQR 6.3 months to 11.0 months). Mean age at pump start was 9.3 years (range 1.1 to 18.4 years). Mean HbA1c at pump start was 7.2 ± 1.2. Youth started on pump therapy were more likely than those not started on pump therapy to be non-Hispanic Caucasian (86 vs. 58%, P<0.001), be privately insured (90 vs. 59%, P<0.001), live with both parents (89 vs. 66%, P<0.001), have a household income > $100,000 (63 vs. 28%, P<0.001), and have college-educated caregivers (71 vs. 48%, P=<0.001). In the multivariate model, each of these factors including clinical center remained significant except for having a college-educated caregiver. In conclusion, insulin pump therapy is commonly initiated in youth within the first year of T1D diagnosis. Race, socioeconomic factors, and clinical center are independent predictors of whether youth with T1D are placed on insulin pump therapy within the first year of diagnosis. Further investigation is needed to explain this finding including an evaluation of center/provider factors.

Supported by: Novo Nordisk, Inc.

1254-P

Outpatient Screening for Depression: Feasibility and Outcomes in Adolescents With Type 1 Diabetes

SARAH D. CORATHERS, NANA-HAWA YAYAH JONES, PEGGY CRAWFORD, ANDREA HOUCHEN, NANCY J. MORWESSEL, LAWRENCE M. DOLAN, KOREY K. HOOD, *Cincinnati, OH, San Francisco, CA*

Outpatient screening for depression in adolescents with type 1 diabetes (T1D) is recommended, but rarely formally conducted. To provide a model for depression screening in tertiary diabetes care settings, we developed a process in which an electronic version of a validated tool, the Children's Depression Inventory (CDI), is self-administered. An automated report is generated for providers with score, interpretation, and referral guidelines. Quality improvement methodology and traditional analytic approaches were used to test the feasibility and preliminary outcomes of routine screening in T1D patients 13-17 years of age.Across 2011, over 1200 CDIs were completed by 453 unique patients (87% of the eligible population). Depression screening increased from <5% in January 2011 to 85% within 3 months and held steady. Preferences of patients and staff were surveyed and 2/3 of patients and all staff rated screening as important. Most patients and staff preferred screening at 6 or 12 months instead of every visit.Chart reviews for 280 of the 453 patients have been completed. This sample has a mean age of 15.3±2.7 yrs, T1D duration of 6.7±7.3 yrs, A1c of 8.9±1.8%, and blood glucose monitoring frequency of 3.9 times per day. CDI scores fell in to these categories: <10 = LOW RISK (84% of the sample), 10-15 = MODERATE RISK (9%), and ≥16 = HIGH RISK (7%). Suicidal ideation was endorsed in 6% of the sample. Elevated scores and/or suicidal ideation generated an average of 2.7 social work and 1.5 psychology referrals weekly.Systematic outpatient depression screening can be implemented successfully in a large tertiary diabetes center with multiple providers, with a high rate of adolescent and staff support. Nearly 20% of those screened were at risk for more significant depression or suicidal ideation and were referred for further evaluation or treatment. We recommend screening at least annually and examining how results relate to diabetes management to inform health-promoting clinical interventions.

1255-P

Diet Quality in Adolescents With Type 1 Diabetes: The Impact of Carbohydrate Knowledge

NIDHI BANSAL, LEONA CUTTLER, ALISON STEIBER, MARYANN O'RIORDAN, JENNIFER DORMAN, MICHAELA B. KOONTZ, *Cleveland, OH*

Recent studies suggest that children with type 1 diabetes (T1D) consume suboptimal diets that do not meet established guidelines for individual nutritional components. However, composite measures of diet quality that account for multiple dietary components have not been reported for youth with T1D, and the determinants of their diet quality remain unexplored. The aim of this study was to evaluate diet quality and its relationship with carbohydrate knowledge in youth with T1D. Forty-one adolescents with T1D were recruited sequentially from an academic pediatric diabetes program. Knowledge about carbohydrate counting and insulin dosing was measured using the validated PedCarbQuiz (PCQ) questionnaire. Diet quality was assessed using the USDA-validated Healthy Eating Index 2005 (HEI), calculated from a standardized 24 hour food recall. Spearman correlations were calculated between PCQ scores and HEI total and component scores. Mean HEI score was 49.8 ± 13.3 (out of maximum score of 100). Diet quality was poor (defined by USDA as HEI score <51) in 54% of participants, and 46% had scores classified as needing improvement (score 51-80); no participants had good diet quality (score >80). Greater knowledge of carbohydrate counting (higher PCQ scores) correlated significantly with higher diet quality (HEI total scores) ($r = 0.40$, $P = 0.01$). Higher PCQ scores also correlated with higher HEI component scores for total vegetables ($r = 0.46$, $P < 0.01$), dark green/orange vegetables and legumes ($r = 0.53$, $P < 0.01$), and oils ($r = 0.38$, $P = 0.01$). HEI scores were not related to age, diabetes duration, number of nutritionist visits, parent income, or parent education. In conclusion, this study, which is the first to report comprehensive diet quality scores in adolescents with T1D, demonstrates poor diet quality in the majority of these youth. Greater carbohydrate knowledge is associated with better diet quality. Interventions to improve carbohydrate counting and insulin dosing may therefore also improve diet quality.

Supported by: FRAP, Rainbow Babies and Children's Foundation

1256-P

Characteristic Insulin Secretion Patterns Persist at the Diagnosis of Type 1 Diabetes in the Diabetes Prevention Trial-Type 1 (DPT-1)

JAY SOSENKO, JAY SKYLER, JEFFREY KRISCHER, KEVAN HEROLD, CARLA GREENBAUM, LISA RAFKIN, DAVID CUTHBERTSON, JERRY PALMER, THE DIABETES PREVENTION TRIAL-TYPE 1 STUDY GROUP, THE TYPE 1 DABETES TRIALNET STUDY GROUP, *Miami, FL, Tampa, FL, New Haven, CT, Seattle, WA*

We assessed whether individuals have characteristic insulin secretion patterns with regard to quantity and timing, and whether those patterns are retained at the time of diagnosis of type 1 diabetes (T1D) in 79 Progressors to T1D (age: 11.1±7.8 years) and 317 Non-Progressors (age: 16.1±10.8 years) who were DPT-1 participants. All were islet cell autoantibody positive. 2-hr oral glucose tolerance tests (OGTTs) were performed at 6-month intervals. Area under the curve (AUC) C-peptide indicated the overall quantity of insulin secretion, the C-peptide difference between fasting and 30 minutes (30-0) indicated early insulin secretion, and the 60 to 120 minute/0 to 60 minute AUC ratio (AUC Ratio) indicated the timing of insulin secretion. Patterns were studied by examining correlations of the C-peptide indices between the baseline and last OGTTs in Non-Progressors, and between the baseline and diagnostic OGTTs in Progressors (interval >2.0 years for all). Correlation coefficients (Pearson) for the C-peptide indices between the baseline and last OGTTs in the Non-Progressors were: 0.57 for AUC, 0.47 for 30-0, and 0.34 for AUC Ratio (p<0.001 for all). Among Progressors, even though insulin secretion decreased from baseline to diagnosis (p<0.001 for AUC), the C-peptide indices were also correlated between the baseline and diagnostic OGTTs [0.70 (p<0.001) for AUC; 0.30 (p<0.01) for 30-0; and 0.42 (p<0.001) for AUC Ratio]. In both Non-Progressors and Progressors, the C-peptide as-

For author disclosure information, see page 797.

sociations between the OGTTs remained significant (p<0.001 for all) with adjustments for age, BMI, AUC glucose of both OGTTs, and length of follow-up. The findings show that there are characteristic persistent insulin secretion patterns within individuals. These are independent of BMI and glucose levels. Moreover, despite a decreasing insulin response to oral glucose, insulin secretion patterns are retained during the progression to a diagnosis of T1D based on OGTT criteria.

Supported by: NIDDK

1257-P

Barriers to Effective Health Care Transition for Young Adults With Type 1 Diabetes

KATHARINE C. GARVEY, HOWARD A. WOLPERT, LORI M. LAFFEL, ERINN T. RHODES, JOSEPH I. WOLFSDORF, JONATHAN A. FINKELSTEIN, *Boston, MA*

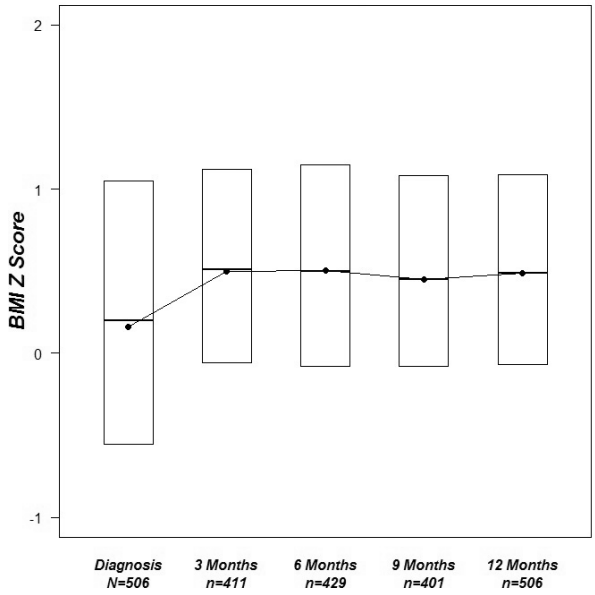
Empiric data to guide the transition from pediatric to adult health care for patients with type 1 diabetes (T1D) are limited. This study examined barriers to successful transition reported by young adults with T1D and evaluated associations between these barriers and gaps between pediatric and adult diabetes care. We developed a survey with paper or web-based completion options to assess the transition experiences of young adults with T1D, ages 22-30, who now receive adult diabetes care. The response rate was 53% (n = 258 of 484 eligible). Respondents were 26.7±2.4 years old, 62% female, 92% Caucasian, 82% college-educated, and had received pediatric diabetes care at 95 U.S. clinics. Current A1c was 8.1±1.3%. Mean transition age was 19.5±2.9 years; 34% reported a gap >6 months between pediatric and adult diabetes care. Reported barriers to timely establishment of adult diabetes care included lack of an adult provider name (47%), competing life priorities (43%), difficulty getting an appointment (41%), lack of adult provider contact information (27%), feeling upset about leaving pediatric providers (24%), and insurance problems (10%). In multivariate models adjusting for pre-transition A1c, gender, education, and transition age, respondents who endorsed lack of an adult provider name as a moderate/major barrier were more likely to report a gap >6 months (OR 7.8, 95% CI 3.6, 17.1), as were those endorsing competing life priorities (OR 7.6, 95% CI 3.7, 15.8), lack of adult provider contact information (OR 7.0, 95% CI 2.6, 18.4) and insurance problems (OR 3.8, 95% CI 1.3, 11.2) as moderate/major barriers. Overall, respondents who reported at least 1 moderate/major barrier (48%) had 4.7-fold greater odds of a gap in care >6 months (95% CI 2.6, 8.7). Our results identify modifiable systems-based barriers to transition that may be amenable to improved care coordination. Study is needed to evaluate strategies to support young adult transition and self-care, especially regarding competing life priorities.

1258-P

Weight Gain in the First Year After Diagnosis of Type 1 Diabetes

BRIGID GREGG, CRAIG KOLLMAN, SIEW WONG-JACOBSON, DESMOND SCHATZ, EDA CENGIZ, BREANNE HARRIS, WILLIAM TAMBORLANE, GEORGEANNA KLINGENSMITH, JOYCE M. LEE, PEDIATRIC DIABETES CONSORTIUM (PDC), *Ann Arbor, MI, Tampa, FL, Gainesville, FL, New Haven, CT, Stanford, CA, Dever, CO*

Children with new-onset type 1 diabetes (TID) gain weight after starting insulin therapy; few multicenter studies have examined weight trajectory in the first yr after diagnosis. The study objective was to assess changes in weight and body mass index (BMI) during this period and differences by age and change in hemoglobin A1c (HbA1c).The Pediatric Diabetes Consortium includes 7 US centers with longitudinal data collected from initial T1D diagnosis through medical record review. This analysis included 506 participants with diabetes duration of at least 1 year and measures of BMI at diagnosis and 12 m.At diagnosis, most children were 5-11 y (59%), 15% were classified as overweight (85^{th}%≤BMI<95^{th}%) and 11% as obese (BMI≥95^{th}%), and the majority (74%) had a HbA1c≥10%. Mean BMI z-score rose from 0.2 (SD ±1.2) to 0.5 (SD ±0.9) in the first 3 m after diagnosis and then remained relatively stable over the yr (figure). Overweight prevalence increased from 26% at diagnosis to 35% at 12 m, for children aged 2-5, vs. 27% to 28% and 24% to 23% for children 5-11 and 12-18, respectively. Normal weight children at diagnosis had a mean BMI z-score change at 1 year of +0.5(0.8) vs. -0.1(0.4) and -0.2(0.5) for overweight and obese individuals. We found a weak negative correlation between change in HbA1c and change in BMI z-score from diagnosis to 12 m (Spearman correlation -0.23, p<0.001).Increases in BMI z-score in the first 3 m may reflect regaining weight lost prior to diagnosis. Given the greater increase in overweight prevalence over the 12 m period for younger (<5 y) compared to older children, physicians may consider close monitoring to prevent excess weight gain in this group.



Supported by: Diabetes Research and Training Center DK02057

1259-P

Blood Glucose Levels in Children With Type 1 Diabetes Attending a Residential Diabetes Camp: A Two Year Review

KAREN T. CARLSON, LISA TOLBERT, GRANT W. CARLSON, LINDA J. DEMMA, *Atlanta, GA*

We retrospectively analyzed blood glucose (BG) levels of children attending a week-long residential camp for children with type 1 diabetes mellitus during 2009 and 2010. Between 2009 and 2010, we instituted the following interventions in order to improve glucose control in campers: 1) Daily, BG levels were highlighted by color according to "high" (>180mg/dL), or "low" (<70mg/dL), giving the endocrinologists a visual pattern on which to make daily insulin adjustments; 2) Low glycemic index foods were used; and 3) campers in 2010 estimated the number of carbohydrates they would eat before a meal and gave a pre-meal bolus of insulin, whereas in 2009 campers gave insulin boluses after the meal. Our objective was to evaluate our overall diabetes management and to determine if these specific interventions were effective in lowering average BG among our campers.BG records were obtained from three camp sessions in 2009 and three in 2010. We included 237 total campers from 2009 and 255 total campers from 2010. Five BG values per day, pre-meal, pre-evening snack, and midnight values, were analyzed. A total of 13,267 BGs were included in the analysis.Mean BG was significantly lower in 2010 compared with 2009 (166mg/dL v. 181 mg/dL, p<0.001). Percentage of BGs in a pre-defined target range (100-200) also improved (50% v. 45%, p<0.01). There were no severe hypoglycemic episodes in either year. There was no association between average BG for each camper and sex, HbA1C, or date of diagnosis.Our study is the largest conducted at a residential diabetes camp. Moreover, the average BGs were lower than published studies. These data show that average BGs of 166 can be achieved with minimal risk of severe hypoglycemia. Although a direct cause and effect relationship between our interventions and the improvement in BG cannot be proven, pre-meal insulin bolusing and low glycemic meals should be encouraged. This study will help establish benchmarks for comparison among camps and begin to identify best-practices.

1260-P

Peripheral Neuropathy in Youth With Type 1 Diabetes

JOANNE T. MOSER, RICHARD FINKEL, SARAH RATCLIFFE, DAVID R. LANGDON, MELISSA A. REARSON, LIBERTY R. FOLEY, TERRI H. LIPMAN, *Philadelphia, PA*

Diabetic peripheral neuropathy (DPN) can be a devastating, long-term complication causing significant morbidity and mortality. DPN is rarely suspected in youth- thought to occur only in older populations, after a long duration of diabetes and poor control. Few studies of DPN in children have been done in the US. The purpose of this study was to determine the prevalence of DPN in youth in a pediatric diabetes center. Study subjects included 2 groups: Group 1: 8-21yr without identified high risk criteria. Group 2: subjects

meeting "high risk" criteria: ≥13 yr, diabetes ≥5 yr, and HbA1c ≥10% at 2/4 visits in the past year. Subjects completed a screening inventory comprised of a questionnaire and physical examination performed by 4 providers. The time needed to complete the screening was recorded. Subjects in Group 1 who screened positive, and all subjects in Group 2, were referred to the pediatric neurologist (PN) for nerve conduction studies (NCS). Positive NCS were diagnostic of DPN. The association of DPN with diabetes duration, age, race, SES, Tanner stage, height, BP and HbA1c was evaluated. 151 children were screened (Group 1=143, Group 2=8). In Group 1, 33 (23%) screened positive and were referred to the PN. Of the 24 subjects who agreed to be evaluated by the PN, 11 (46%) were diagnosed with DPN. In Group 2,6 (75%) screened positive. All 8 high risk subjects were referred to the PN. Five were evaluated. All 5 were diagnosed with DPN including one who screened negative. Of the subjects who had NCS, 16 (55.2%) were diagnosed with DPN; mean age was 16.2 yr (13.6-19.5), mean diabetes duration 6.4 yr (3 mos-12yr) and mean HbA1c 8.7% (7%-12.5%). DPN was not associated with diabetes duration, age, race, SES, Tanner stage, height, BP or HbA1c. We conclude that DPN is more prevalent in youth than was commonly suspected. We demonstrated that DPN can occur in young children, with short diabetes duration, good control and merits routine standardized screening. National DPN screening guidelines for children should be developed.

Supported by: Pediatric Endocrine Nursing Society

1261-P

Sex-Dependent Differences of Carotid Intima-Media Thickness (cIMT) and Atherosclerotic Pathogenesis in Children and Adolescents With Type 1 Diabetes Mellitus (T1D)

KATRIN NAGL, EDITH SCHOBER, BIRGIT RAMI, ANDREA WILLFORT-EHRINGER, GUNTRAM SCHERNTHANER, GERIT H. SCHERNTHANER, *Wien, Austria*

Atherosclerotic disease is the first cause of death in young adults with T1D. We hypothesize that this increased disease burden develops from the onset of T1D in early childhood. Non-invasive cIMT measurement by duplex sonography is the most feasible method to evaluate preatherosclerotic burden. Since a sex-difference in cIMT has been described in young adults without diabetes, we wondered if cIMT would also be sex different in children and adolescent with T1D and whether associated pathogenic factors would differ.In 66 adolescents (32 males) with T1D (age: 15.49±2.27 years) cIMT was measured by duplex sonography. In each patient 12 measurements were done on each common carotid artery (=24), averaged, and correlated with quantitative and qualitative clinical parameters. Associations of cIMT were studied and adjusted by multivariate stepwise backward regression analysis.CIMT (mm) was lower in age-matched girls (0.29±0.05) than in boys (0.32±0.06) (t=3.502; p=0.001). The association of cIMT with clinical parameters was different girls and boys: Whereas cIMT in girls correlated with Body Mass Index (r=0.441; p=0.009), Insulin Units/kg body weight (r=-0.346; p=0.045), and HbA1c (r=0.437; p=0.010) boys did not show such associations. In contrast, their cIMT correlated only with T1D duration at a p-value of <0.1. Stepwise backward regression revealed sex as the most significant independent predictor of cIMT (Beta=0.479; p=<0.001). Sex, age-and-sex-adjusted BMI and Diabetes Duration together explained > 37% of the variation of cIMT.Girls with T1D had lower cIMT than boys. CIMT correlated with weight and glycemia related parameters in girls but not in boys. Our pilot study points towards a possible pathophysiologic difference in the high cardiovascular burden of young women and men with type 1 diabetes mellitus and suggests a higher association of atherogenesis with diabetic condition in girls than in boys.

1262-P

Periodontal Microorganisms in Youth With and Without Type 1 Diabetes

ANWAR MERCHANT, ELAINE MORRATO, PAUL R. WADWA, DAVID MAAHS, RICARDO TELES, LONNIE JOHNSON, FRANZISKA BISHOP, JIAJIA ZHANG, *Columbia, SC, Aurora, CO, Cambridge, MA*

Youth with type 1 diabetes (T1D) are at higher risk for periodontitis and cardiovascular disease. Periodontitis occurs when there is an overgrowth of specific gram negative microorganisms in the oral cavity; a subset of these microorganisms is also positively associated with atherosclerosis. These microorganisms are P. gingivalis, A. actinomytcetemcomitans, T. forsythia, and T. denticola, and will be called atherosclerotic etiologic periodontal organisms. These data are from youth aged 12-19 years with diagnosed T1D for at least 5 years (n=50), and those without diabetes (n=50) matched for age attending clinic at the Barbara Davis Center/University of Colorado. Quantitative estimates of periodontal microorganisms were determined by DNA-DNA hybridization at the Forsyth Institute, Cambridge, MA. Participants with and without T1D were similar (p>0.05) with respect to age (mean 15 y), sex (female 55%), and race (white 89%); mean A1c in T1D participants was 9.04%. The number of bleeding sites per participant were correlated (Spearman) with counts of P gingivalis (r=0.30, p=0.002), C rectus (r=0.32, p=0.002), and A naeslundii (r=-0.25, p=0.01) which were from the etiologic, putative, and health related categories of periodontal microorganisms, respectively. Periodontal damage (≥3 mm clinical attachment loss on at least one tooth site) was 14% in T1D participants versus 8% in those without T1D respectively. Neither periodontitis nor the distribution of atherosclerotic etiologic organisms differed by T1D status, possibly because of the low level of periodontal damage in this population.

Distribution of periodontal microorganisms among youth with and without T1D

	T1D (N=50)%	Controls (N=50)%
Etiologic periodontal organisms	1.71	1.95
Putative periodontal organisms	45.31	40.67
Health related periodontal organisms	52.98	57.38
A actinomycetemcomitans	2.30	2.49
P gingivalis	2.68	3.72
T denticola	1.41	1.74
T forsythia	3.45	2.93

1263-P

Regression of Microalbuminuria (MA) is Common in Youth With Type 1 Diabetes (T1D)

CIELO R. ALLEYN, LISA K. VOLKENING, JYOTI AGGARWAL, LORI M. LAFFEL, *Boston, MA*

While MA predicts diabetic nephropathy, adults with T1D and MA experience a 50-60% rate of regression to normal (NL). To assess rate of MA regression in pediatric patients, we evaluated 105 youth with T1D, previously classified with intermittent (IMA, n=55) or persistent (PMA, n=50) MA during a 2 year baseline period. Spot urines were analyzed for albumin/creatinine (Alb/Cr). MA, based on Alb/Cr ≥20 µg/mg, was defined as PMA with ≥2 elevations or IMA with 1 elevation during baseline and each 2 year follow-up (F/U) period. Regression to normal (NL) was Alb/Cr <20 µg/mg. BP and A1c were averaged over the 2 year baseline and during F/U of 7.9±3.4 years (mean±SD, range 0.2-12.2). Youth provided 838 urines (median 7 samples/patient) after baseline.At baseline, youth (36% male) were 14.6±2.0 years old and had T1D duration of 7.2±2.8 years. A1c was 9.0±1.3% and BP was 110±8/68±5. Baseline IMA vs PMA groups differed in age at T1D diagnosis (8.2±2.8 vs 6.5±3.0, p<.005) and systolic BP (122±8 vs 118±6, p<.05). There were more females in the PMA than IMA group (74 vs 55%, p<.04).Rate of MA regression was similar between baseline IMA and PMA groups (p>.2). In baseline IMA group, 53% regressed to NL, 24% remained IMA, and 24% progressed to PMA. In baseline PMA group, 46% regressed to NL, 38% regressed to IMA, and 16% remained PMA. Only 24 patients (14 with IMA, 10 with PMA at baseline) received ACEI/ARB Rx. Rx was associated with F/U MA (p<.02); 12% of those who regressed to NL had Rx vs 34% of F/U IMA group and 33% of F/U PMA group. Most regression to NL occurred within 2-4 years in the baseline IMA group while regression to NL occurred over 2-10 years in the baseline PMA group. Only F/U A1c and diastolic BP (DBP) differed among F/U NL, IMA, and PMA groups. A1c was 9.4±1.5% in PMA vs 8.7±0.9% and 8.8±1.2% in IMA and NL groups (p≤.05 for both) and DBP was 75±6 in IMA vs 71±5 in the NL group (p<.008); DBP in the PMA group was intermediate.Youth onset T1D patients had a similar rate of MA regression as adults. A1c and BP remain major contributors to MA in youth with T1D.

