# COMPLICATIONS—HYPOGLYCEMIA

## 2235-PUB

### Hypoglycemia in Non-Critically Ill Patients with T2DM Is Independently Associated with Prolonged Hospitalization

THAN SEIN, TRIER TSUI NUM LAU, HUI CHENG TAN, YU KWANG DONOVAN TAY, *Singapore, Singapore*

Hypoglycemia has been associated with prolonged length of stay (LOS) in Caucasian cohorts with T2DM. We examined the association between hypoglycemia and LOS in multi-ethnic non-critically ill cohort with T2DM.

Data for this retrospective cohort study was obtained from electronic databases of patients over a 5 months period in 2016 (n= 203). After exclusion, the sample comprised of 168 admissions. Charlson Comorbidity Index (CCI) excluding DM was used to control for severity of illness. Hypoglycemia was defined by capillary blood glucose level (< 4mmol/L) obtained using point of care monitoring system. Predictors of LOS were evaluated using multiple linear regression analyses. LOS was log transformed in the analyses.

Prevalence of hypoglycemia was 17.9%. Median LOS was 10 days (4-25). Table 1 summarizes the association between variables and LOS. LOS increased by 2.4% and 22% for each year increase in age (1.1-3.7, p<0.01) and point increase in CCI score (11.1-34.0, p<0.01) respectively. Median LOS was 13(6-27) in Chinese, 9(3-33) in Malays and 6(2-13) in Indians and 5(5-9) in Eurasians (p=0.034). LOS of patients with hypoglycemia was 82.4% longer than those without (8.1 to 207.7, p=0.025) and was independent of age, gender, ethnicity, Hba1c, BMI, CCI, eGFR and insulin or sulfonylurea use.

Hypoglycemia is associated with doubling of the LOS in non-critically ill multi ethnic cohort with T2DM.

**Table 1.** Baseline Characterstics, Bivariate, and Multivariable Analyses.

| Variables | | Value | Unadjusted Change in LOS | | Adjusted Change in LOS | |
|---|---|---|---|---|---|---|
| | | | % (95% CI) | P | % (95% CI) | P |
| Age (Year) | | 69.3 ± 13.7 | 2.4 (1.1 to 3.7) | <0.01 | 1.1 (-0.5 to 2.8) | .167 |
| Gender | | | | | | |
| | Female | 68 (40.5) | Reference | | Reference | |
| | Male | 100 (59.5) | -18.8 (-43.8 to 17.3) | .265 | -16.3 (-43.8 – 24.7) | .379 |
| Race | | | | | | |
| | Chinese | 112 (66.7) | Reference | | Reference | |
| | Malay | 15 (8.9) | -6.5 (-50.5 to 76.5) | .836 | 44.1 (-31.3 to 202.4) | .331 |
| | Indian | 36 (21.4) | -44.9 (-64.6 to -14.2) | <0.01 | -18.0 (-51.9 to 40.0) | .465 |
| | Eurasian | 5 (3.0) | -47.7(-81.8 to 50.3) | .227 | -29.9 (-75.1 to 97.7) | .499 |
| Hba1c (%) | | 7.5 ± 2.0 | -11.7 (-19.4 to -3.2) | <0.01 | -8.4 (-18.3 to 2.8) | .134 |
| BMI (kg/m$^2$) | | 24.6 ± 5.5 | -4.6 (-8.0 to -1.0) | 0.012 | -2.8 (-6.5 to 1.0) | .141 |
| CCI Score (exclude Diabetes) | | 1.6 ± 1.8 | 22.0 (11.1 to 34.0) | <0.01 | 12.1 (0.0 to 25.7) | .049 |
| Hypoglycaemia | | 30 (17.9) | 99.3 (25.6 to 216.3) | <0.01 | 82.4 (8.1 to 207.7) | .025 |
| eGFR (ml/min) | | 67.9 ± 29.9 | -0.7 (-1.3 to -0.1) | .020 | 0.0 (-0.7 to 0.7) | .998 |
| Insulin /Sulfonylurea use | | 99 (58.9) | 11.8(-22.7 to 61.6) | .551 | 36.5 (-11.3 to 110.2) | .155 |

Results are presented as mean ± SD or n (%) except as specified otherwise.
Per 1-year increment in age
Per each percentage point in HbA1c
Per every 1 kg/m$^2$ increment in BMI
Per each point increase in CCI score
Hypoglycemia is defined as any documented inhospital episode of glucose < 4 mmol/L, and effect is compared with subjects with no hypoglycemia.