Supported by: DERC #3P30DK03683624S2

1264-P

Interleukin-23 (IL-23A) Gene Variant (rs2066880 G>A) Is Associated With Predisposition to Type 1A Diabetes Mellitus in a Brazilian Cohort

VINICIUS S. COSTA, ARITANIA S. SANTOS, TERESA C. MATTANA, MARIA E. DA SILVA, *São Paulo, Brazil*

Type 1A Diabetes (T1D) is an autoimmune disease resulting from environmental and genetic factors. The humoral and cellular attacks to beta-cells include the activation of Th1, Th2 and Th 17 cells and the liberation cytokines. Increased IL-17 expression has been detected in target tissues of immune-mediated diseases, including diabetes. The differentiation of Th 17 cells from naïve T cells is partially mediated by IL-23 that activates Th 17 cells to promote inflammatory responses. Variants of *IL-23A* gene and of its receptor have been related to autoimmune diseases. Pancreatic islets

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

of mice with autoimmune diabetes exhibited high concentrations of IL-23. There is no study analyzing its involvement in T1AD in humans. This study was conducted to search for mutations or new polymorphisms in the entire coding regions and the boundary intron sequences of *IL-23A* gene in T1D patients and compare with controls. Genomic DNA was extract from 374 Brazilian patients with T1AD(22.3± 12.4 years; 229F/145M), treated with 2 or more insulin injections per day and 361 health controls(27.5±12.8years; 162F/199 M). Direct sequencing of PCR-amplified products of *IL-23A* gene and proximal promoter region was performed initially in a small cohort and revealed a new variant c.-403(C>T) in the 5' proximal region of *IL-23A* gene, present in only one T1D patient, and a known variant in exon 3 (rs11171806-G>A) which genotype and allele frequencies were similar between patients and controls(AA+AG genotypes: 6.4% x 3.8% ; p=0.16). We also analyzed the rs2066880 (G>A) allelic variant in 3' UTR region of *IL-23A* gene, related to psoriasis. The A allele was more prevalent in patients with T1D than controls (86,2% x 80.7%; p= 0,0053; OR 1.49, CI= 1.13-1.97) as well as the AA genotype(76.2% x 64.6%- p= 0.005; OR=1.758; CI= 1.276-2.422). We showed for the first time that the A allele of rs2066880 variant of *IL-23 A* gene is associated with increased predisposition to T1D in a Brazilian cohort.

Supported by: FAPESP

1265-P

Adolescents' Diabetes Management and Control: Risk Factor Profiles and Intervention Targets

MARISA E. HILLIARD, YELENA P. WU, JOSEPH RAUSCH, LAWRENCE DOLAN, KOREY K. HOOD, *Cincinnati, OH*

Deterioration of diabetes management and control are common in adolescence. Identification of risk factor profiles and potential intervention targets would provide clinicians with a powerful tool to prevent or treat suboptimal diabetes outcomes. Thus, we aimed to identify management and control trajectories in subgroups of adolescents with type 1 diabetes across 2 years and to predict membership in each subgroup. Blood glucose monitoring (BGM) frequency and A1c values in 150 adolescents (mean [M] age=15.5±1.4 years) were monitored. Parents and teens reported on depressive symptoms, negative affect surrounding BGM, and diabetes-specific family conflict. Latent group-based trajectory modeling detected 3 subgroups: "optimal" diabetes management and control (40% of sample; M A1c=7.4%, M BGM=4.8 checks/day), "suboptimal I" (40%; M A1c=9.2%, M BGM=2.8), and "suboptimal II" (20%; M A1c=11.2%, M BGM=2.9). Two-thirds of the sample was outside ADA targets, with minimal change in A1c or BGM over this 2-year span. Logistic regressions indicated that older age, single parent status, ethnic minority status, and insulin delivery via injections vs. CSII predicted suboptimal management and control (see table). Elevated emotional distress and family conflict increased the likelihood of membership in the suboptimal I or II subgroup by 1.5-3.5 times. These data establish a risk factor profile (demographic characteristics and insulin delivery method) for suboptimal diabetes management and control and identify intervention targets (individual and family distress) to potentially improve diabetes outcomes in adolescents.

Subgroup characteristics and predictors of suboptimal subgroup membership

	Optimal subgroup (40%)	Suboptimal I subgroup (20%)	Suboptimal II subgroup (20%)	Suboptimal subgroup predicted (vs. Optimal)	Odds Ratios (95% CI)
Age, years	15.5+/-1.5	15.6+/-1.4	15.9+/-1.1	II	1.83 (1.09-3.09)
Insulin delivery mode (% injections)	23%	37%	66%	II	8.41 (1.52-46.67)
Parent marital status (% single)	11%	32%	41%	I	4.29 (1.23-15.01)
Minority status (% minority)	8%	10%	34%	II	5.92 (1.17-30.30)
Depressive symptoms	6.2+/-6.0	9.3+/-7.8	8.9+/-7.2	I	1.07 (1.01-1.15)
BGM negative affecg	13.0+/-3.0	13.5+/-3.4	8.9+/-7.2	II	1.16 (1.00-1.35)
Family conflict	23.7+/-3.7	25.6+/-4.8	29.3+/-7.4	I, II	1.16 (1.06-1.27), 1.28 (1.14-1.43)

Supported by: NIH K23 DK077340 (K.H.)

1266-P

WITHDRAWN

1267-P

Lower Basal to Total Daily Insulin Ratio is Associated With Lower A1c in Youth With Type 1 Diabetes (T1D) Using Pump Therapy

SANJEEV N. MEHTA, KAITLIN C. GAFFNEY, LISA K. VOLKENING, TONJA R. NANSEL, DENISE HAYNIE, LORI M. LAFFEL, *Boston, MA, Bethesda, MD*

In pump-treated youth with T1D, higher basal insulin requirements may reflect less frequent bolus dosing and/or insulin resistance. We assessed association between the ratio of basal to total daily dose (basal:TDD ratio) and A1c, accounting for factors associated with insulin resistance (puberty, daily exercise, and dietary fat intake). Clinical characteristics were obtained by medical record review, physical activity by families' self-report, dietary data from analysis of 3-day food records, and basal and total daily insulin doses from youths' pumps. In 172 pump-treated youth (52% male) with T1D for >1 year, mean (±SD) age was 13±3 years, T1D duration was 7±3 years, zBMI was 0.7±0.8, and A1c was 8.3±1.0%. TDD was 0.9±0.2 U/kg and mean basal:TDD ratio was 0.46±0.10 (range 0.20-0.77). In bivariate analyses, multiple factors were associated with higher basal:TDD ratio: older age (p<0.0001), longer T1D duration (p=0.005), female sex (p=0.04), post-pubertal status (Tanner stage 5) (p=0.001), less frequent daily BG monitoring (BGM)(p=0.01), and higher A1c (p=0.005); zBMI, daily physical activity, and fat intake (as % of total energy intake) were not associated with basal:TDD ratio. Higher A1c was also associated with older age (p=0.002), post-pubertal status (p=0.02) and less frequent BGM (p<0.0001). Multivariate linear regression (R2=0.24, p<0.0001) confirmed the unique association between basal:TDD ratio and A1c: for each 10% absolute decrement in basal:TDD ratio, A1c improved by an absolute amount of 0.2% (p=0.03), after adjusting for age, T1D duration, sex, post-pubertal status, daily BGM, and U/kg/day. In the model, BGM was also associated with A1c: by increasing BGM 1x/day, A1c improved by 0.2% (p<0.0001). In pump-treated youth with T1D, factors associated with insulin resistance did not account for the association between higher basal:TDD ratio and higher A1c. Lowering basal:TDD ratio with greater bolus dosing will likely lead to improved A1c.

Supported by: NICHD (HHSN267200703434C)

1268-P

Discordant Diabetes Family Responsibility Sharing is Associated With Increased Diabetes Family Conflict in Youth With Type 1 Diabetes (T1D)

MICHELLE L. KATZ, LISA K. VOLKENING, BARBARA J. ANDERSON, LORI M. LAFFEL, *Boston, MA, Houston, TX*

Diabetes family conflict (DFC) is related to lower adherence to diabetes management tasks and higher A1c. A source of DFC may be parent & youth disagreement about T1D responsibilities. We assessed if discordant parent & youth reports of responsibility for T1D tasks were associated with higher DFC.Parents & youth each completed the Diabetes Family Responsibility Questionnaire that asks who is responsible for tasks like deciding what to eat or giving insulin. Responses are "child alone, equal, or parent alone" with discordant responses defined as entirely opposite (if either person noted equal, responses were not discordant). Parents & youth also completed the Revised Diabetes Family Conflict Scale to assess if families "Never, Sometimes, or Always Argue" about a range of diabetes tasks.271 youth (median age 13 yrs, range 8-16) with T1D & a parent completed surveys. Youth (44% male, T1D for 5.9±3.5 yrs, 34% on pump) had a mean A1c of 8.3±1.2%, received 0.9±0.3 u/kg/day of insulin, & checked BG 4-5 times/day on average. 65% of families had no discordant responses. Of the discordant responses, 84% were from increased self-attribution (both parent & youth reported they were solely responsible). Higher DFC was associated with higher A1c (r=.2, p≤.001).Discordance in family responsibility was related to youth & parent-reported DFC (r=.1, p=.03 & r =.2, p=.0007, respectively). Higher self-attribution was associated with more parent-reported DFC (r=.2, p=.001). Parent report of DFC was higher in families with any discordant responses than in families with no discordant responses (25.3 vs. 23.8, p=.003).After adjusting for youth age, T1D duration, sex, pump use, daily BG monitoring, & u/kg/day, greater discordance (p=.006) & greater self-attribution (p=.003) were each associated with greater parent reported DFC in separate models. Clarifying & negotiating responsibilities for T1D tasks may help to alleviate diabetes family conflict.

Supported by: Charles H. Hood Foundation and T32 5T32DK007260-35

1269-P

Diabetes Incidence Cohort Study "DiMelli" in Bavaria, Germany: Two-Year Results and Confirmation of a New Tool to Define Insulin Resistance

KATHARINA WARNCKE, MIRIAM KRASMANN, CHRISTINE MILZ, LEONORE THÜMER, FRANK HOFMANN, MANFRED KELLER, EWAN DONNACHIE, ANETTE G. ZIEGLER, *Neuherberg, Germany, Munich, Germany*

Objective: Diabetes incidence in children and youth is increasing worldwide, including autoimmune and non-autoimmune cases. The DiMelli study aims to establish a diabetes incidence cohort registry and to characterize diabetes phenotypes by immunologic, metabolic and genetic markers. The insulin-sensitivity score established within the SEARCH study was reassessed in the DiMelli cohort.Methods: Patients less than 20 years of age with a diabetes duration < 6 months were included. A fasting venous blood sample was obtained to measure islet autoantibodies (Aabs), c-peptide, HbA1c, and lipids, and a structured questionnaire was completed.Results: From 2009 to 2011, 496 patients (54% male) were registered. 81.7% were positive for multiple islet autoantibodies (Aabs; type 1 diabetes), 10.3% for one Aab (intermediate cases), and 8% were islet Aab-negative (type 2 diabetes). In SEARCH, people with diabetes and a score of less than 8.15 were classified as insulin resistant (score = exp [4.64725-0.02032x(waist [cm]) - 0.09779x(HbA1c [%])-0.00235x(triglyceride [mg/dl])]; Dabelea et al., Diabetes Care 2011). This score was reassessed in DiMelli. It ranged from 1.6 to 20.3 (median 8.6, IQR 6.4-11.7). By using the SEARCH cut-off, 38.8% of DiMelli patients with multiple islet AAbs, 52.9% with one AAb, and 75% with no AAbs were insulin resistant. The score was inversely correlated with age (r= -0.6; p=0.01) and body mass index (r = -0.4, p=0.01). Children with islet Aabs had higher scores than children without Aabs (median 8.8, IQR 6.9-11.8 vs. 6.2, IQR 3.7-8.3; p=0.02), and children with c-peptide > 2 ng/ml had lower scores than children with c-peptide ≤ 2 ng/ml (median 4.0, IQR 3.6-8.7; vs 8.9, IQR 7.1-11.9; p=0.03).Conclusions: Application of the SEARCH Insulin-sensitivity score in a second cohort confirms its applicability as a surrogate marker of insulin resistance in diabetes patients under the age of 20 years.

Supported by: BMBF Competence Network (FKZ 01GI0806) and DZD e.V.

1270-P

Partial Remission (PR) during the First 12 Months of Treatment in Youth With Type 1 Diabetes (T1D) in the Pediatric Diabetes Consortium Cohort (PDC)

EDA CENGIZ, BRUCE BUCKINGHAM, GEORGEANNA KLINGENSMITH, MARIA J. REDONDO, DESMOND SCHATZ, WILLIAM TAMBORLANE, SIEW WONG-JACOBSON, CRAIG KOLLMAN, PEDIATRIC DIABETES CONSORTIUM (PDC), *New Haven, CT, Stanford, CA, Denver, CO, Houston, TX, Gainesville, FL, Tampa, FL*

Achieving target A1c levels with intensive diabetes management is the only currently established method for prolonging residual β cell function in patients with T1D but the impact of such treatment on the PR phase of T1D has not been recently examined. The PDC is a group of 7 pediatric diabetes centers prospectively following a cohort of >1,000 youth with T1D from the time of diagnosis. The validation of the Insulin Dose Adjusted A1c (IDDA1c= A1c+ 4x insulin dose unit/kg/day; Mortenson et al, Diabetes Care 32: 1384, 2009), as a surrogate marker of residual β cell function (stimulated c-peptide) has made it possible for us to describe the natural history of the PR, defined as IDDA1c≤9, in this cohort. 654 of 1031 subjects were included in the analysis (351 were excluded for missing A1c or initial visit data and 26 for enrolling in β cell preservation studies). Mean age at diagnosis was 9.2 yrs. 50% were female, and there was considerable racial/ethnic diversity (65% white, 21% Hispanic, 7% African American, 8% other/multiple race). Interestingly, the percentage of patients with IDDA1c ≤9 peaked by 6 mo at 51% and declined to 26% by 12 mo. These natural history data relating to residual β cell function in a multicenter consortium with diverse treatment regimens will help in the design of future clinical trials evaluating the efficacy of immunologicand other therapies aimed at β cell preservation. Furthermore, examiningpredictors for prolonging PR will allow us to determine new targets in diabetes management for better outcomes.

A1c, IDAA1c, total daily insulin during the 1st yr of T1D

	Diagnosis	3 Months	6 Months	9 Months	12 Months
	N=623	N=506	N=540	N=503	N=654
A1c *mean ± SD (%)*	11.5± 2.4	7.2± 1.1	7.2± 1.3	7.6± 1.4	7.8± 1.5
A1c≤7.0%	3%	49%	50%	39%	34%
IDAA1c *mean ± SD (%)*	N/A	9.4± 1.9	9.3± 2.0	9.9± 2.0	10.3± 2.1
IDAA1c≤9.0		50%	51%	34%	26%
Total insulin ≤0.5 U/kg/day		54%	53%	46%	34%

Supported by: Novo Nordisk, Inc.

1271-P

How Common are Episodes of Diabetic Ketoacidosis (DKA) and Severe Hypoglycemia (SH) in the First Year of Diagnosis With Type 1 Diabetes (T1D)?

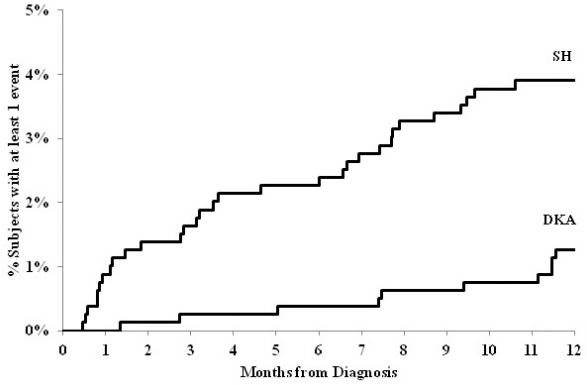
EDA CENGIZ, SIEW WONG-JACOBSON, CRAIG KOLLMAN, MOREY HAYMOND, GEORGEANNA KLINGENSMITH, JOYCE LEE, WILLIAM TAMBORLANE, PEDIATRIC DIABETES CONSORTIUM, *New Haven, CT, Tampa, FL, Houston, TX, Denver, CO, Ann Arbor, MI*

DKA and SH are still the major life threatening complications of T1D and not widely studied for children in the 1st yr into their T1D diagnosis during which many have retained some beta cell reserve. The frequency of DKA & SH in children (<19 yrs) during the 1st yr of diagnosis was assessed in the Pediatric Diabetes Consortium (PDC) database comprised of web- based electronic case report forms to capture longitudinal clinical data. DKA is defined as venous/arterial blood pH <7.3 or serum HCO_3 <15 mEq/l. SH is defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions to treat. We analyzed data from 795 subjects who had T1D for at least 1 yr as of 12-22-11. Mean age was 9.2 ± 4.1 yrs with an age distribution of 18% 0-<5yo, 56% 5-<12yo, 26% 12-<19yo and 65% were white, 21% Hispanic, 7% AA, 7% other/multiple race. HbA1c was 7.2±1.3 at 6 mon and 7.8± 1.5 at 1 yr; Insulin dose adjusted A1c (A1c+ 4x insulin dose unit/kg/day) was ≤9 (a marker of retained β-cell function) in 51% at 6 mon and 27% at 1 yr. 10 subjects had 14 DKA episodes (1.6 events/100 patient yrs) and 31 subjects had 42 SH episodes (4.8 events/100 patient yrs) (Figure). These event rates are lower than previously published rates in pediatric patients with established T1D longer than 1 yr. These data demonstrate that retention of endogenous insulin secretion during the 1st yr of T1D reduces but does not eliminate the risk of DKA and SH during the 1st yr of the disease.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

Figure 1: Cumulative Incidence of DKA and Severe Hypoglycemia (SH) within First Year of T1D (N=795)



Supported by: Diabetes Research and Training Center DK02057

1272-P

Insulin Glargine Enhancement of Growth in Prepubertal Children With Diabetes Mellitus Type 1

GEORGE W. MOLL, MICHAEL Y. TORCHINSKY, *Jackson, MS*

Insulin glargine activates human insulin-like growth factor-1 receptors (IGF-1R) to a much greater extent than human insulin or synthetic insulin detemir when present in high doses. IGF-1R activation brings about procellular tissue growth. Insulin glargine's potential influence upon abnormal cell growth is debated. However, 24-hour insulin (FDA approved for children glargine or detemir) regimens are highly successful for dibetes mellitus type 1 (IDDM) control. We hypothesize glargine can enhance physical growth of prepubertal children in similar IDDM control to a greater extent than detemir. Methods: We performed an IRB approved retrospective review of our IDDM patients that identified 330 who employed glargine and 178 who employed detemir within IDDM control regimens of at least 1 year duration. For comparable stable growth patterns we chose prepubertal 6 to 10 y/o girls and boys with glycohemoglobins (HgbA1c) less than or equal to 8.5% for the up to 4 year assessment of their 5 to 8 month interval growth rates (cm/year). We arrived at 16 girls and 12 boys using glargine and 16 girls and 12 boys using detemir as our study groups, and t-statistic comparisons of means of unequal variance were performed for comparable group data sets.Results: Our patient groups consisted of pre-pubertal girls (G) and boys (B)of similar age ranges and HgbA1c levels. Growth rates showed statistically significant upward trends for the glargine groups versus the detemir groups.Means(±SEM) for Detemir vs GlargineAge 8.2±0.2(G), 8.1±0.3(B) vs 7.7±0.4(G), 7.4±0.4(B) yearsHgbA1c 7.4±0.2(G), 7.6±0.2(B) vs 7.3±0.1(G), 7.4±0.1(B) %Growth Ht 5.9±0.5(G), 5.8±0.6(B) vs 6.7±0.4(G)*,7.0±0.5(B)**cm/yGrowth Wt 3.4±0.6(G), 3.4±0.7(B) vs 3.9±0.4(G), 4.0±0.5(B) kg/y*p<0.2, **p<0.1Discussion: We conclude insulin glargine can enhance growth velocity relative to insulin detemir within prepubertal children with well controlled IDDM 24-hour insulin regimens. Weight gain for all groups was statisically similar.

Supported by: Mississippi Department of Health-Children's Medical Program-DM Clinic

1273-P

Reliability and Validity of a Novel Rating Scale for Wolfram Syndrome: The WURS

CHAU NGUYEN, AIDEN BONDURANT, HEATHER LUGAR, BESS MARSHALL, NEIL H. WHITE, JAMES HOEKEL, JON WASSON, ALEXANDER PACIORKOWSKI, AMY VIEHOVER, ALAN PERMUTT, TAMARA HERSHEY, *St. Louis, MO, Washington, WA*

Wolfram Syndrome (WFS) is a rare, neurodegenerative disease characterized by juvenile-onset diabetes mellitus followed by optic atrophy, neurosensory hearing loss, diabetes insipidus, and other neurological dysfunction. A WFS-specific assessment would be important for describing disease severity across studies and sites, monitoring progression, and possibly determining outcomes of treatment. We have developed the Wolfram Unified Rating Scale (WURS) as a measure of disease severity for WFS and determined its reliability and validity. We tested 13 WFS subjects recruited through the Washington University International WFS Registry (age range 6-25 yrs.; 5 males, 8 females). Each subject was evaluated by 2 pediatric neurologists using the WURS. Motor symptoms and balance were tested, anxiety and mood questionnaires completed and structural brain MR images collected. The WURS had high interrater reliability in the hands of pediatric neurologists (ICCs>.93) and demonstrated good concurrent validity. The WURS Physical Scale correlated with motor and balance tests (n=12, r_s>.67, p<.03) and retinal thickness measures (n=11, r_s=-.64, p=.03). In addition, the WURS Behavioral Scale correlated well with parent and self reports of mood and behavior (n=8, r_s>.76, p<.04). Finally, the WURS Total Scores correlated well with brainstem volume (n=10; r_s=-.82, p=.004). In summary, the WURS has good interrater reliability and concurrent validity and captures individual differences in disease severity. Future work will increase the sample size evaluated, determine the sensitivity of the WURS to longitudinal change and its ability to be reliably administered by non-neurologist physicians or researchers.

Supported by: Jack & J.T. Snow Fund; G. Decker & J.V. Santiago Pediatric Diabetes Fund

1274-P

Finding Common Ground? Parent vs. Teen Beliefs About Transition in Diabetes Care

JENNIFER K. RAYMOND, DANNY C. DUKE, LISA SHIMOMAEDA, MICHAEL A. HARRIS, *Portland, OR*

The purpose of this study was to compare parent and youth beliefs and knowledge about the transition of diabetes care from pediatric to adult providers. Parallel questionnaires about transition were distributed to youth with diabetes and their parents over a 6-month time period during routine clinic visits. Respondents included 123 youth with diabetes (13 to 19 years of age) who had not transitioned to adult diabetes care and their parents. Analyses included comparison of teen and parent responses to questions on the previously reported Diabetes Transition Questionnaire. The findings indicate no statistically significant differences between paired teen/parent responses. They have not discussed the transition of care (2-sided Fisher's Exact Test 0.66), they do not have a transition plan (2-sided Fisher's Exact Test 0.82), and they believe adult diabetes care is similar to pediatric care (2-sided Fisher's Exact Test 0.89). Teen/parent pairs agreed the discussion of the transition process (t = 1.16, p = 0.25) and seeing the diabetes provider alone (t = -1.22, p = 0.23) should occur ~17 years of age. Although not likely clinically significant, teens felt patients should transition at a slightly younger age when compared to their parents (18.03 yr and 18.37 yr respectively, t = -2.21, p = 0.03).While there were relatively no surprises regarding transition beliefs and knowledge of youth with diabetes and their parents, this was one of the first US studies examining the issue in families of youth with diabetes. It is remarkable that teens and parents were in close agreement on transition issues despite the ubiquitous nature of parent/teen conflict with differing opinions on most diabetes and non-diabetes related issues. These data are critical in developing and implementing interventions for teens with diabetes transitioning to adult care. A "family-based" intervention is likely the most efficient and useful approach given teens and their parents are basically in the same place regarding the transition of care.

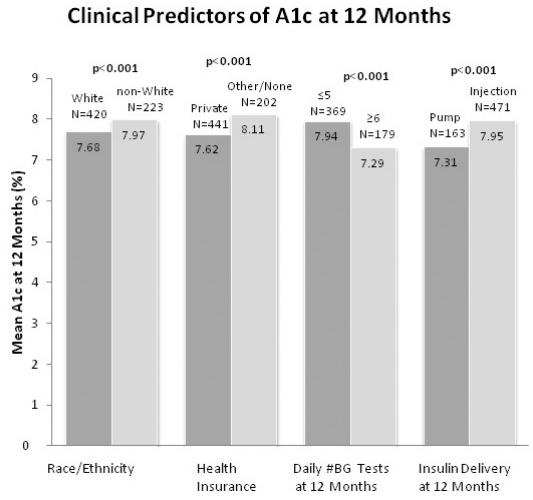
1275-P

Characteristics of Pediatric Type 1 Diabetes (T1D) that Predict HbA1c at One Year

MARIA J. REDONDO, SIEW WONG-JACOBSON, BRUCE BUCKINGHAM, CRAIG KOLLMAN, GEORGEANNA J. KLINGENSMITH, JANET H. SILVERSTEIN, WILLIAM TAMBORLANE, JAMIE WOOD, PEDIATRIC DIABETES CONSORTIUM (PDC), *Houston, TX, Tampa, FL, Stanford, CA, Denver, CO, Gainesville, FL, New Haven, CT, Los Angeles, CA*

We aimed to identify factors that predict HbA1c at 1 year of T1D diagnosis in participants in the Pediatric Diabetes Consortium (PDC). The PDC consisting of 7 U.S. centers longitudinally collected data on youth <19 year old with newly diagnosed T1D. This analysis includes 654 PDC participants with T1D for at least 1 year and HbA1c measured at 365 ± 45 days. Fifty percent of the participants were male and 65%, non-Hispanic white. Mean (SD) age and HbA1c at diagnosis were, respectively 9.2 years (4.1) and 11.5% (2.4). One third presented with diabetic ketoacidosis (DKA) and 94% expressed ≥1 anti-islet autoantibody. Mean (SD) HbA1c at 1 year was 7.80% (1.5). In univariate and multivariate analyses, lower HbA1c at one year was associated with non-Hispanic white race, private health insurance, higher frequency of blood glucose monitoring (BGM) and use of an insulin pump (Figure 1). There was no detectable association with age, gender, anti-islet autoantibodies, DKA at onset, HbA1c at onset, frequency of visits to diabetes provider or, for non-pumpers, the number of daily insulin injections. In conclusion, sociode-

mographic factors and type of treatment predict HbA1c at 1 year of onset in children with T1D. Further investigation is needed to identify potentially modifiable factors that mediate these associations.



Supported by: Novo Nordisk, Inc.

1276-P

Implications of Family History (FHx) of Diabetes (DM) for Youth With Type 1 Diabetes (T1D)

JESSICA T. MARKOWITZ, SUZANNE S. MICKEY, EMILY A. FISHER, DENISE HAYNIE, TONJA R. NANSEL, SANJEEV N. MEHTA, LORI M. LAFFEL, *Boston, MA, Bethesda, MD*

FHx of DM may impact outcomes for youth with T1D. We assessed associations between FHx of DM with sociodemographic factors, DM treatment, and A1c in 283 youth (51% male), aged 13.3±2.9 yrs, with T1D for 6.4±3.4 yrs. Families completed surveys to measure adherence, DM-specific family conflict, and DM family responsibility-sharing. Treatment data derived from the EMR. FHx of DM was self-reported by parents for family members living in the youth's household. Analyses included t-tests, chi-square, and multivariate analyses.29% of families had FHx of T1D (15%), T2D (8%), or both (6%). Youth with FHx of DM did not differ in age, sex, zBMI, T1D duration, or DM responsibility-sharing from youth without FHx. Youth with FHx of DM demonstrated significantly less frequent BG monitoring (BGM), less pump use, less treatment adherence (parent-report questionnaire), greater DM-specific family conflict, and higher A1c vs youth with no FHx. There were a higher proportion of non-whites and non-bachelor's degree educated parents in those with FHx of DM vs no FHx (table).In multivariate analyses controlling for ethnicity, parent education, BGM frequency, insulin regimen, adherence, and conflict, FHx was no longer related to A1c. Thus the association between positive FHx of DM and higher A1c was explained by these psychosocial and treatment factors. While one might expect families of youth with a positive FHx of DM to be more aggressive with T1D management issues, it appears that such families may display less attention. Pediatric patients with FHx of DM may need additional support and interventions aimed at optimizing glycemic control.

N=283	Positive Family History of DM (29%)	Negative Family History of DM(71%)	P value
BGM frequency (times/day)	4.6 ± 2.1	5.6 ± 2.2	0.001
Pump use (%)	50%	72%	<0.001
Adherence questionnaire	70.7 ± 14.0	75.4 ± 13.0	0.007
Conflict score	26 ± 6.4	24.3 ± 4.2	0.011
A1c (%)	8.9 ± 1.4	8.5 ± 1.4	0.018
Non-white families (%)	17	7	0.001
Education < bachelor's degree (%)	48	19	<0.001

Mean±SD or %

Supported by: NICHD (HHSN267200703434C)

1277-P

Do Protein and Fat Impact Glycemic Control in Youth With Type 1 Diabetes (T1D)?

MICHELLE L. KATZ, LEAH B. BELLMAN, CHRISTINA M. KELLEY, TONJA R. NANSEL, LEAH M. LIPSKY, SANJEEV N. MEHTA, LORI M. LAFFEL, *Boston, MA, Bethesda, MD*

Although glycemic excursions result mainly from ingested carbohydrates, data suggest a need also to consider protein and fat when calculating insulin doses. We sought to assess associations between fat and protein intake with A1c in youth with T1D.Families completed 3-day food records for 250 youth (median age 13 years, range 8-18) with T1D for >1 year (median 5.8 years). Youth (51% male) had a mean A1c of 8.5±1.3%, received 0.9±0.3 u/kg/day, and checked BG 5-6 times/day on average. Most youth (69%) used pump therapy. Mean total energy intake was 1988±520 kcal/day. Diets consisted of 35.9±5.6% of calories from fat, 16.0±2.8% from protein, and 49.7±6.6% from carbs (no differences in pump vs. injection treated youth). An A1c ≥8.5% was termed suboptimal. All multivariate analyses included adjustment for age, sex, T1D duration, z-BMI, u/kg/day, BG monitoring frequency, and pump use. There were no associations between percent of daily calories from protein with A1c in bivariate or multivariate analyses. Those with suboptimal A1c's ingested a greater percent of calories from fat compared to those with A1c's <8.5% (36.9% vs. 35.1%, p=.01). This difference was attributable exclusively to pump-treated youth, in whom those with suboptimal A1c's ingested 37.6% of calories from fat versus 34.8% (p=0.001) for those with A1c's <8.5%.In multivariate analyses, there was no association between percent of calories from fat with suboptimal A1c. However, there was a significant interaction between pump use and percent of daily calories from fat (p<0.05), supporting the association between proportion of fat intake and A1c in pump-users. In pump-treated youth, each increasing quartile of percent dietary fat was associated with 1.7 times the odds of having a suboptimal A1c (95% CI 1.2-2.3, p=0.003).A higher percent of daily calories from fat was associated with suboptimal glycemic control in pump-treated youth with T1D. Reducing excess dietary fat or accounting for dietary fat in insulin dose calculations may improve A1c.

Supported by: NICHD contract HHSN267200703434C, T32 5T32DK007260-35

1278-P

Perceptions of Health Care Transition in Young Adults With Type 1 Diabetes

KATHARINE C. GARVEY, HOWARD A. WOLPERT, MARGARET G. BESTE, DONNA LUFF, MARILYN D. RITHOLZ, *Boston, MA*

Data to guide the transition from pediatric to adult care for patients with type 1 diabetes (T1D) are limited. The purpose of this qualitative study was to explore perceptions of the transition process reported by young adults with T1D. A purposive sample of 26 T1D patients (age 26.2 ± 2.5 years, 62% females, 81% white, 85% college degree, diabetes duration 16.3 ± 4.7 years, transition age 20.3 ± 3.2 years) participated in 5 focus groups based on A1c level. Three groups had lower A1c (n = 16, A1c 7.4 ± 0.60%) and 2 groups had higher A1c (n = 10, A1c 9.8 ± 1.0%). Groups were audio-recorded, transcribed, and analyzed using thematic analysis aided by NVivo software. Four main themes emerged from our qualitative analysis: 1) *Reasons for Transition/ Provider-Initiated vs. Natural Progression*: many patients reported "hitting an age limit" or being "kicked out" of pediatrics or "forced to" transition; others described "growing out" of pediatrics, wanting a "new approach" or being "ready for change." Patients in lower A1c groups more often endorsed the provider-initiated transition. 2) *Non-Purposeful Transition*: patients had no explicit preparation for transition by pediatric providers; many described periods of loss to follow-up, particularly in college. 3) *Unexpected Aspects of Transition*: patients were "surprised" that adult care was "so different" and required patients to "do more on our own." There were no clear differences between higher and lower A1c groups for these two themes. 4) *Recommendations for Improved Transitions:* patients had many suggestions for facilitating successful transitions, including dedicated transition preparation visits; improved handoffs between pediatric and adult providers; programs to orient young adults to the adult clinic; and young adult peer mentors and support groups in the adult clinic. Our findings identify modifiable deficiencies in the T1D transition process and underscore the importance of a planned transition with enhanced patient preparation and orientation to adult care.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

1279-P

Calcitriol and Bone Turnover in Type 1 Diabetic Adolescents

NICOLA NAPOLI, ROCKY STROLLO, DARIO PITOCCO, CARLA BIZZARRI, ERNESTO MADDALONI, DARIA MAGGI, SILVIA MANFRINI, ANN SCHWARTZ, PAOLO POZZILLI, IMDIAB GROUP, *Rome, Italy, San Francisco, CA*

Vitamin D supplementation in childhood improves the achievement of peak bone mass. We investigated the effect of calcitriol on bone turnover in recent-onset type 1 diabetes (T1D). Moreover, the association between osteocalcin (OC) and parameters of metabolic control was examined.We conducted a post-hoc analysis of a double-blind, placebo-controlled study of calcitriol supplementation to preserve β-cell function. Twenty-seven recent-onset T1D, mean age 25.6 years (age range 10-35) were randomized to calcitriol (0.25 μg/die) or placebo (1:1) and followed up for 1 year. Changes in bone formation (OC) and resorption (β-CTx) markers, and differences between placebo and calcitriol-treated group were evaluated.*At T1D diagnosis*, OC levels were significantly lower in females than in males (P<0.01). No significant correlations were found in relation to HbA1c, insulin requirement and C-peptide. *At 1 year follow-up*, OC levels were increased (11%) in the placebo group while dropped by 25% in the calcitriol group, but their levels were not significantly different compared to diagnosis. By stratifying patients according to age, we found that at 1 year follow-up as compared to diagnosis, calcitriol-treated patients ≤18 years of age (n=6) showed significant 61% drop of OC (P=0.04) and a 67% reduction in β-CTx (P=0.09). In the same subgroup, OC tended to be lower (P=0.08) and β-CTx were significantly reduced (P=0.03) compared to placebo. Differences were not significant in patients >18 years of age (n=13). In the placebo group, OC levels were inversely related to C-peptide (r=-0.79; P<0.01) and tended to be positively related to insulin requirement (r=0.59; P=0.07). Baseline OC levels were inversely related to C-peptide changes from baseline (r=-0.68; P=0.03).Our preliminary data suggest that calcitriol decreases bone remodeling in T1D adolescents and may preserve bone mass. After 1 year of insulin treatment in the placebo group, OC was negatively associated with C-peptide, thus questioning the role of OC as stimulator for β-cells.

Supported by: Ministero Università e Ricerca Scientifica, Progetti di Interesse Nazionale

1280-P

β-Cell Autoantibody Number has no Effect on c-Peptide Recovery or Loss in Children With T1D

INGRID LIBMAN, VINCENT C. ARENA, MARIBEL CEDILLO, MASSIMO PIETROPAOLO, DOROTHY J. BECKER, *Pittsburgh, PA, Ann Arbor, MI*

We have previously reported that children who are overweight at onset of T1aD have higher baseline and initial recovery of c-peptide but have a more rapid decline after 6 months. We evaluated the relationship between β-cell destruction reflected by number of β-cell autoantibodies (ICA, GAD, IA-2, insulin) measured within 1 week of onset and post-meal c-peptide levels at onset and follow up visits (FUV) 1, 2, 3 and 4 (mean ± s.d. 2.2 ± 0.3, 5.4 ± 0.7; 11 ± 0.8 and 13.2 ± 0.9 months, respectively) in 184 children < 19 years, diagnosed with insulin requiring diabetes from 2004 to 2006. 95% were Caucasian, 40.5% female, mean onset age 9.5±3.9 years, BMI percentile at onset 50.4 ± 32.9 and at FUV1 73.1 ± 20.6, HbA1c (%) at onset 11.9 ± 2.4 and at FUV1 7.3 ± 0.8. The table shows c-peptide levels (ng/ml) (median [interquartile range]) at each time. There were no significant differences in onset age, HbA1c and BMI-SDS at onset between the autoantibody groups. However, BMI-SDS at 3 months was different (1.2±0.7, 0.6±0.7, 1.0±0.8 and 0.6±0.8, respectively, p=0.002).

C-peptide levels	Autoantibodies				
	Negative (n=18)	1 positive (n=25)	2 positive (n=60)	≥ 3 positive (n=81)	p-value
Onset	0.4[0.2-0.9]	0.6[0.2-0.9]	0.6[0.2-0.9]	0.6[0.2-0.8]	0.66
FUV1	1.0[0.5-1.8]	1.4[0.7-2.4]	1.8[0.8-3.0]	1.2[0.7-2.6]	0.59
FUV2	0.9[0.5-0.9]	1.4[0.8-2.0]	1.5[0.6-2.3]	1.0[0.5-2.2]	0.49
FUV3	1.8[0.4-2.9]	0.9[0.3-1.2]	0.7[0.2-1.3]	0.7[0.2-1.1]	0.11
FUV4	0.9[0.2-2.0]	2.4[0.7-2.7]	0.8[0.4-1.2]	0.4[0.2-1.0]	0.28

There were no differences in the degree of recovery of c-peptide or subsequent decline between the autoantibody groups. The degree of β-cell destruction, indicated by autoantibody number, has no effect on the rate of c-peptide loss after remission. These results suggest that C-peptide levels initially do not differentiate those children with insulin-requiring diabetes with negative or fewer autoantibodies.

Supported by: NIDDK

1281-P

Increased Social Networks and Higher Socioeconomic Status Improve Metabolic Control in Type 1 Diabetes

ASHBY WALKER, DESMOND A. SCHATZ, JANET SILVERSTEIN, KATHRYN PARKER, ANASTASIA ALBANESE-O'NEILL, HENRY ROHRS, *Mars Hill, NC, Gainesville, FL*

While research within the social sciences broadly demonstrates the importance of socioeconomic status (SES) in many areas of life experience, little is known about how SES impacts youth living with type 1 diabetes. This study examined ways in which SES as a demographic variable and its impact on social networking mitigates the experiences of youth living with T1D. Surveys were completed by patients with T1D (two or more years since onset) between ages 12-19 years (mean age 16±2 yr[SD]) as well as by their parents/caregivers. Surveys contained closed and open-ended questions assessing basic demographic information, overall perceptions about managing diabetes, and specific measures for youth's social networks (the number of activities youth engage in on a regular basis to help manage diabetes). Informed consent was obtained from 52 patients with 24 responses returned. HbA1c levels were collected for participating youth as a measure of metabolic control (mean duration of disease 7± 4 yr). Results from this mixed-method design indicate that as SES (measured by total household income, parent's level of education, and homeownership) increases, HbA1c decreases (r = -.328). As SES increases, social networks for youth increase substantially (r = .470, p .05). Increased social networking was associated with significantly lower HbA1cs (r = -.473, p .05). Furthermore, our data showed that in middle-to-upper-class families, there is a reorganization of life around diabetes that provides youth with dense social networks. In contrast, youth from poor and working class families have fewer opportunities to engage in enrichment activities and remain isolated from larger diabetes support systems. These findings highlight the importance of social networks in maintaining good metabolic control and indicate that SES and health disparities warrants further attention.

1282-P

Evolution of Social Networking Influence on Information Exchanges: Content Analysis of Type 1 Diabetes Discussions Among Impacted Families

TASHA WENZEL, GNANAGURUDASAN PRAKASAM, CAROL PARISE, MALIA GONSALVES, *Sacramento, CA*

Previous studies have commented on the multiplexity of online support networks, but few have sought to distinguish where patients seek support and information retrieval against the background of the evolving Internet. The SacKidsDiabetes Listserv was started in 2003 to provide a forum for families with one or more patients diagnosed as Type 1 Diabetics to discuss concerns not sufficiently addressed by healthcare providers. The purpose of this study was to explore the issues of greatest importance to people posting to this listserv and assess variances of utilization of the listserv over time. Messages from posts between 2004 and 2007 were analyzed for content and categorized as biomedical, socioemotional, and organizational with 11 subcategories within each category. Of the 547 members subscribed from 2004-2007, a total of 272 individuals posted 2657 unique messages. The majority of contributors were parents and other family members (93.2%) versus patients with diabetes (4.2%). Of the 272 individuals, 209 (77.9%) were women, 53 (19.5%) were men, and 10 (3.7%) were unknown. Analysis of the 2657 messages posted to the listserv revealed a predominance messages regarding socioemotional support, such as Support Offers/Empathy (23.2%) and Emotional Coping (18.9%). Other prevalent topics were in biomedical information with specialized exchanges about care management products (18.7%) and Medical Supply Inventory (12.6%). Over the 4-year period, the number of total posts declined from 803 in 2004 to 524 in 2007, which is likely due to an increase in online resources and changes in Internet accessibility. Social networking is an important supplemental tool for caregivers and patients to exchange care-management information while simultaneously aiding psychosocial coping and support. The healthcare sector can utilize social networking to improve chronic disease management with little impact on healthcare economics.

1283-P

Are Children Newly Diagnosed With Type 1 Diabetes Overweight?

INDRAJIT MAJUMDAR, KATHLEEN BETHIN, TERESA QUATTRIN, *Buffalo, NY*

Weight loss at time of type 1 diabetes (T1DM) diagnosis is common. While traditionally children with T1DM are thin, about 30% of the US population aged 2-19 years is overweight/obese. Dietary education in T1DM emphasizes carbohydrate (CHO) counting. However, patients may ignore caloric intake from fat and protein leading to excess energy intake. We hypothesize

that patients with T1DM may not be all underweight at diagnosis and gain excessive weight after diagnosis due to increased energy intake. The aim of our study is to establish the prevalence of obesity in children at T1DM diagnosis and BMI changes after initiation of insulin. Presented herein are BMI data at diagnosis and 2 weeks post diagnosis, and dietary assessment at 6 weeks. Inclusion criteria: age 2-18 years, T1DM by ADA criteria, absence of acanthosis nigricans and at least 1 positive autoantibody. Weight (wt) and height (ht) were measured, and BMI calculated at diagnosis and 2 weeks post-diagnosis. At diagnosis ht and wt were measured in parents (n=31) and BMI calculated. At the 2-week follow-up, parents were asked to recall daily energy and CHO intake recommended at diagnosis. At 6 weeks parents completed a 3-day food record. Data are expressed as mean+/-SD. Forty-three patients meeting inclusion criteria were approached consecutively and 39 enrolled. BMI at diagnosis was >85 percentile in 39% of children (> 95percentile in 23%) and 1 parent was overweight in 87%. At 2 weeks, BMI-z score increased from 0.45+/-1.2 to 0.67+/-1.1 ($P < 0.001$). While all parents correctly reported their child's daily recommended CHO intake, only 34% recalled the energy intake. Food records indicate that 10 and 40% subjects exceeded recommended daily CHO and energy goals respectively; only 10% met recommended intake of fruits and vegetables. In conclusion, obesity is prevalent in newly diagnosed children withT1DM and their parents. Quality of CHOs and energy derived from fat and protein should be stressed at diagnosis. Moreover current BMI and goal BMI should be reviewed.

1284-P

Assessment of Growth and Final Height in Patients With Type 1 Diabetes Mellitus

CLAUDIA A. COUTINHO, LUIS E. CALLIARI, RENATA M. NORONHA, CRISTIANE KOCHI, OSMAR MONTE, *São Paulo, Brazil*

The impact of type 1 diabetes mellitus(T1DM) on height is still a controversial topic. The goal of the study was to analyze, in T1DM patients, the final stature and the height progression at specific moments: at diagnosis and at onset of puberty.This was a retrospective study of 360 medical records of patients with T1DM followed in an outpatient clinic in an University Hospital. Data collected: Chronological age(CAD) and height at diagnosis(HD), height at onset of puberty(HOP), final height(FH) and target height(TH). All measurements(cm) were converted to Z score. 97 patients met the required criteria: 63 were pre-pubertal(PP) and 34 pubertal(P) at diagnosis. Statistical analysis-SIGMA-STAT3.5. Results-mean(SD): n=97; CAD = 8.4y(3.4); zHD=0.3(1.0); zHOP= -0.26 (0.94); zFH= -0.75(0.8); zTH= -0.84(0.8).At diagnosis, patients were taller than what expected for familial height(zHD=0.3(1.0) vs ZTH= -0.84(0.8), $p \leq 0.001$), but they ended up with a final height similar to the TH(zFH= -0.75(0.8), p=ns). Males and females had the same zFH(M:n=41, zFH= -0.7 (0.8) vs F:n=56, zFH= -0.94 (0.9);p = ns). FH was higher in patients diagnosed during or after puberty vs those diagnosed pre-pubertal(P:n=34, zFH= -0.42(0.8) vs PP: n= 63, zFH= -1.1(0.8);p = 0.001). This was confirmed by comparison with target height: zFH-zTH: PP vs P = -0.16 (0.9) vs 0.5 (1.0); $p \leq 0.001$. In 49 patients it was possible to evaluate the total pubertal growth(TPG): Females: n=27, TPG=19,9cm (5.3) and Males: n=22, TPG=27,2cm(4.8). There was a decrease in height from diagnosis to final height, and this occurred before, during and after puberty.We concluded that patients with T1DM are taller at diagnosis, but obtain final height similar to the expected target height. Those who were diagnosed during or after puberty had higher final height, suggesting that the time course of diabetes may interfere with patients' stature.

1285-P

Glycated Albumin in Infants is Lower than that in Adults and Correlate With Both Age and Albumin

SHIGERU SUZUKI, MASAFUMI KOGA, NORIYASU NIIZEKI, AKIKO FURUYA, HIRONORI TAKAHASHI, KUMIHIRO MATSUO, YUSUKE TANAHASHI, TOMOMI KAWATA, HIROKO ASAI, ETSUSHI TSUCHIDA, FUMIKATSU NOHARA, TOSHIO OKAMOTO, KEN NAGAYA, HIROSHI AZUMA, *Asahikawa, Japan, Itami, Japan*

We previously reported that glycated albumin (GA),but not A1C, reflects glycemic control in patients with neonatal diabetesmellitus. However, GA in healthy infants has not been investigated. We studied total58 healthy full-term newborn infants (4-352 days of age) on serum samples todefine the reference values of GA and to investigate the relationship to plasmaglucose (PG) and albumin. The infants were categorized into 3 groups accordingto age [group A; 5 (4-6) median (range) days: n=18, B; 33 (30-38) days: n=19, C;181 (50-352) days of age: n=21). We also studied 212 non-diabetic adults [53(28-78) years of age] (group D) for comparison. In healthy infants, GA stronglypositively correlated with logarithmic transformation of age [log(age)] ($y=2.31x+5.50$, $r=0.831$, $p<0.0001$), which made it possible to calculate the 95%confidence interval. GA in group A, B, C and D were 7.3±1.0%, 8.6±1.1%, 10.9±0.8% and 14.0±1.1%, respectively (A vs. B, p=0.003, between theother groups, $p<0.0001$). GA positively correlated with PG ($r=0.596$,$p<0.0001$). However, with comparison of PG among the groups, PG in group B(89.4±11.4 mg/dl) was not different from that in group C(90.3±8.7 mg/dl) (p=0.986), whereas PG in group A (67.8±15.1 mg/dl) was significantly lower than those of allthe other groups ($p<0.0001$) and PG in group D (98.4±7.9 mg/dl) was significantly higher than those of allthe other groups (D vs. B or C, $p<0.0001$). GA more strongly positivelycorrelated with albumin ($r=0.768$, $p<0.0001$) than with PG. Stepwise multiplelinear regression analysis showed that log(age) ($\beta=0.495$, $p<0.0001$), albumin ($\beta=0.308$, $p=0.005$) and PG ($\beta=0.173$, $p=0.041$) were significant explanatoryvariables. In conclusion, this study showed the reference range of GA ininfants, which is low and increases with age. This phenomenon was due toage-related elevation of albumin, whose metabolism is believed to facilitate ininfancy, rather than that of PG. Consequently, GA in infants should be comparedwith the reference values based on age.

1286-P

Antibodies to GAD65, ZnT8, IA2 and Rota- and Entero- Viral Antigens in Maternal and Cord Blood Sera

ZVI LARON, CHRISTIANE HAMPE, LESTER SHULMAN, SHOSHANA ISRAEL, KEREN MILLER, FARIBA VAZIRI-SANI, YURI PEREPLIOTCHIKOV, BARI KAPLAN, AVI BEN-HAROUSH, *Petach Tikva, Israel, Tel-Aviv, Israel, Seattle, WA, Tel Hashomer, Israel, Jerusalem, Israel, Malmo, Sweden*

To establish the feasibility of verifying whether childhood T1DM starts prenatally as a result of virus infection transmitted by the mother, sera to beta cell auto-antibodies to GAD65, ZnT8, and IA2 were compared with anti-viral antibodies to Rota (SA11) and Enterovirus (coxB3) in maternal blood of healthy women at birth and cord blood (n=105) during 2 successive winter viral seasons. (2010, 2011). Auto-antibodies titers were determined by radio-ligand binding assays, anti-viral antibodies by ELISA, and newborn HLA DRB1 and DQB1 allele frequencies by PCR.The Table show the summary. Sera from 10% of chord and 8% of maternal serum samples were positive for GAD65Ab. Of these, 20% and 25% had high Ab titers to rotavirus and 50% and 50% had high Ab titers to enterovirus, respectively (Table). Of the remaining samples, only one mother and child had antibodies to ZnT8, while no sample had antibodies to IA2. Class II HLA allele frequencies in individuals with high auto-antibodies and/or antiviral Abs were similar to the frequencies in all enrolled newborns.The presence of significant GAD65Ab titers in 10 newborns and 8 of their mothers may indicate autoimmune damage to their β cells "in utero" possibly caused by the transmission of a viral infection from the mother. Follow-up will determine whether this early trigger event will progress to development of T1D and to what extent it is related to HLADRB1/DQB1 haplotypes. The relationship between high maternal anti-viral Abs and auto-antibody levels could not be established in this pilot study due to the unavailability of sufficient numbers 21/108 of first trimester maternal sera.

Number and % of 105 paired maternal and cord blood samples

	Cord Blood Antibodies	Cord Blood Antibodies	Cord Blood Antibodies	Postpartum Maternal Antibodies	Postpartum Maternal Antibodies	Postpartum Maternal Antibodies
	GAD 65	Rotavirus	Enterovirus	GAD 65	Rotavirus	Enterovirus
GAD 65	10 (9.5%)	2/10 (20.0%)	5/10 (50.0%)	8 (7.6%)	2/8 (25.0%)	4/8 (50.0%)
Rotavirus	2/22 (9.0%)	22 (20.9%)	11/22(50.0%)	2/12 (16.7%)	12 (11.4%)	3/12 (25.0%)
Enterovirus	5/48 (10.4%)	11/48(22.9%)	48 (45.7%)	4/34 (11.8%)	3/34 (8.8%)	34 (32.4%)

Supported by: Sano Ltd., Israel

PEDIATRICS—TYPE 2 DIABETES

Guided Audio Tour: Pediatric Assessment of Glycemic Control and Insulin Resistance *(Posters 1287-P to 1294-P), see page 17.*

1287-P

Racial Differences in Hemoglobin A1c in U.S. Children and Adolescents

NAYLA G. KAZZI, ACHAMYELEH GEBREMARIAM, JOYCE M. LEE, *Ann Arbor, MI*

Although studies have documented racial differences in HbA1c among adults, we are unaware of studies that have evaluated similar differences in children.Our objective was to examine racial and ethnic differences in A1c in a nationally representative sample of children and adolescents. Our

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

study population consisted of 3,351 children aged 12-18 years of age without diabetes who had HbA1c and fasting plasma glucose (FPG), using data from the National Health and Nutrition Examination Surveys (1999-2006). We conducted bivariate and multivariate analyses assessing the relationship between HbA1c and demographics, BMI, systolic and diastolic BP, HOMA-IR, and FPG.Unadjusted mean HbA1c for the overall population was 5.15% (SE 0.00), and was 5.09% (SE 0.00) for white children (n=852), 5.23% (SE 0.01) for black children (n=1081), 5.12% (SE 0.00) for Mexican-American children (n=1155), and 5.16% (SE 0.01) for children of other races (n=263). In bivariate analyses, independent predictors of HbA1c included age, race, gender, BMI percentile, HOMA-IR, and FPG. After adjustment for all of these factors, mean A1c was 5.09% (SE 0.01) for whites, 5.24% (SE 0.01) for blacks, 5.11% (SE 0.01) for Mexican-Americans, and 5.17% (SE 0.02) for children of other races.HbA1c levels are higher for black children compared with white children. This has important policy implications given that Hemoglobin A1c is now the preferred test for diagnosing children with diabetes and thresholds of 5.7% and 6.5% are the designated thresholds for defining prediabetes and diabetes regardless of race.

Supported by: NIDDK K08 DK082386 (J.L.); Clinical Sciences Scholars Program

1288-P

Is Pre-Diabetes Associated With Increased Arterial Stiffness in Youth?

AMY S. SHAH, ZHIQIAN GAO, ELAINE M. URBINA, PHILIP R. KHOURY, THOMAS R. KIMBALL, LAWRENCE M. DOLAN, *Cincinnati, OH*

Hyperglycemia plays a central role in the development of atherosclerotic cardiovascular (CV) disease. Increased arterial thickness and stiffness are potential mechanisms linking these processes. Whether early glucose derangements such as those seen in pre-diabetes are associated with intermediate CV outcomes such as arterial thickness and stiffness in adolescents and young adults is not known. Thus we studied 62 youth with pre-diabetes (mean age =18.3 ± 3.4 yrs, 60% African American, 52% male, avg BMI = 34.3 ± 8.5) and 62 age, race, sex and BMI matched controls (selected on propensity score). Pre-diabetes was defined as either impaired fasting glucose or impaired glucose tolerance as defined by ADA criteria. Clinical, biochemical data, and arterial stiffness and thickness measures - carotid intima media thickness (IMT), pulse wave velocity femoral (PWVf), augmentation index (AIx) and brachial distensibility (BrachD) were measured. T-tests and nonparametric tests were used to evaluate group differences. Non -linear variables were log transformed. Linear regression modeling was used to determine whether having pre-diabetes was an independent predictor of increased arterial disease after adjustment for covariates. Full models included group, age, sex, race, BMI, systolic and diastolic blood pressure (BP), lipids (total, LDL, HDL cholesterol and triglycerides) and HbA1c. There were no differences in BP and total, LDL and HDL cholesterol between groups. Despite similar BMIs, individuals with pre-diabetes had higher triglycerides, fasting insulin and glucose. Linear models revealed pre-diabetes was an independent predictor of PWVf (model R^2= 0.53) but not carotid IMT, AIx or BrachD. Other risk factors important in the outcomes were age, race, sex, BMI-Z, BP and HbA1c. We conclude: 1) hyperglycemia before the onset of diabetes is an independent risk factor for increased arterial stiffness, and 2) changes in arterial stiffness as detected by PWVf may be the most sensitive marker of early arterial disease.

Supported by: NHLBI R01 HL076269, USPHS UL1 RR026314

1289-P

Association Between Iron Deficiency and Hemoglobin A1c in US Adolescents

NAYLA G. KAZZI, CATHERINE KIM, JOYCE M. LEE, *Ann Arbor, MI*

Studies in adults have shown that iron(Fe) deficiency increases HbA1c levels independent of glycemia, but we are unaware of studies that have evaluated this relationship in children.Our objective was to examine the relationship between measures of Fe deficiency and anemia with HbA1c distribution among US adolescents without known diabetes.Our study population consisted of 5,416 adolescents 12-18 years without self-reported diabetes, who had HbA1c levels, complete blood counts, and Fe studies using data from the National Health and Nutrition Examination Surveys (1999-2006). Fe deficiency was defined as 2 out of 3 abnormal tests: high free erythrocyte protoporphyrin, low serum ferritin, or low transferrin saturation. Fe deficiency anemia was defined as Fe deficiency plus low hemoglobin levels (age and sex-adjusted). We also evaluated the relationship between Fe deficiency, and the likelihood of having an HbA1c≥5.5% or ≥5.7%, adjusting for demographics, BMI%, smoking status, and C Reactive Protein.Approximately 8.5% (n=602) of adolescents had Fe deficiency, 1.8% (n=158) had Fe deficiency anemia, 8.7% (n=588) had an HbA1c≥5.5%, and 1.9% (n=147) had an HbA1c≥5.7%. Mean HbA1c for the population was 5.12 (0.01), and was 5.12 (0.01) for adolescents with normal iron levels vs. 5.18 (0.02) for adolescents with iron deficiency. There was a greater odds of having an HbA1c≥5.5% for adolescents with iron deficiency compared with those without (OR 2.17 (95%CI:1.31-3.57)) and for adolescents with iron deficiency anemia compared with those without (OR 3.17 (95%CI:1.45-6.90)). Similar trends were seen for having an HbA1c≥5.7% for those with Fe deficiency (OR 1.93 (95%CI:0.94-3.97)) and for those with Fe deficiency anemia (OR 1.72 (95%CI:0.80-3.72)), although these trends were not significant.Fe deficiency is associated with shifts in the HbA1c distribution in children. This has policy implications given the recent ADA recommendation regarding use of Hemoglobin A1c for diagnosis of prediabetes and diabetes.

Supported by: NIDDK K08 DK082386 and Clinical Sciences Scholars Program

1290-P

Plasma Ceramides are Elevated in Female Children and Adolescents With Type 2 Diabetes and Correlate Inversely With Adiponectin and Measures of Insulin Sensitivity

XIMENA LOPEZ, ALLISON B. GOLDFINE, WILLIAM L. HOLLAND, RUTH GORDILLO, JORDAN STREETMAN, RITA MARTIN, PHILIPP E. SCHERER, *Dallas, TX, Boston, MA*

Accumulation of ceramides within tissues induces insulin resistance. Animal data show that adiponectin exerts its beneficial metabolic effects through ceramide catabolism and formation of its metabolite sphingosine-1-phosphate (S1P). The objective of this study is to quantitate circulating plasma ceramides in children and adolescents with type 2 diabetes (T2D), and relate levels with adiponectin and measures of insulin sensitivity.We analyzed fasting plasma ceramide subspecies by quantitative tandem mass spectrometry in 14 obese female subjects with T2D, ages 10-17, and 14 lean healthy females of the same age.T2D subjects had higher concentrations of C22:0 and C20:0 ceramide, with a 2-fold increase in C18:0 and C24:1 dihydroceramide (P<0.05 all) (Figure 1). C22:0, C20:0 and C18:0 ceramide correlated with decreased adiponectin levels (P≤0.01), and with increased HOMA-IR (P≤0.004), triglyceride levels (P≤0.0002), fasting blood glucose (P≤0.03) and BMI Z-score (P≤0.04).On the other hand, C24:1 glucosylceramide was decreased in the T2D group (P<0.05), and correlated with adiponectin levels (P=0.01) and with decreased BMI Z-score (P=0.01). C24:1 glucosylceramide and C16:0 glucosylceramide were higher in the T2D subjects receiving metformin (P=0.03 and P=0.0005, respectively). S1P concentrations were similar.Plasma C18:0, C20:0, C22:0 ceramide and C24:1 dehydroceramide are elevated in female children and adolescents with T2D. This may be a reflection of tissue insulin resistance and could be a result of low adiponectin levels.

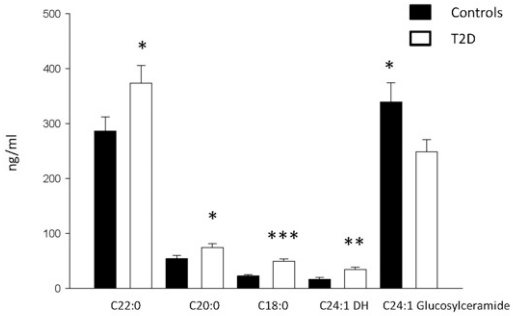


Figure 1. Plasma concentrations of ceramide subspecies in T2D vs. control subjects. *P<0.05, **P<0.002, ***P<0.00001

Supported by: Children's Medical Center Foundation Grants

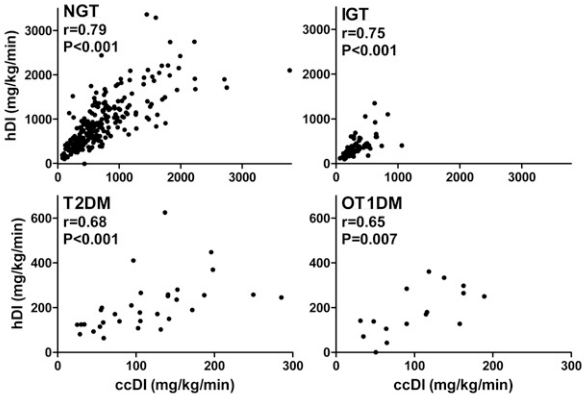
1291-P

Measuring Beta-Cell Function Relative to Insulin Sensitivity in Pediatric Research: Does the Hyperglycemic Clamp Suffice?

LINDSEY A. SJAARDA, SOJUNG LEE, FIDA BACHA, HALA TFAYLI, ELISA ANDREATTA, SILVA ARSLANIAN, *Pittsburgh, PA, Houston, TX, Beirut, Lebanon*

Insulin secretion is coupled to insulin sensitivity, hence the importance of expressing beta-cell function relative to insulin sensitivity, i.e. the disposition index (DI). Given the childhood obesity epidemic and its consequence of dysglycemia, methods for precisely and feasibly assessing DI in pediatric research are of paramount importance. Therefore, the aim of this study was

to compare the DI calculated from two separate clamp experiments (ccDI), as the product of insulin sensitivity from the hyperinsulinemic-euglycemic clamp and first phase insulin from the hyperglycemic clamp, to the DI calculated as the product of first phase insulin and insulin sensitivity both derived from a single hyperglycemic clamp (hDI). A total of 342 normal weight to obese youth (ages 8 to <20 years old, 43% African-American/55% Caucasian, 58% female) with normal glucose tolerance (NGT, n=235), impaired (IGT, n=59), type 2 diabetes (T2DM, n=32) or obese type 1 diabetes (OT1DM, n=16), completed both a 2-hr hyperglycemic (~225 mg/dl) and a 3-hr hyperinsulinemic-euglycemic clamp. Spearman correlations between ccDI and hDI were evaluated. The hDI correlated significantly with ccDI in all the groups combined (r=0.86, P<0.001) and within each group separately (Figure). In conclusion, a single hyperglycemic clamp may be used to provide a measure of beta-cell function relative to insulin sensitivity in youth with varying glucose tolerance when two clamp studies are not feasible due to participant burden or research costs.



Supported by: NIH (R01HD27503, K24HD01357 and UL1RR024153)

1292-P

Metabolomic Profiling of Amino Acids and Metabolic Risk for Type 2 Diabetes in Youth

SARA F. MICHALISZYN, STEPHANIE J. MIHALIK, SOJUNG LEE, DONALD H. CHACE, VICTOR R. DEJESUS, JERRY VOCKLEY, SILVA ARSLANIAN, *Pittsburgh, PA, Sunrise, FL, Atlanta, GA*

In adults, elevated amino acid concentrations are associated with heightened risk of developing type 2 diabetes. In contrast, we found that youth with type 2 diabetes have lower amino acid concentrations compared with their non-diabetic peers (Diabetes Care, in Press). The aim of the present investigation was to examine the relationships between plasma amino acid concentrations and the metabolic risk for type 2 diabetes exemplified in insulin sensitivity (IS) and beta cell function relative to insulin sensitivity i.e. disposition index (DI). Metabolomics analysis for fasting plasma amino acid concentrations was performed by tandem mass spectrometry in 113 (57 male/56 female; 52 black/61 white) normal weight to obese adolescents (BMI 81.5 ± 26.3%; mean age 13.1 ± 1.7yrs; Tanner stage II-V) with normal glucose tolerance. *In vivo* IS was evaluated by a 3-hr hyperinsulinemic-euglycemic clamp and first-phase insulin secretion by a hyperglycemic (~225 mg/dl) clamp. DI was calculated as the product of first-phase insulin and IS. IS showed positive associations with leucine/isoleucine, valine, phenylalanine, glycine, histidine, arginine and serine (range r = .21 to .45, $p \leq 0.03$). Similarly, beta-cell function relative to insulin sensitivity showed positive associations with valine, phenylalanine, methionine, alanine, histidine, glycine and serine (range r = .18 to .31, $p \leq 0.05$). These associations remained significant after adjusting for Tanner stage and percent body fat. There were no sex or race related differences in the associations between amino acids and IS or DI.In conclusion, in youth in contrast to adults, higher concentrations of plasma amino acids are associated with a lower metabolic risk profile for the pathophysiology of type 2 diabetes. We theorize that these youth/adult contrasting results are of evolutionary nature, dependent on time and the aging process against the backdrop of progressive obesity.

Supported by: R01 HD-27503 (S.A.), K24 HD-01357 (S.A.), R01 DK-78775 (J.V.)

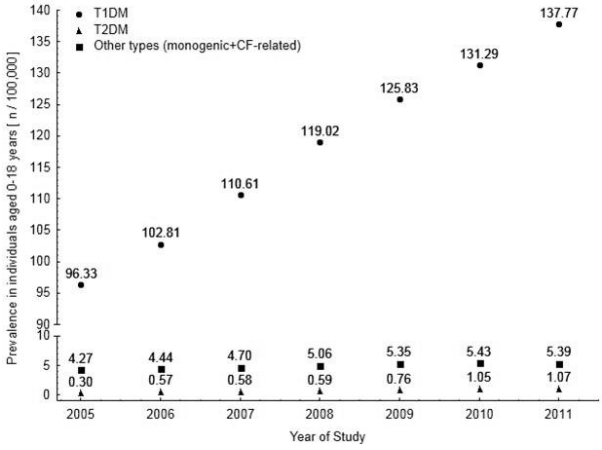
1293-P

Monogenic Diabetes is Five Times More Frequent than Type 2 Diabetes in Polish Children: PolPeDiab Epidemiology Report

WOJCIECH FENDLER, MACIEJ BOROWIEC, ANNA BARANOWSKA-JAZWIECKA, GRAZYNA DEJA, ILONA TECHMANSKA, PRZEMYSLAWA JAROSZ-CHOBOT, MALGORZATA MYSLIWIEC, AGNIESZKA SZADKOWSKA, WOJCIECH MLYNARSKI, *Lodz, Poland, Katowice, Poland, Gdansk, Poland*

Recent data on childhood diabetes in Poland showed a rapid increase of incidence despite a relatively low prevalence of obesity (<5%). Merging these epidemiologic data with the results of the National Registry for Monogenic Diabetes (the TEAM program) we compared the prevalence of T1DM, T2DM and other types of diabetes (cystic fibrosis-related and monogenic diabetes (MD)). Genetically confirmed MD included: MODY, neonatal diabetes, Wolfram and Alstrom syndromes. The study group covered over 2,700 children (age below <18 yrs) treated for diabetes in three regions inhabited by 1.78 million out of 7.52 million children in Poland (23.7%) between 2005-2011. We observed statistically significant increases in the prevalence of T1DM and T2DM (annual increase by 7.0 and 0.12 per 100,000 respectively; both p<0.001). T2DM constituted 0.3 to 0.8% of all cases of childhood diabetes, resulting in prevalence of 0.3-1.07 per 100,000 (fig. 1). Other types of diabetes (MD and CF-related) were detected in 3.7-4.2% of patients. Their prevalence rose from 4.2 to 5.4/100,000 due to an increase of CF-related cases (p<0.001). MD showed a stable prevalence of 4.2-4.6/100,000 children. MD was confirmed in 92 out of 311 referred cases. Median delay between diagnosis of diabetes and successful genetic diagnosis equaled 0.93 years. A majority of patients with MD was diagnosed with GCK-MODY (86%). Seven patients had neonatal (1:300,000) and 14 had CF-related diabetes (1:150,000). The prevalence of MD and CF-related diabetes in children with a moderate prevalence of obesity is at least fivefold higher than that of T2DM.

Figure 1



Supported by: The TEAM Programme of the Foundation for Polish Science

1294-P

Impact of Acute Moderate Intensity Exercise on Blood Glucose (BG) in Youth With Type 2 Diabetes Mellitus (T2D)

PAULA G. NEWTON, NEIL H. WHITE, *St. Louis, MO*

T2D accounts for 8-45% of new onset diabetes in youth, a 33% increase over the past 10-15 years. About 3700 youth < 20 yrs old are diagnosed with T2D each year. Benefits of exercise as part of T2D management have been variably shown in adults; however, studies in youth are limited. This study was performed to examine the effects of moderate intensity exercise on BG during the subsequent day in youth with T2D.We enrolled 10 subjects 14-20 yrs old with T2D for at least 6 months. All were using metformin and insulin. Subjects participated in 2 separate days of testing, an Exercise (EX) and a Sedentary (SED) day. During the afternoon on the EX day subjects rode a stationary bicycle for three 10-min periods (with 5 min rest) at approximately 75% HR_{max} corresponding to approximately 65% VO_{2max}. BG was measured prior to EX, during and immediately following EX, and at 15-min intervals for one hour following EX. An identical (except for no EX) SED day was completed 1-2 weeks before (or after) in random sequence. On both days, the target BG at the start of the EX or SED period was 100-250 mg/dL. Subjects wore a continuous glucose monitoring system (CGM; iPro Medtronic) to assess BG for 24 hours before and 48 hours after EX or SED. EX decreased BG

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

from 135±42 mg/dL to 94±36 (Δ=42±17; p=0.004) compared to SED 130±42 to 121±36 (Δ=9±17; p=0.143; EX vs SED p=0.009). Despite this lowering of BG during EX, CGM readings over the next 16 h (1600h-0800h) showed no difference in mean BG (169±60 mg/dL vs 175±44; p=0.61), %BG <70 (0.1±0.1% vs 0.9±2.8%; p=0.35), %BG >150 (50±34% vs 52±36%; p=0.96) or %BG 70-150 (41±33% vs 47±36%; p=0.72) after EX compared to SED. EX did not significantly increase the risk of hypoglycemia during this time period. We conclude that a single bout of moderate intensity exercise that lowers BG during the exercise does not have a sustained effect on BG during the subsequent 16 hours. Whether exercise of higher intensity, longer duration, or increased frequency would have lasting effects on BG remains to be studied.

Supported by: Endocrine Fellows Foundation Marilyn Fishman Grant for Diabetes Research

1295-P

Insulin Resistance Rises before Puberty, Independently of Body Fat, and Signals Deteriorating Metabolic Health: A 10-Year Longitudinal Study

ALISON N. JEFFERY, BRAD S. METCALF, JOANNE HOSKING, ADAM J. STREETER, MOHAMMOD B. MOSTAZIR, LINDA D. VOSS, TERENCE J. WILKIN, *Plymouth, United Kingdom*

Insulin resistance (IR) is known to be higher in puberty, but it is not clear when it starts to rise, nor the impact of its doing so. Only longitudinal data can establish the relevant trends and their interactions. We sought to establish from a cohort study when the 'pubertal' rise in IR begins, and to track the behaviour of its metabolic co-variables. We followed 139 healthy boys (B) and 128 girls (G) annually from 5-15y, measuring HOMA-IR, % body fat by DEXA, fasting triglycerides, cholesterol-HDL ratio (CHR), and adiponectin, luteinising hormone (LH), systolic and diastolic BP (SBP, DBP). Pubertal onset was defined by the age at which LH first became permanently detectable (≥0.2 mu/l). Linear mixed effects models were constructed for the pre-pubertal period, and adjusted for exact age and %fat.IR started to rise up to 4 years before pubertal onset: B mean 3.86y before onset (2.08-4.29), G mean 3.99y (3.64-4.40y). During the pre-pubertal period, mean IR rise in B was +19.7% (0.52-0.80 HOMA-IR units) and +12.7% in G (0.66-1.08 units), both p<0.001. Each unit increase in HOMA-IR was associated with the metabolic changes below, independently of body fat.The early rise in IR, independent of body fat and puberty, together with the associated adverse metabolic changes, have not been reported before. The increases in triglycerides and DBP, in particular, were substantial and revealed only by the longitudinal observation of a cohort of uniform age. The pathological implications of these increases will become clearer as the cohort matures.

Prepubertal metabolic changes associated with change in HOMA-IR

	Boys		Girls	
	Estimate (back-transformed)	p	Estimate (back-transformed)	p
Adiponectin	-10.6%	0.020	-8.0%	0.006
CHR	+1.1%	0.521	+3.2%	0.021
Triglycerides	+43.9%	<0.001	+20.6%	<0.001
SBP	+0.7%	0.659	+2.0%	0.004
DBP	+5.0%	0.002	+2.7%	<0.001

Supported by: Novo Nordisk, UK Research Foundation

1296-P

Genetics of Metabolic Syndrome in Mexican American Children: The San Antonio Family Assessment of Metabolic Risk Indicators in Youth (SAFARI) Study

SHARON P. FOWLER, SOBHA PUPPALA, VIDYA S. FAROOK, JENNIFER SCHNEIDER, GEETHA CHITTOOR, ROY G. RESENDEZ, KELLY J. HUNT, BENJAMIN S. BRADSHAW, EUGENIO CERSOSIMO, RECTOR ARYA, LAURA ALMASY, JOANNE E. CURRAN, ANTHONY G. COMUZZIE, DONNA M. LEHMAN, CHRISTOPHER P. JENKINSON, JANE L. LYNCH, RALPH A. DEFRONZO, JOHN BLANGERO, DANIEL E. HALE, RAVINDRANATH DUGGIRALA, *San Antonio, TX, Charleston, SC, Houston, TX*

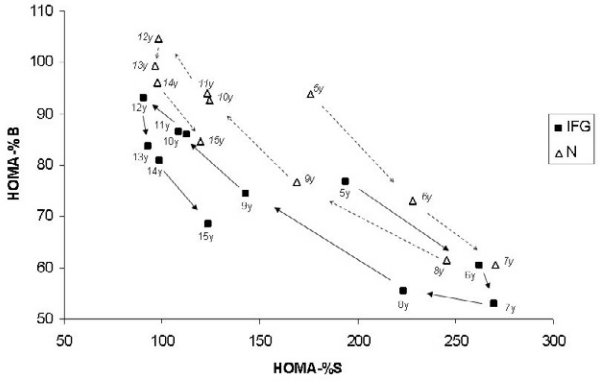
Metabolic syndrome (MS) and its risk factors have increased alarmingly in children, especially among minority groups such as Mexican Americans (MAs). Given the paucity of data on the genetics of MS in children, the purpose of this study is to examine the prevalence of MS and its components among 670 high-risk, non-diabetic MA children from our SAFARI study (age range: 6-17 years; mean age: 12 yrs; girls: 49%), and to determine the genetic basis of MS and its risk factors in them. Our MS definition requires the presence of 3 or more of the following 6 components: increased waist circumference (≥ 90th percentile for age, sex, ethnicity); insulin resistance (fasting insulin > 75th SAFARI cohort percentile for all ages and both sexes); glucose intolerance, defined as impaired fasting glucose (IFG: ≥ 100 and < 126 mg/dL), impaired glucose tolerance (IGT: ≥ 140 and < 200 mg/dL) or both; high triglycerides (≥ 110 mg/dL); low HDL cholesterol (HDL: ≤ 40 mg/dL); and high blood pressure (≥ 90th percentile for age, sex, and height). Using the above criteria, the prevalence of MS was 19%. Prevalence of the 6 MS components ranged from 12% (high blood pressure) to 32% (Low HDL and abdominal obesity). The heritability of MS was extremely high (h2 = 1.00, P = 0.0008). MS components were also highly heritable (P < 0.05; range: 0.51 [HDL] to 1.00 [insulin resistance and high blood pressure]). We examined the genetic correlations between number of MS components (MS score: range: 0 to 5) and the following: obesity (OB: BMI ≥ 95th percentile for age and sex), Matsuda Insulin Sensitivity Index (ISI), inflammation (hs C-reactive protein: hsCRP), and Harvard Step Test physical fitness score (PFS). The genetic correlations between MS score and these traits were moderate-to-high and significant (P < 0.05): OB: 0.82, ISI: -0.58, hsCRP: 0.59, and PFS: -0.43. In summary, we found that MA children are at high risk for MS and its components, which were found to be under strong genetic influences.

1297-P

Mapping Glucose Control in Children at Risk of Type 2 Diabetes: A 10-Year Longitudinal Study

TERENCE WILKIN, JOANNE HOSKING, ALISON JEFFERY, BRAD METCALF, LINDA VOSS, *Plymouth, United Kingdom*

Blood glucose is controlled by the interplay between insulin demand (tissue sensitivity) and insulin supply (beta cell function). While HOMA is unsuitable, on theoretical grounds, for calculating the disposition index, the vector which links HOMA-S to HOMA-B can be used to track changes in their relationship on a simple X-Y plot.The EarlyBird study has monitored the metabolic progress of 307 children from the age of 5-15y, using annual fasting blood samples to calculate HOMA. Fifty-five children have shown impaired fasting glucose (IFG, ≥5.6 mmol/l), most of them after 12y, and we compared the path taken by their HOMA vector with that of children whose fasting glucose remained normal (N).The trajectories followed by the mean vectors of the two groups were distinct. The IFG children traced a path which was displaced vertically downwards in relation to that of the N children. Accordingly, their HOMA-B was systematically lower than that of the N children (p<0.01), while their HOMA-S remained similar (>0.1 at all time points).Vector plotting provides a visual representation of the infinitely variable interaction between S and B over time. IFG is a risk factor for future diabetes, and children who show IFG are distinguished by a beta cell defect which is already present at 5y of age. Vector mapping is likely to have wide application to the visualisation of glucose control over time.



Path followed over time by the vector linking insulin demand (HOMA-%S) to insulin supply (HOMA-%B) of 55 children showing IFG (⟶) compared with that of 252 normal controls (⇢)

1298-P

Demographic and Cardiovascular Profiles in Identification of Pre-Diabetes in Adolescents

AMISHA WALLIA, KIARRI KERSHAW, DANIEL PORTILLO, MERCEDES CARNETHON, MARK MOLITCH, *Chicago, IL*

There are limited data on the differences in demographic and cardiovascular (CV) profiles of adolescents identified by different testing modalities (ie fasting glucose [FG], oral glucose tolerance [OGTT], and Hemoglobin A1c [A1c]) for pre-diabetes (preDM).In 1139 adolescents (age ≥ 12 and ≤ 19 years)

from NHANES 2005-2008 free from DM, we compared the distribution of demographic characteristics and CV risk factors across testing profiles. Analysis of variance with survey weighting was used to compare those identified as normal by all 3 tests (71.6%), PreDM by ≥ 2 tests (3.5%), and PreDM by 1 test only (24.9%).Results are summarized in Table. Those + by 1 test only were significantly younger, predominantly male, and had higher fasting insulin levels and systolic BP, when compared to normal. Those + by HbA1c only were predominantly black.Testing adolescents for pre-diabetes in diverse demographic settings may require both fasting and non-fasting modalities of testing at an early age.

Table	Normal	2 ≥ + tests	FG + only	A1c + only	OGTT+ only
N	816	40	226	27	30
Age, mean yrs (SE)	15.8 (0.1)*	14.3 (0.4)	15.2 (0.2)†	15.4 (0.6)	14.6 (0.6)
Male (%)	44.6*	37.1	74.2†	71.1	52.7
Race, n (weighted %)‡				†	
Mexican	250 (10.4)	15(17.5)	85 (15.1)	2 (2.7)	10 (7.3)
Hispanic	45 (4.3)	5(13.3)	23 (7.1)	1 (3.4)	4 (13.2)
Black	253 (14.8)	14 (24.4)	40 (8.9)	22 (77.2)	5 (4.3)
Other	37 (6.3)	1(12.8)	12 (6.6)	0 (0)	0 (0)
White	231 (64.2)	5 (43.5)	66 (62.3)	2 (16.7)	11 (75.2)
Systolic BP, mm Hg (SE)	109.0 (0.6)*	111.7 (4.2)	113.2 (1.0)	111.7 (2.0)	113.9 (2.8)
Total cholesterol, mg/dl (SE)	156.9 (1.7)	161.8 (3.9)	157.5 (2.8)	158.1 (3.4)	188.3 (10.0)
Waist circumference, mean cm (SE)	81.3 (0.7)	85.0 (5.3)	83.2 (2.2)	80.2 (4.0)	86.6 (5.1)
BMI, mean kg/m2 (SE)	23.5 (0.3)	24.8 (2.0)	23.8 (0.8)	24.3 (2.2)	25.1 (1.8)
Fasting Insulin levels, uU/mL (SE)	11.1 (0.4)*	22.9 (4.0)	15.5 (0.9)	12.6 (1.8)	14.7 (1.9)

p<0.0125 for multiple pairwise comparisons with*composite 1+ test group†normal group‡ p-values for race are based on categories where Hispanic and Other are combined

1299-P

The Factor Structure of the Metabolic Syndrome and Its Genetic Basis in Mexican American Children

RECTOR ARYA, SOBHA PUPPALA, SHARON P. FOWLER, VIDYA S. FAROOK, JENNIFER SCHNEIDER, GEETHA CHITTOOR, ROY G. RESENDEZ, KELLY J. HUNT, BENJAMIN BRADSHAW, EUGENIO CERSOSIMO, LAURA ALMASY, JOANNE CURRAN, ANTHONY G. COMUZZIE, DONNA M. LEHMAN, CHRISTOPHER P. JENKINSON, JANE L. LYNCH, RALPH A. DEFRONZO, JOHN BLANGERO, RAVINDRANATH DUGGIRALA, DANIEL E. HALE, *San Antonio, TX, Charleston, SC, Houston, TX*

The prevalence of Metabolic Syndrome (MS) has increased alarmingly in children, particularly among minority groups such as Mexican Americans. There have been continued efforts to define it and to examine its genetic basis. As part of our San Antonio Family Assessment of Metabolic Risk Indicators in Youth (SAFARI) Study (N = 670, aged 6-17 years [mean age = 12 yrs], girls = 49%, obesity = 34%, and pre-diabetes = 13%), we defined MS based on the presence of 3 or more of the following 6 components: increased waist circumference (WC), insulin resistance, glucose intolerance, high triglycerides (TG), low high-density cholesterol (HDL-C), and high blood pressure. Using these criteria, the prevalence of MS was 19%. In this study, we examined factor structures that underlie the correlations among the 8 MS-related quantitative traits used to define MS: WC, fasting insulin (FI), fasting glucose (FG), 2-hr glucose (2hr-G), HDL-C, TG, systolic (SBP) and diastolic (DBP) blood pressure. For this, we used principal component factor analysis (PCFA) and the available data for all 8 traits. PCFA yielded three constructs: adipo-insulin-lipid factor (WC, FI, HDL-C, and TG), blood pressure factor (SBP and DBP), and glucose factor (FG and 2hr-G). These factors are different from adult MS factors we reported earlier. The three factors together explained 65.0% of variation in the data. After adjusting for age, sex, and pubertal status, they were found to be significantly heritable (h^2: $P < 0.05$): adipo-insulin-lipid factor = 0.79, blood pressure factor = 0.70, and glucose factor = 0.35. In addition, we conducted bivariate genetic analyses to determine genetic correlations between the MS traits. WC, for example, was significantly ($P < 0.05$) genetically correlated with FI (0.53), HDL-C (-0.49), and TG (0.53); and SBP with DBP (0.88) and TG (0.34). In summary, our data reveals the complex genetic architecture of MS in MA children, in turn suggesting possible distinct biological processes underlying the MS structure.

Supported by: NIH (R01 HD049051)

1300-P

Utilizing Novel Interventions to Prevent Diabetes in Youth (UNITY)

EVA M. VIVIAN, *Madison, WI*

Utilizing Novel Interventions to Prevent Diabetes in Youth (UNITY)The overall objective of this randomized controlled pilot study was to test a culturally appropriate translated version of the Diabetes Prevention Program (DPP) lifestyle intervention that was accessible and affordable to families with children at risk for type 2 diabetes (T2DM). The central hypothesis for this study was that obesity due to poor nutritional habits and sedentary lifestyle are major contributors to the increasing prevalence of T2DM in youth and these processes can be reversed with good nutrition and physical activity. A sample of 66 children and their parents were recruited from neighborhood community centers, churches, and clinics. The mean age of the children was 12.34 ± 0.84 years and they were predominantly female (≥60%). Thirty eight children (57.6%) self-reported as Hispanic/Latino, 23 as African American (34.8%), and five as Native American (7.6%). Children randomized to the intervention group participated in physical activity classes 3 to 4 times a week at a neighborhood community center after school hours. The children and their parents also participated in monthly family nutrition and behavior modification sessions. Families randomized to the control group received monthly nutrition and physical activity educational materials through the mail. At baseline, 51 (77%) of 66 children exhibited BMI z-scores above the 95th percentile and 15 (23%) had BMI z-scores above the 85th percentile. There were no differences in BMI group by race or ethnicity. The mean change in BMI z-score in the intervention group was -0.1105 (95% CI -0.095 to -0.125, p= 0.04) compared with children in the control group. After one year, this community based intervention decreased BMI z-score in children at high risk for T2DM. This model demonstrates promise for communities throughout the country who face the threats of childhood obesity and T2DM.

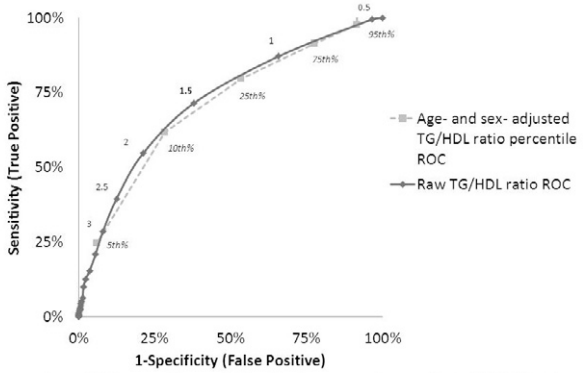
Supported by: NIH/CTSA (UL 1RR025011)

1301-P

TG/HDL Ratio as a Predictor of Insulin Resistance in U.S. Adolescents

DONNA S. ENG, JOYCE M. LEE, *Ann Arbor, MI*

Insulin resistance (IR) is a risk factor for Type 2 Diabetes. Difficulties arise in identifying children with IR due to the lack of standardization of insulin assays. Studies suggest fasting triglyceride-to-high-density lipoprotein ratio (TG/HDL) can be used as an alternative test for identifying children with IR although this has not been validated in larger samples. Our objective was to compare test performance of TG/HDL ratio raw values versus TG/HDL ratio percentiles for identifying adolescents with IR in a population-based sample.TG/HDL ratio and HOMA-IR was calculated from 2078 adolescents ages 12-18 yrs who participated in NHANES (2003-2008) with complete data on fasting triglyceride, HDL, fasting insulin and glucose. For the TG/HDL ratio we divided TG(mg/dl) by HDL (mg/dl). We established age- and sex-specific percentiles (10th, 25th, 50th, 75th, 95th) for TG/HDL ratio based on a subset of normal weight adolescents, and IR was defined as a HOMA-IR >4.39. We created receiver operating characteristic (ROC) curves predicting IR using both raw TG/HDL ratios and TG/HDL ratio percentiles and compared area under the ROC curve (AUC). Half of the population was female, 14% were black, 11% were Mexican-American, and 16% had IR. The figure shows the ROC curves. AUC for the raw TG/HDL ratio (0.71(SE 0.01)) was slightly higher than for the TG/HDL percentiles (0.70(SE 0.01))(p=0.01). A cutoff of 1.5 conferred a sensitivity of 71% and specificity of 62%. Raw TG/HDL ratios are superior to percentiles and have reasonable test performance for identifying adolescents with IR; 1.5 may be a reasonable test cutoff.



Comparison of ROC curves for predicting IR using age- and sex -adjusted TG/HDL ratio percentile (AUC 0.70 [0.68-0.73]) vs. raw TG/HDL ratio (AUC 0.71 [0.69-0.74])

For author disclosure information, see page 797.

Guided Audio Tour poster

ADA-Funded Research

1302-P

Relationships among A1c, 2hr Plasma Glucose, and OGTT AUC With Continuous Glucose Monitoring

CHRISTINE L. CHAN, KIM MCFANN, KRISTEN NADEAU, LINDSEY NEWNES, PHILIP S. ZEITLER, MEGAN KELSEY, *Aurora, CO*

Inclusion of hemoglobin A1c (A1c) in the diagnostic criteria for diabetes has significantly increased screening rates in the pediatric population. Studies comparing the performance of the A1c in diagnosing diabetes to the 2hr plasma glucose after 75 gram glucose load (2hr PG) or fasting plasma glucose (FPG) have reported discrepancy with the 2hr PG, which is considered the gold standard in the screening setting. To better understand these discrepancies, we examined relationships among A1c, FPG, 2hr PG and the OGTT area under the curve (AUC) as measured by continuous glucose monitoring (CGM), a broader measure of glucose tolerance, in obese adolescents. Fifty-seven obese adolescents ages 10-18 yrs participated and were 40% male; 60% Hispanic, 28% white, 10% black, BMI ≥85th%ile, A1c ≤7.5%, and not on pharmacologic diabetes treatment. FPG, A1c, 2hr PG and OGTT AUC by CGM from 0 to 120 min after glucola ingestion were measured. Pearson correlation coefficients were used to examine the relationships among variables.The concordance rate between A1c and 2hr PG prediabetes categories was 56% (12 subjects had 2hr PG ≥140mg/dl with A1c ≤5.7%; 13 subjects had A1c ≥5.7% with 2hr PG <140 mg/dl). A1c correlated with OGTT AUC (r=0.46, p=0.0013), as well as 2hr PG (r=0.55, p<0.0001), and FPG (r=0.33, p=0.0125). 2hr PG was strongly correlated with OGTT AUC (r=0.76, p<0.0001) but not with FPG. FPG did not correlate with OGTT AUC.In summary, both A1c and 2hr PG explained variability in OGTT AUC, and 2hr PG demonstrated a strong correlation with OGTT AUC. However, FPG correlated to A1c, but not 2hr PG. This suggests that A1c and 2hr PG measure different but overlapping components of glycemic pathology and are not interchangeable. Therefore, comparing A1c performance to 2hr PG may not be the best approach to understanding the value of A1c measurements in adolescents. Further data collection with 72hrs of CGM on free-living diets is underway to better understand the relationship between A1c and 2hr PG in this at-risk population.

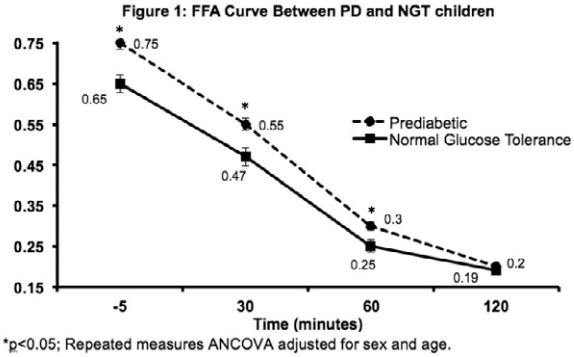
1303-P

Elevated Free Fatty Acid (FFA) Levels as a Risk Factor for Type 2 Diabetes (T2D) in Overweight Latino Youth

CLAUDIA M. TOLEDO-CORRAL, PAOLA SEQUEIRA, KEVIN MOUA, TARA SUTHERLAND, PRASANNA K. MOHANTY, PRAJAKTA PARAB, TING LIU, MICHAEL I. GORAN, MARC J. WEIGENSBERG, *Los Angeles, CA*

In adults, elevations in plasma FFA have been linked to defects in -cell secretion ("lipotoxicity") and independent risk for developing T2D. Our objectives are: 1) to describe FFA levels between children with pre-diabetes (PD) vs. those with normal glucose tolerance (NGT); 2) determine the relationship between FFA exposure and beta cell function. From 94 healthy overweight Latino children and adolescents (63M/31F; age 14.0±2.7 yrs; BMI-z: 1.96±0.55), we defined 2 groups: Normal Glucose Tolerant (NGT, n=67; fasting glucose <100mg/dL, 2hr glucose <140mg/L, and A1C =100 mg/dL and/or 2hr glucose 140-199 mg/dL and/or A1C 6.0-6.4%) Measures included A1C, OGTT glucose, insulin and FFA; body fat by DeXA; Disposition index (a measure of beta cell function) was determined by FSIVGTT/Minimal Model. Compared to NGT, PD was no different by age, sex, Tanner stage or total % body fat (p>0.05). However PD had higher A1C, fasting and 2 hr glucose and insulin than NGT (p<0.05). At -5, 30, and 60 minutes, PD had higher FFA levels compared to NGT (Figure 1, p<0.002); at the 120 min there was no difference in FFA. PD had significantly larger area under the FFA curve (AUC) than NGT (0.71±0.02 vs. 0.61±0.01, p<0.001) after adjusting for age and sex. For the study population as a whole, linear regression analysis revealed that FFA AUC was negatively related to disposition index (standardized = -0.23, p=0.03) adjusting for age and sex. Overweight Latino youth with prediabetes may experience greater overall exposure to circulating FFA. These results are consistent with the lipotoxicity theory of diabetes development.

Figure 1: FFA Curve Between PD and NGT children



*p<0.05; Repeated measures ANCOVA adjusted for sex and age.

Supported by: NIH NCMHD 3P60 MD0025

PREGNANCY

Guided Audio Tour: Pregnancy—Clinical Practice and Outcomes *(Posters 1304-P to 1309-P), see page 15.*

1304-P

Gestational Weight Gain Is Associated With Increased Neonatal Fat Mass: The Healthy Start Study

DANA DABELEA, JOHN BRINTON, DEBORAH GLUECK, TESSA CRUME, CURTIS HARROD, HENRY GALAN, MARY KOHN, *Aurora, CO*

Maternal obesity and excessive gestational weight gain (GWG) have been associated with increased fetal growth and an increased risk for childhood obesity. However, it is not known if these associations are mediated through direct effects on neonatal fat mass.We analyzed preliminary data from 203 pregnant women enrolled in the Healthy Start Cohort Study in Colorado: 118 non-Hispanic white, 37 Hispanic, 35 African-American, 13 other; mean age 28 years. Pre-pregnant body mass index (BMI) was based on self-reported pre-pregnant weight and measured height. Weight during pregnancy was obtained from clinical and research measures (on average 8 per participant). GWG was assessed using absolute weight gain (model predicted weight at term minus model predicted weight at conception). Neonatal fat mass was assessed within 2 days after birth by air displacement plethysmography. The relationship between GWG and neonatal fat mass was assessed using backward regression analysis, controlling for the effect of potential confounders.Percent neonatal fat mass was significantly higher in offspring of overweight/obese (BMI ≥ 25 kg/m2) vs non-obese (BMI < 25 kg/m2) mothers (10.4% vs. 8.5%, p=0.002). GWG ranged from -6 kg to 41 kg, with a mean value of 16 kg (SE=0.5 kg). Women at higher BMI had significantly lower GWG of 0.30 kg for every unit increase in BMI (p=0.0006). After adjusting for pre-pregnant BMI, gravidity, maternal age, race/ethnicity, birth weight, and gestational age , an estimated one kg increase in GWG was associated with a 0.08% higher neonatal fat mass (95% CI=0.005 to 0.170, p=0.03). Other independent correlates of neonatal fat mass were higher pre-pregnant BMI (p=0.003) and higher birth weight (p<0.0001). Interactions between GWG and BMI were non-significant (p=0.8).Our study documents a direct effect of GWG on neonatal fat mass. Careful control of maternal weight gain during pregnancy could reduce neonatal adiposity and possibly related long-term adverse outcomes.

Supported by: R01TK76648

1305-P

Impact of Restricted Maternal Weight Gain on Fetal Growth and Neonatal Morbidity in Obese Women With Type 2 Diabetes

BJÖRG ÁSBJÖRNSDÓTTIR, SIGNE S. RASMUSSEN, LOUISE KELSTRUP, PETER DAMM, ELISABETH R. MATHIESEN, *Copenhagen, Denmark*

We evaluated fetal growth and neonatal morbidity in relation to maternal gestational weight gain in obese women with type 2 diabetes mellitus (T2DM).Clinical data were identified from the records of 58 singleton pregnancies in obese women (BMI≥30kg/m^2) with T2DM who gave birth in Jan. 08 to Oct. 11. The women were recommended to gain between 0-5 kg during pregnancy, which is less than recommended by the Institute of Medicine. Birth weight was evaluated by standard deviation z-score to adjust for gestational age and gender. Large and small for gestational age (LGA, SGA) were defined as a birth weight > 90th or < 10th percentile, respectively. Neonatal morbidity was defined as the presence of either perinatal death, major congenital malformation, jaundice, transient tachypnea, neonatal hypoglycaemia (< 2.5 mmol/L) or admission to Neonatal Special Care Unit. Maternal characteristics and pregnancy outcomes in the women gaining ≤5 kg compared to the remaining women are shown in the tables.

Maternal characteristics Median (range)	Weight gain ≤ 5 kgn: 17 (29%)	Weight gain > 5 kgn: 41 (71%)	p-value
Pre-pregnancy BMI (kg/m^2)	33.5 (30-52.7)	36.8 (30-48.2)	0.037
HbA1c at first visit (%)	6.7 (5.1-8.1)	6.7 (5.3-13.2)	0.365
HbA1c at last visit (%)	5.7 (5.4-6.6)	6.0 (4.8-8.2)	0.620
Weight gain in total (kg)	3.7 (-4.7-5.0)	12.1 (5.5-25.5)	
Insulin treatment before first visit	5 (29%)	11 (27%)	0.843
Insulin treatment at last visit	17 (100%)	38 (93%)	0.256
Insulin doses at last visit (IU/kg)	0.72 (0.12-1.80)	1.29 (0.50-2.75)	0.003

Outcomes Median (range)	Weight gain ≤ 5 kgn: 17 (29%)	Weight gain > 5 kgn: 41 (71%)	p-value
Gestational age at birth (days)	268 (221-284)	262 (206-280)	0.039
z-score	-0.53(-3.41-1.96)	1.04(-2.45-3.89)	0.007
LGA	2 (12%)	17 (41%)	0.034
SGA	3 (18%)	5 (12%)	0.681
Neonatal Morbidity	6 (35%)	29 (73%)	0.009

In obese women with T2DM, maternal gestational weight gain ≤ 5 kg was associated with delivery closer to term, a more proportionate birth weight and less neonatal morbidity compared to women gaining more.

1306-P

ATLANTIC DIP—Closing the Loop: A Change in Clinical Practice Can Improve Outcomes for Women With Pre-Gestational Diabetes Mellitus

LISA A. OWENS, GLORIA AVALOS, LOUISE CARMODY, FIDELMA DUNNE, ATLANTIC DIP, *Galway, Ireland*

Objective: Prospective evaluation of pregnancy outcomes in pre-gestational diabetes over a 6 year periodResearch Design/Methods: The ATLANTIC Diabetes in Pregnancy group, established in 2005, represents 5 antenatal centres in a wide geographical location along the Irish Atlantic seaboard. The group provides care for women with diabetes before, during and after pregnancy. In 2007 the group examined outcomes from 2005-2007 and showed that women were poorly prepared for pregnancy and pregnancy outcomes were sub-optimal when compared with women without diabetes. A change in practice occurred, offering women centralised, specialist-led, evidence-based care. We now compare outcomes from 2005-2007 with 2008-2010.Results: There was a significant increase in the number of women attending pre-conception care and using folic acid. The numbers achieving HbA1C<7% pre-pregnancy increased and glycemic control throughout pregnancy improved. There was an overall increase in live births, with a decrease in miscarriage and stillbirths. There was a significant decrease in large-for-gestational-age babies in mothers with Type 1 Diabetes, a reduction in the number of babies admitted to neonatal intensive care and an overall reduction in premature deliveries. Elective Caesarean section rates increased, emergency section rates decreased.Conclusions: Auditing and changing clinical practice can improve outcomes in pre-gestational diabetes.

Pregnancy outcomes comparing period 1 (2005–2007) with period 2 (2008–2010) for *ATLANTIC DIP*

Outcomes	**Study period 1 2005–2007**	**Study period 2 2008–2010**	**P value**
N	104	168	
Type 1 Diabetes (T1DM)	80	87	
Type 2 Diabetes (T2DM)	24	81	
Pre-pregnancy Care	28%	52%	P=0.01
Folic Acid (5 mg)	41%	62%	P=0.2
Mean first HbA1C	7.3%	6.9%	P<0.001
% achieving target HbA1C <7%	48%	63%	P=0.038
Live birth rate	74%	92%	P<0.001
Perinatal mortality rate	n=5 (6.2%)	n=1 (0.65%)	P<0.001
Miscarriage	22%	8%	P<0.001
Still birth	4%	1%	P<0.001
Large for gestational age babies	T1DM- 30% T2DM- 18%	26% 25%	P=0.02 P=0.02
Caesarean section	56%	67%	P=0.01
Elective section	23%	55%	P=0.01
Emergency section	33%	27%	NS
Neonatal intensive care admission	61%	56%	P=0.554
Mean BMI% with BMI > 30kg/m^2	T1DM- 26 ±4.32 kg/m2 T2DM- 30 ±5.6 kg/m2 T2DM- 50%	T1DM 26±4.81 kg/m2 T2DM- 33 ±6.4 kg/m2 79%	P=0.93 P=0.25

1307-P

The Infant and Maternal Outcomes of a Regional Pre-Pregnancy Care (PPC) Program in Women With Type 1 and Type 2 Diabetes

ELHAYTHAM MUSTAFA, SAMIR KHALIL, BREDA KIRWAN, LOUISE CARMODY, THERESA GALLACHER, MARIE TODD, SHU HOASHI, MAEVE DURKAN, FIDELMA DUNNE, *Galway, Ireland, Ballinasloe, Ireland*

Specialized PPC can reduce the rate of adverse outcomes in pregnancies complicated by Diabetes. Through the ATLANTIC DIP program we are undertaking a single arm prospective study to compare pregnancy outcomes in women who attend (Attenders) PPC to those who decline an invitation to attend (Non-attenders).To date 551 women of childbearing age have been identified (272 Type1 and 269 type2). 158 (29%) of invited patients have attended 97(36%) Type 1, 61(23%) Type 2. All received a protocol driven pregnancy specific education program on glucose targets, hypoglycaemia awareness/ treatment, dietary advice, optimization of weight, review of medication and complications, screening for thyroid disease and commencement of 5mg folic acid.To date there are 79 pregnancies in attendees. 100% received folic acid. The mean HbA1c was 6.5% (5.2-8.5) prior to conception and >80% achieved HbA1c<7%. There are 27 pregnancies in non-attenders. Uptake of folic acid was less at 18% (P<0.001). The mean HbA1c was 7.9% (5.2-11.7 (P <0.001) at conception and 30% achieved HbA1c <7%. (p <0.001)62 pregnancies are completed in attenders and 15 in non-attenders. The miscarriage rate was 10% and 15% in attenders and non attenders respectively (P = 0.008) while admission to neonatal unit (NNU) was 35% and 73 % respectively (P=0.008). Premature delivery (<37 completed weeks) was 13% and 33% in attenders and non-attenders respectively (P=0.01). The composite of infant morbidities was significantly less in attenders at 18% compared to 53% in non-attenders (P= 0.034). There was no difference in maternal morbidities.This regional PPC program has resulted in improved glycaemic control and uptake of folic Acid. This has translated into an increased take home baby rate with lower infant morbidities. The improved glycaemic control may have long term benefits for the mother and infant. Attendance at the PPC program remains disappointingly low and further research into the use of social networking is warranted.

Supported by: Health Research Board, Ireland

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

1308-P

Postpartum Weight Loss is Associated With Improved Glucose and Insulin Homeostasis in Women With a History of Gestational Diabetes (GDM)

ASSIAMIRA FERRARA, SAMANTHA F. EHRLICH, JUANRAN FENG, CHARLES P. QUESENBERRY, SUSAN D. MOORE, MONIQUE M. HEDDERSON, *Oakland, CA*

Women with history of GDM are at high risk of developing type 2 diabetes. They represent at high risk young population that might benefit from early intervention for weight reduction to prevent diabetes. However, there is a lack of data on postpartum weight loss and glucose and insulin homeostasis. Among a subset of 72 women from the Diet, Exercise and Breastfeeding Intervention study, a randomized controlled trial of diabetes prevention in women with GDM, we examined whether weight loss between 6 weeks and 12 months postpartum was associated with improved changes in glucose and insulin measured fasting and 2 hours after a standard 75-gr OGTT. As shown in the table, at 12-m postpartum, women who lost > 2 kg had statistically significant decreased levels of fasting and 2-h glucose and fasting and 2-h insulin than women who maintained (-/+ 2 kg) or who gained weight (> 2 kg). In linear regression models adjusted for age, weight at 6-wk and breastfeeding, 1 kg of weight loss between 6-wk and 12-m postpartum was associated with a significant decrease in fasting glucose, 2-h glucose, and 2-h insulin [difference in mean change (95%CI): -0.47 (-0.91 to -0.03) mg/dl, p = 0.04; -2.43 (-3.97 to -0.89) mg/dl, p = 0.002; and -2.44 (-4.42 to -0.46) µU/mL, p = 0.02, respectively], and a non- statistically significant decrease in fasting insulin [-0.12 (-0.42 to 0.18) µU/mL]. Postpartum weight loss resulted in improved glucose and insulin homeostasis. Interventions are needed to help women with GDM manage postpartum weight to prevent diabetes.

	Fasting glucose mg/dl	2-h glucose mg/dl	Fasting insulin µU/mL	2-h insulin µU/mL
	Mean (SD)			
Lost weight				
At 6-wk	90.9 (9.7)	115.0 (33.6)	5.4 (3.2)	33.9 (24.5)
At 12-m	93.1 (10.8)	100.0 (24.8)	7.5 (6.3)	35.8 (24.1)
Change	2.2 (7.2)	-15.0 (34.7)	2.1 (3.8)	1.9 (20.8)
Maintained or gained weight				
At 6-wk	91.4 (12.0)	104.2 (27.8)	8.7 (3.9)	41.2 (23.3)
At 12-m	99.5 (10.7)	108.7 (23.9)	12.7 (6.3)	71.1 (39.0)
Change	8.1 (9.5)	4.5 (20.3)	4.0 (4.7)	29.9 (34.2)
P values for comparing group means				
At 6-wk	0.85	0.15	0.003	0.29
At 12-m	0.02	0.14	0.009	0.001
Change	0.004	0.005	0.15	0.002

Supported by: NIDDK

1309-P

Prevention of Diabetes Following Gestational Diabetes (GDM): The Diabetes Prevention Program Observational Study (DPPOS) 10 Year Follow-Up

ROBERT E. RATNER, COSTAS A. CHRISTOPHI, SHARON L. EDELSTEIN, VANITA ARODA, PING ZHANG, WILLIAM H. HERMAN, ELIZABETH BARRETT-CONNOR, LINDA DELAHANTY, MARIA G. MONTEZ, RONALD T. ACKERMANN, XIAOHUI ZHUO, WILLIAM C. KNOWLER, DPP RESEARCH GROUP, PRAJAKTA KHARE-RANADE, *Hyattsville, MD, Rockville, MD, Atlanta, GA, Ann Arbor, MI, San Diego, CA, Boston, MA, San Antonio, TX, Chicago, IL, Phoenix, AZ, St. Louis, MO*

The Diabetes Prevention Program reported higher 3-year risk of progression from IGT to diabetes in women with a history of GDM than in women without that history. We report the 10-year follow-up of DPPOS. 350 women in the DPP gave a GDM history compared with 1416 parous women without a GDM history. Participants were randomized to placebo, metformin or intensive lifestyle for 3.2 years, after which the DPP was concluded and the DPPOS observational study begun with 88% of the original cohort continuing in the open label follow-up. All participants received group-implemented lifestyle intervention, while the metformin group continued metformin therapy and the intensive lifestyle group received additional lifestyle support. Although the women with a history of GDM were 8.5 years younger than the non-GDM cohort, they had similar baseline BMI, fasting and 2-hour post-OGTT glucose levels, insulin levels and insulin resistance. During a mean of 10 years' follow-up, women with a history of GDM in the placebo group had a 65% higher risk of developing diabetes compared with women without a GDM history (11.4/100 versus 6.9/100 person-years, respectively). Metformin and lifestyle reduced progression to diabetes similarly among those with a GDM history (41% and 35% risk reduction, respectively), compared with placebo. Intervention effects were greater than in those without a GDM history (4% metformin and 28% lifestyle), independent of age or BMI.The DPPOS demonstrates persistently increased risk of diabetes an average of 20 years beyond the index pregnancy complicated by GDM. Diabetes incidence was significantly higher than in women without a GDM history despite similar baseline metabolic status. Women with GDM history responded even better to interventions than women with no GDM history. We conclude that women with a history of GDM have a sustained long-term risk of developing diabetes that can be reduced with either metformin or lifestyle intervention.

Supported by: NIDDK (U01-DK048489)

Guided Audio Tour: Pregnancy and Gestational Diabetes—Metabolic Markers *(Posters 1310-P to 1314-P), see page 15.*

1310-P

Fetal Exposure to Maternal Type 1 Diabetes is Associated With Differences in Genome-Wide DNA Methylation Analysis

JEAN-FRANCOIS GAUTIER, RAPHAEL PORCHER, LILA S. FETITA, CHARBEL ABI KHALIL, FLORENCE TRAVERT, SIMÉON P. CHOUKEM, JEAN-PIERRE RIVELINE, SAMY HADJADJ, ETIENNE LARGER, PHILIPPE BOUDOU, LOUISE MORBOIS-TRABUT, BERTRAND BLONDEAU, RONAN ROUSSEL, PASCAL FERRÉ, ERIC RAVUSSIN, PATRICK VEXIAU, MICHEL MARRE, *Paris, France, Poitiers, France, Baton Rouge, LA*

We reported previously that fetal exposure to maternal diabetes is associated with reductions in insulin secretion and kidney function in offspring of T1D mothers. It may confer them an increased risk of diabetes and of renovascular diseases. The objective of this work was to study the potential epigenetic origins of these anomalies.For this purpose, the methylation profile of 2,578 CpG sites was analyzed from circulating leukocytes in 29 adult, non-diabetic offspring of mothers T1D (exposed group) and 29 adult, non-diabetic offspring of T1D fathers (control group), using the Human Methylation27 BeadChip platform Illumina Infinium ®.Age, sex ratio, glucose tolerance, and percent body fat were similar in exposed and control subjects. We found 214 sites differently methylated between the two groups. Global methylation of these 214 sites was lower in the exposed group (average 5.3%, 95% CI 3.8 to 6.9, p <0.0001). It was not correlated with insulin secretion measured in response to oral glucose (OGTT) and to IV glucose (glucose ramp). Conversely, a positive correlation was observed between the overall level of methylation and basal glomerular filtration rate (^{51}Cr-EDTA) in exposed subjects (r = 0.50, p = 0.036), while such relationship was not observed in controls. Twenty four sites were more methylated and 190 sites were less methylated in the exposed vs. control subjects. The gene encoding the DNA methyltransferase 1 (DNMT1), a key enzyme in maintaining methylation patterns during cell division was one of the genes most affected by hypomethylation in exposed subjects.These first data from genome-wide methylation analysis suggest that epigenetic mechanisms may contribute to fetal programming linked to a hyperglycemic environment.

Supported by: Direction de la Recherche Clinique (PHRC AOR 04032)

1311-P

MARCKS Phosphorylation Mediates the Teratogenicity of Maternal Diabetes Leading to Neural Tube Defects

PEIXIN YANG, XUEZHENG LI, E. ALBERT REECE, *Baltimore, MD*

Prolonged activation of specific Protein Kinase C isoforms (PKCα, PKCδ and PKCβII) is associated with maternal diabetes-induced neural tube defects (NTD). Targeted deletion of either the *prkcd* gene or the *prkca* gene significantly ameliorates maternal diabetes-induced NTD, suggesting the importance of the PKC pathway in diabetic embryopathy. However, the roles of intermediates downstream of these PKC isoforms have not been adequately studied. Myristoylated alanine-rich C-kinase substrate (MARCKS) is a prominent PKCα and PKCδ substrate that primarily resides in neural tissues. Our objective was to determine the role of MARCKS phosphorylation in maternal diabetes-induced NTD. Targeted deletion of the *prkca* gene abolished maternal diabetes-induced MARCKS phosphorylation, confirming that MARCKS is a PKCα substrate. MARCKS is localized to the plasma membrane, and phosphorylation at serine residues of its phosphorylation site domain (PSD) inhibits its association with the plasma membrane. Maternal diabetes sig-

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 797.

nificantly reduced the amount of total MARCKS associated with mitochondria and endoplasmic reticulum (ER), suggesting that loss of MARCKS may account for mitochondrial dysfunction and ER stress in diabetic embryopathy. To test the functional outcome of MARCKS phosphorylation, we used a small peptide MARCKS inhibitor (A-PSD), where four key serine residues in PSD were substituted with asparagine (A), entered embryonic compartments after *in vitro* treatment in cultured embryos and inhibited high glucose (20 mM glucose)-induced MARCKS phosphorylation. Under high glucose conditions, eight out of ten cultured embryos exhibited NTD, whereas in the presence of 100 μM A-PSD, only two out of ten embryos had NTD. This NTD reduction by A-PSD was statistically significant by *Chi*-Square test. Under 5 mM glucose, none of cultured embryos developed to NTD. We conclude that MARCKS phosphorylation, a main PKC substrate, plays a causative role in diabetic embryopathy.

Supported by: NIH R01 DK083243 (P.Y.) and R01 DK083770 (E.A.R.)

1312-P

Metabolomics Reveals Broad-Scale Metabolic Perturbations in Hyperglycemic Mothers During Pregnancy

DENISE M. SCHOLTENS, JAMES R. BAIN, MICHAEL J. MUEHLBAUER, ROBERT D. STEVENS, ALAN R. DYER, LYNN P. LOWE, BOYD E. METZGER, CHRISTOPHER B. NEWGARD, WILLIAM L. LOWE, HAPO STUDY COOPERATIVE RESEARCH GROUP, *Chicago, IL, Durham, NC*

Maternal hyperglycemia less than diabetes is associated with greater offspring adiposity, as indicated by the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study, and possibly increased childhood obesity and metabolic disorders, as in offspring of diabetic mothers. Mechanisms for these associations are unknown, but the mother's metabolic profile impacts the intrauterine milieu. To characterize metabolites across the range of maternal glucose, we compared 50 Northern European ancestry HAPO mothers with high (>90th %ile) to 50 comparable mothers with low (<10th %ile) fasting plasma glucose (FG) but identical BMI, and analyzed serum collected at 28 weeks gestation. Targeted mass-spectrometry (MS) of amino acids and acylcarnitines was combined with biochemical analyses of conventional clinical metabolites. We also performed non-targeted gas chromatography/MS metabolomics and applied a statistical mixture-model analysis to accommodate non-detectable metabolites. High FG mothers had a metabolic profile consistent with insulin resistance, including higher levels of multiple free fatty acids and glycerol (indicative of increased mobilization of peripheral lipid stores by lipolysis), byproducts of fatty acid oxidation (ketones and TCA cycle intermediates), multiple amino acids, including alanine and branched-chain amino acids, and fructose, gluconate, pentitols, and hexitols. Simultaneous elevation in triglycerides, gluconeogenic precursors, and assorted sugars is consistent with recent demonstration of insulin resistance that is "selective" for failure to suppress gluconeogenesis but with normal anabolic effects of insulin on lipogenesis. High FG mothers had *lower* levels of 1,5-anhydroglucitol, suggesting recent hyperglycemic excursions, and campesterol, a dietary phytosterol. Thus, metabolomics reveals that high FG mothers exhibit perturbations in metabolism of all major macronutrients, potentially impacting offspring outcome.

1313-P

Maternal Lipids and Insulin Resistance Influence Neonatal Body Fat: The Healthy Start Study

TESSA L. CRUME, JOHN T. BRINTON, CURTIS S. HARROD, DEBORAH GLUECK, MERCEDES MARTINEZ, JACOB E. FRIEDMAN, ANNE LYNCH, DANA DABELEA, *Aurora, CO*

Fetal over-nutrition is considered a developmental pathway to obesity. However, the mechanisms responsible for these effects are unclear. A gestational environment complicated by maternal insulin resistance (IR) and elevated fuels (glucose, lipids) may be involved in programming of neonatal fat. We assessed the association between maternal fuels and IR and neonatal fat mass among 227 ethnically diverse mother-infant pairs enrolled in the longitudinal Healthy Start cohort study. Maternal glucose, insulin, free fatty acids (FFA) and triglycerides (TG) were measured twice in fasting blood samples taken at 15-23 and 24-32 weeks of gestation. IR was estimated using fasting insulin and HOMA-IR. Neonatal fat mass was measured with air displacement plethysmography (PEA POD). All models were adjusted for maternal age and race/ethnicity, infant sex, birth weight and gestational age. Estimated maternal IR at the first prenatal visit was associated with higher neonatal fat mass: for each 1 unit increase in maternal insulin (μU/ml) and HOMA-IR, neonatal fat mass increased by 3.4 g (p=0.01) and 0.7 g (p=0.03), respectively. Maternal FFA at the second prenatal visit was also associated with fat mass: 0.18 g increase in fat mass for each 1 mg/dl increase in maternal FFA. There were no associations between neonatal fat and maternal glucose or TG levels at either prenatal visit. The effects of maternal IR and FFA on neonatal fat mass were stronger for women with higher pre-pregnancy BMI (p=0.048 and p=0.04, respectively for effect modification by pre-pregnant BMI). Our results suggest that maternal insulin resistance and increased lipid levels in women with higher pre-pregnancy BMI contribute to the programming of neonatal adiposity.

Supported by: NIH, NIDDK

1314-P

Fasting Circulating GLP-1, GIP, PYY and PP Levels in Gestational Diabetes Mellitus

PANAGIOTIS HALVATSIOTIS, PETROS KARAKITSOS, PERIKLIS PANAGOPOULOS, KONSTANTINE PATSOURAS, MARIA ALEPAKI, LAMBROS BATALIAS, CHARALAMBOS CHRELIAS, DEMETRIUS KASSANOS, GEORGE DIMITRIADIS, *Athens, Greece*

Gestational diabetes mellitus (GDM) is a pathological state of carbohydrate intolerance, first recognized during pregnancy. Insulin resistance, a central component of GDM, has been documented as an independent variable predictive of diminished incretin secretion. While there is ample evidence for type 2 diabetes and other insulin resistance states, however we are lacking information for GDM and thus the purpose of our study was to investigate, if the presence of GDM is related with changes in the serum fasting concentrations of incretin hormones. GLP-1, GIP, PYY and PP were measured in 13 women with GDM (29,17+1,4 yo) and 11 matched for BMI, before pregnancy (GDM 28,05+2,1 vs NGD 26,75+2,9) , and age nondiabetic mothers (NGD) (30+1,3 yo), just before delivery, by a multiple bead array by the means of internally colour-codes microspheres with fluorescent dyes excited by laser beams. Statistical analysis performed with unpaired t-test and regression analysis. All pregnancies were uncomplicated and the GDM group demonstrated significantly higher serum insulin levels than NGD (12,45+1,2 vs 6,43+0,9 μIU/ml) (p=0,0018), while at the same euglycemic levels, indicating the presence of insulin resistance. HOMA test (2,53+0,3 vs 1,01+0,12) (p<0,0007) for GDM and NGD respectively. GHbA1c levels were within normal limits. There was no difference in the weight gained during pregnancy between the groups but circulating levels of both GLP-1 (110,14+22,7 vs 56,35+4,9 pg/ml) (p<0,04) and GIP (14,28+2,4 vs 6,88+0,7 pg/ml) (p<0,037) were significantly higher in GDM group than NGD. PP levels did not differ but PYY were lower in GDM 66,47+8,3 vs NGD 111,1+6,1 pg/ml (p<0,0066). The weight gained during pregnancy was inversely correlated to GIP (p<0,0326, r = -0,5195) and HOMA values to PYY (p<0,0316, r = -0,5960), irrespectively of the diabetes presence. Our results suggest that the imbalance of the incretin hormones during pregnancy might considered essential in the progression to gestational diabetes.

1315-P

Lower Adiponectin Levels at First Trimester of Pregnancy are Associated With Higher Risk of Developing Gestational Diabetes, Independently of Adiposity

MARILYN LACROIX, MARIE-CLAUDE BATTISTA, MYRIAM DOYON, PATRICE PERRON, MARIE-FRANCE HIVERT, *Sherbrooke, QC, Canada, Boston, MA*

Gestational diabetes (GD) results from an imbalance between insulin resistance and insulin secretion capacity during pregnancy. Adiponectin is an adipokine that is suspected to have a role in insulin sensitivity. Low adiponectin levels have been associated repeatedly with increased risk of type 2 diabetes incidence, but reports on GD are inconsistent.We hypothesized that lower adiponectin levels at first trimester are associated with higher risk of developing GD during pregnancy.We recruited and followed prospectively a cohort of pregnant women representative of the general population delivering at our institution; we performed anthropometric measurements and blood samples at 1st (between 6-13 weeks) and 2nd trimesters (between 24-28 weeks). Diagnosis of GD was made at 2nd trimester, based on a standard 75g oral glucose tolerance test (International Diabetes Federation criteria). This analysis included 285 participants: 260 women with normal glucose tolerance (NG) and 25 women who developed GD (incidence rate of GD = 9 %).Participants who developed GD were older (NG = 28.3 years old; DG = 30.7 years old; p = 0.007) and had lower 1st trimester adiponectin levels (NG = 11.18 ± 4.45 μg/ml; DG = 8.97 ± 3.47 μg/ml; p = 0.02), but had similar mean body mass index (BMI) (NG = 25.2 ± 5.4 kg/m2; DG = 25.8 ± 5.8 kg/m2; p = 0.58) and body fat percentage (BFP) (NG = 31.2 ± 8.3 %; DG = 32.0 ± 10.3 %; p = 0.69) measured at 1st trimester. Lower adiponectin levels were associated with higher risk of developing GD (β = -2.72; p = 0.02) and this association remained statistically significant after adjustment for age and

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

BMI (β = -2.84; p = 0.02), or for age and BFP (β = -2.89; p = 0.01).Our results suggest that lower adiponectin levels at 1st trimester are associated with increased risk of developing GD, independently of adiposity measurements in a prospective, population-based cohort.

Supported by: Fonds Recherche Sante Quebec

1316-P

Impact of New Diagnostic Criteria for Gestational Diabetes Mellitus (GDM) on Perinatal Maternal and Fetal Outcomes

MOHAMMAD S. KHAN, BRENDAN T. KINSLEY, SEAN F. DALY, CAROLINE E. WALSH, AILBHE MCCARTHY, *Dublin, Ireland*

A new and clinically risk based criteria for diagnosis of GDM has been recently adopted by International Association of Diabetes and Pregnancy Study Group (IADPSG) after the results of Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) trial. The new fasting plasma glucose (FPG) of 92 mg/dl is considered diagnostic of GDM compared to old criteria of FPG 105 mg/dl. This study aim to determine the incidence of perinatal outcomes in those with FPG between 92-104 mg/dl on 100g 3-hours oral glucose tolerance test (OGTT).Hospital record of 3,583 screening OGTT's performed in one hospital in 2008-2009 was reviewed. Rate of GDM and perinatal outcomes were compared in three groups (G) based on the OGTT results. Group 1 = Normal OGTT old criteria (FPG <105 mg/dl), Group 2 = GDM old criteria and Group 3 = GDM based on FPG 92-104 mg/dl new criteria.Rate of GDM using 100g 3-hour OGTT (old criteria) was 157/3583 (4.3%), rate of GDM using new FPG criteria alone (≥ 92 mg/dl) was 382/3583 (10.6%). Perinatal outcomes are outlined in the table. When outcomes in an untreated G-3 were compared with G-1 and G-2, rate of higher Birth Weight, Caesarean Sections, Gestational age >37 weeks, booking weight 70-99.9 kg and Body Mass Index (BMI) of ≥30 at first visit were higher in G-3. Also rate of Macrosomia and Shoulder dystocia was higher in G-3 but statistically not significant.New FPG criteria will result in a 100% increase in rate of GDM even prior to the use of a 75g glucose load. Treatment of G-3 (FPG 92-104 mg/dl) as now recommended may improve outcomes, however, the impact of these changes on clinical outcomes and workload remains uncertain.

	Group-3 (Normal) *n= 3201*	Group-2 (GDM) *n = 157*	Group-3 (FPG 92-104mg/dl) *n = 225*	*p* values
Booking weight 70-99.9 kg	1426(44.5%)	65(41%)	117(52%)	G3 vs.G1= *p 0.001* G3 vs.G2= *p 0.03*
Booking BMI ≥30	891(27.8%)	69(43%)	106(47%)	G3 vs.G1= *p 0.001* G3 vs.G2= *p 0.21*
Gestational age ≥ 37 weeks	3054(95%)	142(89%)	217(96%)	G3 vs.G1= *p 0.21* G3 vs.G2= *p 0.01*
Neonatal weight >4,000g	3.6 ± 0.8804 (25%)	3.4 ± 0.622 (14%)	3.7 ± 0.669 (30%)	G3 vs.G1= *p 0.02* G3 vs.G2= *p 0.001*
Macrosomia	27(0.84%)	2(1.2%)	3(1.3%)	G3 vs.G1= *p 0.21* G3 vs.G2= *p 0.5*
Shoulder Dystocia	31(0.9%)	3(1.8%)	6(2.6%)	G3 vs.G1= *p 0.06* G3 vs.G2= *p 0.30*
Caesarean section	527(16.4%)	22(14%)	51(22%)	G3 vs.G1= *p 0.016* G3 vs.G2= *p 0.013*

1317-P

HbA1c-Directed Testing at First Prenatal Visit Predicts Diagnosis of Gestational Diabetes

UMA GUNASEKARAN, BRANDON A. PERRY, ELAINE B. KING, LI WANG, ETOI A. GARRISON, BENNETT SPETALNICK, NANCY M. LORENZI, SHUBHADA M. JAGASIA, *Nashville, TN*

Complications following gestational diabetes (GDM) can be decreased by reducing the duration of exposure to hyperglycemia. We hypothesized that HbA1c-directed testing at the first prenatal visit could independently predict the risk of subsequent GDM.Women at a single academic center had HbA1c tested at their first prenatal visit. They were stratified using ADA guidelines into normal (<5.7%), prediabetes (5.7-6.4%), and diabetes (≥6.5%) cohorts. Prediabetic women underwent standard GTT screening early and normal patients (pts) were rescreened between 24-28 weeks gestation.Of the 1233 pts that underwent HbA1c testing at the first prenatal visit, 25 pts had an HbA1c > 5.7% and a subsequent diagnosis of GDM. In 13 pts (median HbA1c, 5.9; range, 5.7-8.7), the diagnosis was based on first trimester screening and 12 patients were diagnosed at 24-28 weeks gestation. HbA1c was significantly higher at first prenatal visit with an eventual diagnosis of GDM compared to non-GDM women (mean, 5.66 vs. 5.26, p<0.001). Pts with GDM were older (30 y vs. 26 y, P=0.002) and had an higher body-mass index (BMI) (31.7 vs. 26.7, P<0.001). Prior history of GDM (14% vs. 1%, P=0.005) and family history of DM (26% vs. 12%) were more prevalent in pts with GDM. In multivariable analyses (logistic regression), prenatal HbA1c (odds ratio (OR) = 2.2, 95% CI 1.1-4.4), age (OR= 2.1, 95% CI 1.2-3.8), BMI (OR= 1.7, (95% CI 1.0-3.0) and prior history of GDM (OR= 2.3, 95% CI 0.7-7.3), were independent predictors of GDM. The area under the receiver operating characteristic curve of the model was 0.8 (95% CI 0.6-0.9). The model was internally validated using the bootstrapping technique (300 replications).Our study suggests that prenatal HbA1c is a predictor of GDM and can identify patients earlier and reliably. This model needs to be validated in an independent cohort to allow for wide-spread implementation. Earlier intervention strategies based on prenatal HbA1c screening could translate into reduced complications and cost savings.

1318-P

Ethnic Differences in β-cell Compensation for Pregnancy Induced Insulin Resistance: A Population Based Cohort Study

KJERSTI MØRKRID, ANNE K. JENUM, LINE SLETNER, SIRI VANGEN, KÅRE I. BIRKELAND, *Oslo, Norway*

In normal pregnancies β-cells increase insulin secretion to maintain normo-glycaemia. We recently reported GDM (IADPSG criteria) in 42% of South Asian (SA), 37% of Middle Eastern (ME) and 24% of Western European (WE) women living in Norway. Here we present changes in insulin resistance and β-cell function during and after pregnancy in women from WE, SA and ME, and in women with and without GDM.In this population-based cohort study 823 (74% of the invited) healthy pregnant women were included. Fasting blood samples, anthropometrics and demographics were collected at <20 (V1) and 28±2 (V2) weeks' of gestation, and 3 months postpartum (V3). The 75-g OGTT was performed at V2. β-cell function (HOMA β) and insulin resistance (HOMA IR) were estimated from fasting plasma glucose (FPG) and C-peptide. In total 776 (WE=316, SA=193, ME=119), the present study sample, had HOMA values from at least two visits.SA were younger with lower prepregnant BMI (p<0.01), but equal postpartum BMI compared with WE, ME had higher prepregnant and postpartum BMI (p <0.01). SA and ME had higher HOMA IR at all visits, compared with WE. HOMA IR increased equally from V1 to V2 by ~50% in all groups. HOMA β increased less for SA compared with WE from V1 to V2 (p=0.001). In GDM versus non-GDM women, HOMA IR was higher at all visits and increased more from V1 to V2 ((60% vs. 40%) p<0.0001), HOMA β increased less from V1 to V2 (29% vs. 44%, p<0.0001), was lower at V2 (p=0.0008) and higher at V3 (p=0.02). SA were more insulin resistant and showed poorer compensation in β-cell function than WE women.

HOMA β and HOMA IR for the ethnic groups. Data presented as median (Inter Quartile Range)

	Western Europe	South Asia	Middle East	p-value SA vs. WE	p-value ME vs. WE
HOMA IR **V1**	1.0 (0.5)	1.2 (0.7)	1.1 (0.7)	<0.0001	0.01
HOMA IR **V2**	1.5 (0.7)	1.8 (0.9)	1.6 (1.1)	<0.0001	0.05
HOMA IR **V3**	1.2 (0.7)	1.6 (0.8)	1.4 (0.9)	<0.0001	0.04
HOMA β **V1**	126.2 (35.1)	143.8 (44.9)	135.6 (43.9)	<0.0001	0.11
HOMA β **V2**	172.6 (54.4)	178.5 (54.9)	167.6 (54.8)	0.06	0.73
HOMA β **V3**	121.2 (39.7)	138.5 (46.5)	126.6 (39.9)	<0.0001	0.43

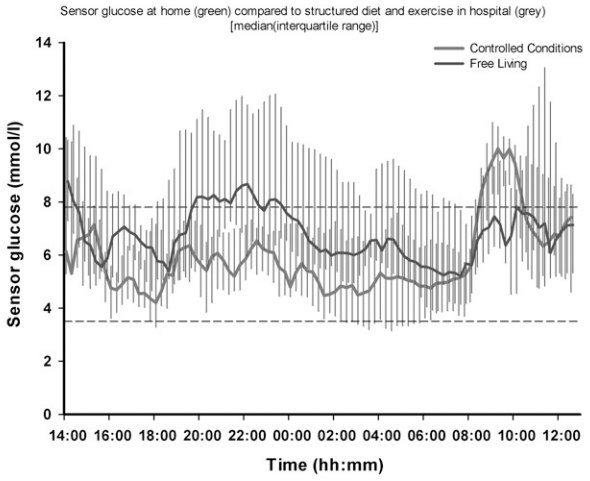
1319-P

Physical Activity Energy Expenditure and Glucose Levels in Pregnant Women With Type 1 Diabetes during Free-Living and Controlled Conditions

KAVITA KUMARESWARAN, SOREN BRAGE, KATE WESTGATE, DANIELA ELLERI, JANET ALLEN, MARIANNA NODALE, MALGORZATA WILINSKA, STEPHANIE AMIEL, ROMAN HOVORKA, HELEN MURPHY, *Cambridge, United Kingdom, London, United Kingdom*

We evaluated activity patterns and glucose control in 10 pregnant women (age 32.9yrs, gestation 19weeks, BMI 27.1kg/m$^{2)}$ with type 1 diabetes (duration 14.8yrs, HbA1c 6.4%, insulin pump 2.0yrs), during a typical day at home (free-living) compared with a 24-hour stay in hospital with scheduled light (three 20-min self-paced walks) and moderate (two 55-min sessions brisk treadmill walking) intensity physical activity. Women wore a combined heart rate and movement sensor (Actiheart; Cam Ntech Ltd, Papworth, UK) to derive individually calibrated estimates of physical activity energy expenditure (PAEE), and a continuous glucose monitor (FreeStyle Navigator®Abbott

Diabetes Care, USA) measuring sensor glucose. Compared with the in-hospital study, PAEE was lower during free-living [21.2 vs. 15.9kJ/kg/day, p=0.24], with less than 2% time (27min) spent in moderate intensity activity. Overall mean sensor glucose was higher during free-living [7.7±2.5 vs. 6.0±0.6mmol/l; p=0.03]. Under controlled diet and exercise in hospital, glucose control was improved, with less time in hyperglycaemia [0.0% vs 19%, p=0.03] and lower glucose variability overnight [0.7 vs 1.3mmol/l, p=0.02], without any increase in time hypoglycaemic [4.9 vs. 2.4%, p=0.16]. In conclusion, this is the first objective evaluation of activity patterns and PAEE in pregnant women with type 1 diabetes during free-living. Even in these well controlled women, glucose levels at home were sub-optimal. Structured low and moderate intensity physical activity and controlled diet may improve glycaemic control.



Supported by: Diabetes UK

1320-P

Carriers of the TCF7L2 rs7903146 Variant With GDM have an Increased Risk of Developing Impaired Glucose Regulation after Pregnancy

GIOVANNA STEFANELLI, ROMINA FICARELLA, CLAUDIA IPPOLITO, MARIANGELA MANICONE, MARIA BARBARO, CLAUDIA CORAZZA, LUIGI LAVIOLA, FRANCESCO GIORGINO, *Bari, Italy*

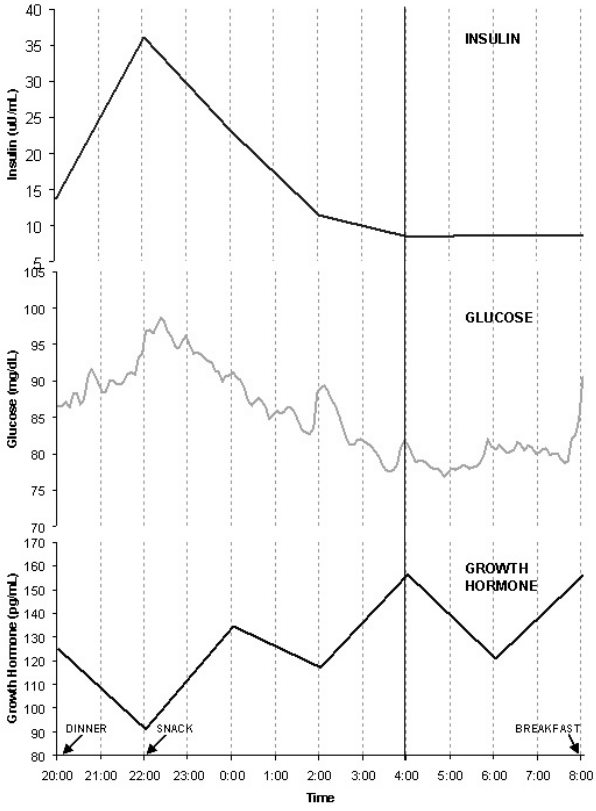
Genetic and epidemiological studies suggest an association between the transcription factor 7-like 2 (TCF7L2) rs7903146 (C/T) allele and an increased risk of both type 2 diabetes (T2D) and gestational diabetes mellitus (GDM). We aimed to compare the CC, CT and TT genotype frequencies of the TCF7L2 rs7903146 in women with history of GDM who remained normotolerant (NGT) or developed impaired glucose tolerance (IGT) or T2D after pregnancy. Forty-three women with previous GDM were challenged with an oral glucose tolerance test (OGTT) after a mean of 18.37 months following pregnancy. The TCF7L2 rs7903146 single nucleotide polymorphism was genotyped. The OGTT test identified 22 women with NGT and 21 with impaired glucose regulation (17 IGT, 4 T2D). Clinical features were similar in the two groups, except for a younger age at the time of GDM diagnosis (34.1 vs 36.8 y, P<0.05), fasting insulin (11.91 vs 13.29 mUI/L, P=0.08), and insulin 120 min after the glucose load (59.82 vs 92.23 mUI/L, P=0.059) in the NGT group. The CC, CT and TT genotype frequencies of the TCF7L2 rs7903146 variant differed significantly between the 22 NGT women and the 21 women who developed IGT or T2D (OR 4.25 [95% CI 1.06- 16.77]; P<0.05). TCF7L2 rs7903146 was significantly associated with both pre-gravidic and current BMI (P<0.05) and with increased waist (P<0.05). Interestingly, NGT women showed a lower intima-media thickness of the common carotid artery at ultrasound (0.6 vs 0.75 mm, p<0.0001). In conclusion, the TCF7L2 rs7903146 variant is associated with an increased risk for developing T2M or IGT after pregnancy in women with GDM, and this may be possibly modulated by its association with excess body fat. The identification of this risk genotype can potentially represent a marker of impaired glucose metabolism in tailored follow-up programs for women with history of GDM.

1321-P

Has the Dawn Phenomenon Finally Set In Pregnancy?

ALICIA MANDUJANO, ALICIA THOMAS, LARRAINE PRESLEY, SAEID B. AMINI, SYLVIE HAUGUEL-DEMOUZON, PATRICK M. CATALANO, *Cleveland, OH*

The dawn phenomenon (DP) is a transient rise in blood glucose between 4-6 AM attributed to the pulsatile release of pituitary growth hormone (PGH). In pregnancy, PGH is suppressed by placental growth hormone (PLGH). Therefore we hypothesize there is no DP during pregnancy and hence no significant changes in GH, insulin, and glucose concentrations between 4-6 AM. Twenty normal glucose tolerant women with singleton gestations between 28-36 weeks were recruited. Women with medical or obstetrical problems were excluded. Subjects were admitted from 6 PM to 8 AM to the Clinical Research Unit and had a Medtronic iPro placed for continuous glucose monitoring. Insulin and GH were measured at 8 and 10 PM, and 12, 2, 4, 6 and 8 AM. Since there is no assay for PLGH, we measured GH (PLGH and PGH) using ELISA (R&D Systems, Quantikine DGH00). Glucose was analyzed using time series analysis. GH was grouped into Time 1 (8 and 10 PM), Time 2 (12 and 2 AM), and Time 3 (4, 6, 8 AM) for changes over time. Further analysis was performed using Time 1b (8, 10 PM, and 12, 2 AM) and Time 2b (4, 6, 8 AM). Insulin was analyzed at 4, 6, and 8 AM. Data presented as mean ± SE. Glucose, insulin, and GH concentrations are shown in the figure. Glucose decreased over time (p<0.001). There were no differences in GH between Time 1, 2, and 3 (108±25, 125.8±23.9, 143.9±30.6 pg/mL; p=.45) or Time 1b and 2b (116.9±23.7, 143.9±30.6 pg/mL; p=.12). Insulin increased after meals but there were no changes in concentrations from 4, 6, or 8 AM (8.5±1.4, 8.7±1.0, 8.6±1.1 uU/mL; p=0.98). In conclusion, glucose and insulin concentrations show no increase between 4 and 8 AM, and though there is variability in GH, there is no evidence for DP in late pregnancy.



Supported by: CWRU/Cleveland Clinic CTSA Grant #UL1 RR024989, NIH NCRR

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research

1322-P

Rising Prevalence of Pregnancy Complicated by Type 2 Diabetes in Scotland

DAVID CARTY, SCOTTISH DIABETES RESEARCH NETWORK, *Glasgow, United Kingdom*

Secular increases in T2DM are well described in the general population and causing concern in pregnancy. We used comprehensive national diabetes databases (Scottish Care Information Diabetes Collaboration) and obstetric discharge information to assess the number of deliveries to women with diabetes in Scotland.There were 2338 live births to women with known pre-existing diabetes between 4/1/1998 and 3/31/2008, representing 1 in 239 births. Numbers of women with T1DM were similar to national audits in 1999 and 2004 with on average 195 live births to women with T1DM per year, unchanged across the 10 years. Deliveries of women with T2DM rose from 20 live births in 1998/9 to 51 in 2007/8, rising from 10% of deliveries to women with diabetes to 17-24% by 2005-8. Considering liveborn singletons, unadjusted birthweight (mean±SD T1DM 3457±805g vs T2DM 3413±817g P=0.34) and rates of macrosomia (>4.5kg T1DM 8.1% vs T2DM 7.9% P=0.50) were similar but mothers with T1DM were delivered earlier (T1DM 36.8± 2.3 wks vs T2DM 37.4 ±2.3wks P<0.05) with higher rates of preterm birth (<37 wks T1DM 32.8% vs T2DM 21.9% P<0.05). Birthweight z-scores were increased in both T1 and T2DM and stable with time. Mothers with T1DM were more likely to undergo Cesarean section (T1DM 67% vs T2DM 56% P<0.05) particularly emergency section (T1DM 39% vs T2DM 28% P<0.05). There were 51 stillbirths and 10 early (first week) neonatal deaths over the 10 years with stillbirth rates and perinatal mortality of 21.3 and 25.5 per 1000 births respectively- both 3 to 4 fold that of the background population. Rates of stillbirth were not different between T1 and T2DM (19.6 and 30.3 per 1000 births respectively P=0.18).Discharge information alone recorded 70% of diabetes cases, and is not reliable for detecting diabetes in pregnancy. Record linkage reveals an increase in pregnancy complicated by T2DM over 10 years. Stillbirth and perinatal mortality remain higher in offspring of mothers with diabetes; preterm and operative delivery appear particularly high in women with T1DM.

1323-P

Women With Recent Gestational Diabetes have Faster Decline in Insulin Sensitivity and Beta-Cell Compensation than Their Normal Parous Siblings and Cousins

ANNY H. XIANG, MIWA TAKAYANAGI, MARY HELEN BLACK, ENRIQUE TRIGO, RICHARD M. WATANABE, THOMAS A. BUCHANAN, *Pasadena, CA, Los Angeles, CA*

Cross-sectional studies show that women with gestational diabetes mellitus (GDM) have multiple metabolic defects compared to women without GDM. Data are lacking on the longitudinal changes comparing the two groups. We assessed changes in diabetes-related metabolic measures between non-pregnant women with GDM <5 years ago and their non-pregnant parous siblings and cousins without history of GDM at study entry. A total of 164 non-diabetic Mexican American women (76 prior GDM and 88 non-GDM) completed DEXA for measurement of body fat percentage (BFP), oral-, and intravenous glucose tolerance testing to assess insulin sensitivity (S_I), acute insulin response (AIR) and beta cell compensation (disposition index, DI) at baseline and after a median follow-up of 4.1 yrs. At baseline, women with prior GDM were younger (36 vs. 39 yrs), had similar BMI (30.5 vs. 29.7 kg/m^2), BFP (39.3% vs. 38.3%), and S_I (2.56 vs. 2.61 10^{-3} min^{-1} per pmol/l) compared to the non-GDM women. The prior GDM group had significantly lower AIR (275 vs. 426 uU/ml x min; p=0.001) and DI (703 vs. 1113; p=0.0001) at baseline. During follow-up, women with GDM had more negative rates of change in S_I (-0.21 vs. 0.01 units/yr, p=0.002) and DI (-45 vs. -12 units/yr, p=0.01) than the non-GDM women. Both groups had similar rates of change in BMI and BFP. Adjustment for baseline age, parity, BMI or BFP, calorie intake, physical activity, and changes in BMI or BFP did not alter these results. Change in SI appeared to have an important impact on change in DI in that rates of change in DI were no-longer significantly different between groups after adjustment for changes in SI (p=0.32). These findings demonstrate that Hispanic women with recent GDM had more rapid decline in insulin sensitivity and beta cell function than their parous siblings/cousins without GDM despite similar degree of body fat. Mechanism/other risk factors responsible for such differences over time remain to be studied.

Supported by: NIDDK

1324-P

ATLANTIC DIP: Index Pregnancy Factors Associated With Progression to Pre-Diabetes/Diabetes up to 5 Years Post Gestational Diabetes in the West of Ireland

EOIN NOCTOR, CATE CROWE, GLORIA AVALOS, LOUISE CARMODY, BREEGE WICKHAM, PAULA O'SHEA, GERALDINE GAFFNEY, FIDELMA DUNNE, *Galway, Ireland*

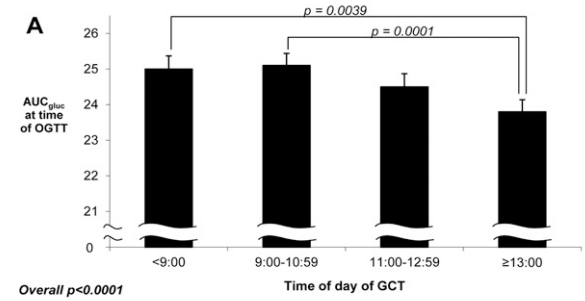
Our regional diabetes in pregnancy programme (ATLANTIC-DIP) has previously shown an 18% prevalence of pre-diabetes/diabetes in women with gestational diabetes mellitus (GDM) re-screened with a 75g OGTT 12 weeks post-partum. However, longer-term data on progression to type 2 diabetes in an Irish population is lacking.We compared Caucasian women with previous GDM (n=211) with women having normal glucose tolerance (NGT) during pregnancy (n=265) using a 75g OGTT, to determine the prevalence of diabetes/pre-diabetes up to 5 years post index pregnancy, and to identify index pregnancy factors associated with progression to abnormal glucose tolerance. Women with abnormal OGTT 12 weeks post-partum (n=36) did not undergo repeat OGTT, but were included in the analysis. ADA diagnostic criteria for IFG/IGT/DM were used. 11% (19/175) of GDM women rescreened had pre-diabetes/DM, giving a prevalence of 26.1% (55/211), versus 3.4% (9/265) of women with NGT during pregnancy.Logistic regression analysis was used to identify predictive factors for development of pre-diabetes/diabetes. These were: first-degree relative with DM (OR 2.0 95% CI 1.1, 3.7, p=0.02), insulin use during pregnancy (OR 3.1, 95% CI 1.5, 6.2, p=0.02), fasting glucose during pregnancy (OR for glucose ≥ 5.6mmol/L 3.5, 95% CI 1.6, 7.9, p= 0.002). Breastfeeding only conferred a benefit in those women who breastfed for one month or more (OR 0.50, 95% CI 0.27, 0.93, p=0.03). Neither age nor BMI in pregnancy was associated with pre-diabetes/diabetes.The high prevalence of diabetes/pre-diabetes up to 5 years post partum in this population suggests a national recall/rescreen programme is warranted. Such a programme should focus on those requiring insulin for GDM, those with a fasting glucose > 5.6 mmol/l on OGTT in pregnancy and those with a positive family history of Diabetes. Breastfeeding is an important modifiable factor which should be emphasised in the early post-partum period.

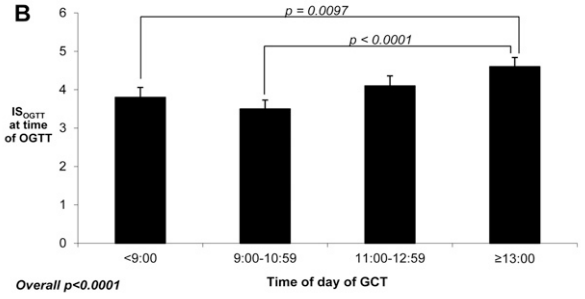
1325-P

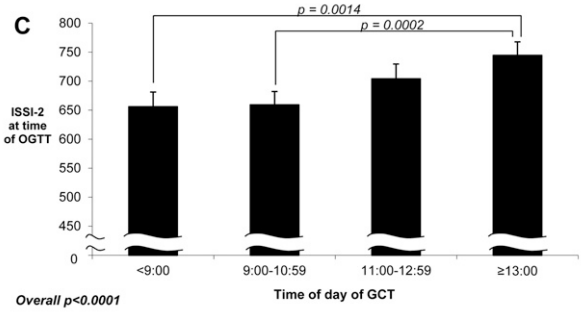
Circadian Variation in the Response to the Glucose Challenge Test in Pregnancy: Implications for Screening for Gestational Diabetes

ROBERT J. GOLDBERG, CHANG YE, MATHEW SERMER, PHILIP W. CONNELLY, ANTHONY J. HANLEY, BERNARD ZINMAN, RAVI RETNAKARAN, *Toronto, ON, Canada*

One approach to GDM screening is the testing of all pregnant women by 1-hr, 50g glucose challenge test (GCT), followed by diagnostic OGTT if the GCT is positive (≥7.8 mmol/l). Importantly, the GCT is performed at any time of day, without considering circadian effects on glucose homeostasis. Thus, we sought to characterize the metabolic profile of women with positive GCTs in relation to the timing of their test. In this study, 927 women with positive GCTs were stratified into 4 groups based on time of day of their GCT: <9:00 (n=171); 9:00-10:59 (n=288); 11:00-12:59 (n=189); and ≥13:00 (n=279). Their metabolic function was then assessed on 3-hr, 100g OGTT performed in early AM. On this OGTT, the prevalence of GDM progressively decreased across the GCT groups from <9:00 (26.9%) to 9:00-10:59 (25.0%) to 11:00-12:59 (21.7%) to ≥13:00 (21.5%)(p=0.0022). After covariate adjustment, mean adjusted area-under-the-glucose curve (AUC_{gluc}) on the OGTT decreased across the groups, while insulin sensitivity (IS_{OGTT}) and beta-cell function (Insulin Secretion-Sensitivity Index-2 (ISSI-2)) both increased (all p<0.0001) (Fig A-C). In particular, compared to the <9:00 and 9:00-10:59 groups, women in the ≥13:00 group had lower AUC_{gluc}, and better insulin sensitivity and beta-cell function (all p≤0.0097). In summary, when compared on subsequent OGTT, women with a positive GCT in the afternoon have a better metabolic profile and lower risk of GDM than those with a positive GCT earlier in the day. Thus, GDM screening protocols that include the GCT should account for the impact of time of day on test performance.







Supported by: CIHR

1326-P

Immediate Postpartum Glucose Values Do Not Predict Type 2 Diabetes in Gestational Diabetics

HILARY A. ROEDER, JENNIFER AGUAYO, NEHA R. TRIVEDI, SALLY E. AGENT, THOMAS R. MOORE, GLADYS A. RAMOS, *San Diego, CA*

Postpartum (PP) screening of women with gestational diabetes (GDM) is suboptimal due to poor compliance. Our objective was to determine if screening with fasting plasma glucose (FPG) in the hospital during the immediate PP period was equally effective to formal screening (FS) 6 weeks later with either a 2-hour glucose tolerance test or Hemoglobin A1C. This retrospective cohort study included patients diagnosed with GDM at our institution from January 2008 to December 2010. Data abstracted included maternal demographics, gestational age at diagnosis of GDM, classification of A1 or A2 GDM, anti-hyperglycemic medications administered, fasting and postprandial plasma glucose levels immediately PP, and the results of FS performed at 6 weeks PP. A total of 545 patients with GDM were identified and 165 (30%) obtained FS at 6 weeks PP. Ten (6.1%) had a final diagnosis of Type 2 diabetes mellitus (T2DM) on FS. Of the 165 screened, 111 had immediate PP FPG available for review. Nine patients had a FPG >126 mg/dl. Two of the 9 patients met diagnostic criteria for T2DM on FS, and the other 7 would have been misdiagnosed with T2DM. Six of the 111 patients would have been false negatives as they had FBS<126 mg/dl immediately PP and were subsequently diagnosed with T2DM on FS. Fasting values obtained in this 111 patient cohort immediately after delivery were higher than those obtained during FS (101±20 mg/dl vs. 93±35 mg/dl, p=0.015). Immediate PP FPG values are consistently higher than those obtained 6 weeks PP. The predictive value of immediate PP plasma glucose levels in diagnosing T2DM is poor. Therefore follow up in the PP period should be encouraged, and patients should continue to obtain FS 6 weeks after delivery.

1327-P

Reducing Sedentary Behavior and Increasing Physical Activity during Pregnancy: A Feasibility Study

JESSICA MARCINKEVAGE, ADOLFO CORREA, USHA RAMAKRISHNAN, ANDREA SHARMA, K.M. VENKAT NARAYAN, GUILLERMO UMPIERREZ, *Atlanta, GA, Jackson, MS*

Minority women are more likely than non-Hispanic white women to enter pregnancy overweight or obese, have higher gestational weight gain (GWG) and develop gestational diabetes (GDM). To help shape interventions to prevent excessive GWG and reduce rates of GDM, we are conducting a feasibility trial among overweight/obese black women receiving prenatal care at a large urban hospital. Women are randomly assigned to receive regular care or regular care plus a lifestyle intervention -- monthly meetings focused on reducing sedentary behavior and increasing levels of moderate physical activity (PA). In the first trimester and at 24-28 weeks gestation we measure weight; glucose levels through a 5-step 75g oral glucose tolerance test; and self-report PA. We present data from 55 women currently enrolled (mean±SD weeks gestation: 14.4±2.8 wk), 36(65%) of whom have attended their mid-pregnancy visit (17[71%] intervention and 19[83%] regular care). Attendance for sessions is high, with 88% of intervention participants attending all sessions scheduled prior to their mid-pregnancy visit. Preliminary analyses show a decrease in median(range) total activity in both groups from first visit to mid-pregnancy: 340.8(86.5-744.6) to 286.2(76.3-553.3) MET-h/wk for intervention and 402.8(70.7-668.4) to 366.9(131.3-969.1) MET-h/wk for regular care. Additionally we observe a reduction in sedentary behavior from first trimester to mid-pregnancy in intervention but not regular care participants, from 76.4(6.3-195.0) to 73.5(21.5-154.5) MET-h/wk. The median(range) GWG at mid-pregnancy is similar for both groups: 4.5(-0.9-9.8)kg for intervention vs 3.5(-5.1-13.1)kg for regular care. At mid-pregnancy, we see lower median fasting and 30min glucose values in intervention vs regular care participants (81.9 vs 86.9mg/dL and 113 vs 122mg/dL, respectively). These preliminary data demonstrate the feasibility of modifying lifestyle during early pregnancy in underserved black women.

1328-P

Microarray Profiling of Insulin and Diabetic Pathways in Visceral Versus Subcutaneous Adipose Tissue in Pregnant Women

DOTUN OGUNYEMI, JUN XU, AARON TURNER, DANIELE FELDMAN, JACQUELINE C. YANO, YAWEN CHENG, CAROLYN AKEXANDER, JEROME I. ROTTER, Y.D. CHEN, *Los Angeles, CA*

Our aim was to characterize in non-obese pregnant women differentially expressed genes between visceral and omental adipose tissue relevant to insulin signaling and diabetic pathways. We carried out microarray gene profiling of matched abdominal subcutaneous (SAT) and visceral (VAT) adipose tissue obtained during non-laboring cesarean sections in a fasting state from 14 non-obese non-diabetic pregnant women using Illumina HumanHT-12 V4 Expression BeadChips. We identified genes involved in insulin signaling and diabetic pathways using the Kegg pathway. We validated our findings by measuring transcript levels of selected genes based on their biological function using quantitative real-time PCR.Regarding insulin signaling pathway, 2 genes were up-regulated in VAT versus SAT: fructose-1,6-bisphosphatase-1 which stimulates glycolysis and protein-phosphatase-1-regulatory-subunit-3C which inhibits glycogen formation. Conversely 6 insulin signaling pathway genes were down-regulated in VAT compared to SAT; these included insulin-receptor-substrate-1 which is crucial for insulin sensitivity and sorbin-SH3-domain-containing-1 which is required for insulin stimulated glucose transport. Six genes associated with type-1-diabetes-pathway were up-regulated in VAT versus SAT, including carboxypeptidase-E which links hyperlipidemia and beta-cell death pathways in diabetes; and interleukin-1-beta which independently increases the risk of diabetes. Three type-2-diabetic-pathways genes were down-regulated in VAT versus SAT which included adiponectin, an important adipokine involved in fat metabolism and insulin sensitivity, with direct anti-diabetic, anti-atherogenic and anti-inflammatory activities. In conclusion, visceral fat in comparison to subcutaneous fat in healthy non-obese pregnancy is associated with a microarray profile of insulin resistance with predilection to diabetes.

For author disclosure information, see page 797.

Guided Audio Tour poster ADA-Funded Research