## 2236-PUB

### Detection of Potentially Under-Reported Real-World Hypoglycemic Burden with Text Mining and Electronic Health Records

PÄIVI M. PALDÁNIUS, GERASIMOS PETRATOS, GIOVANNI BADER, *Basel, Switzerland, New York, NY*

Detection of subclinical and potentially under-reported hypoglycemic events (HEs) is challenging in the absence of frequent blood glucose testing or patient awareness. We explored the real-world burden of HEs, the rate of subclinical HEs and presence of symptoms indicative of potentially undiagnosed HEs and clinical interventions using computerized electronic health records (EHRs). A convenience population of 347,348 U.S. patients and associated 2 million longitudinal records (2010-2013) were used for comparison of subgroup combinations of HEs using standard database query and natural language processing techniques of 20 pre-defined signs or symptoms and 14 different physician intervention options related to HE management. The EHR population comprised of 7.8% (n=27,175) diagnosed with T2DM of those, 5.6% (n=1,522) had documented hypoglycemia: 91.8% with symptoms and, of those, 84.8% led to an intervention. Yet, out of 25,653 subjects with no documented hypoglycemia, 80.8% reported ≥1 symptom of potentially under-reported HEs, of those, 65.7% had a documented intervention. Subjects with potentially under-reported HEs had multiple comorbidities. The subjects were mostly treated with insulin (43.8%), biguanides (25.7%) or sulfonylurea (23.6%). Indicators of HEs such as chills, confusion, tachycardia, dizziness, hunger, sleepiness, blurred vision, numbness, headache, weakness, lack of coordination and seizure were documented more often among those with a documented HE. These symptoms of HEs also more often lead to a therapy switch (OR=1.6; 95% CI 1.4, 2.0), change in dose or frequency (OR=2.3; 95% CI 1.9, 2.7), a consultation (OR=1.6; 95% CI 1.4, 1.8) or a referral to a diabetes educator (OR=2.2; 95% CI 1.3, 3.6). Providers with modern and well supported EHR systems have potential for proactive detection, testing and documentation for HEs. Quality surveillance of the patient records can alert providers and also include suggestions for an intervention.

*Supported By: Novartis*

## 2237-PUB

### Prediction of Lowest Nocturnal Blood Glucose (LNBG) Levels in Japanese Type 2 Diabetic (T2D) Patients Treated with Insulin

YUKO KAWAI, MASANORI YAMAZAKI, KAZUNORI SAKURAI, MITSUHISA KOMATSU, *Matsumoto, Japan*

Objective: In Japan, continuous glucose monitoring (CGM) and flash glucose monitoring are not available for all T2D patients at risk of nocturnal hypoglycemia (NH). This study aimed to investigate how to predict LNBG levels with self-monitoring of blood glucose (SMBG) data.

Methods: In a formula making (FM) group of 29 insulin-treated Japanese T2D inpatients (12 female) with CGM data from February, 2012 to July, 2013, prediction formula of LNBG level was created by multiple linear regression analysis, followed by finding of adjusted determination coefficient ($R^2$) and standard error of calibration (SEC). Diet, exercise and other medication were not considered for the prediction. In a formula validation (FV) group of 24 insulin-treated T2D patients (21 female) with CGM data from August, 2013 to March, 2016, the validity of formula was assessed by standard error of prediction (SEP) from simple linear regression analysis of actual and predicted values. Clinical impact on prediction was evaluated by Parkes error grid analysis.

Results: In the FM group, mean age, fasting blood glucose (FBG) level, total insulin dose (TID), basal insulin dose (BID), and actual LNBG level were 62.0 ± 12.8 y, 139.4 ± 35.6 mg/dL, 26.0 ± 15.2 U/day, 8.7 ± 8.5 U/day, and 98.4 ± 13.9 mg/dL, respectively. The following predictive formula was established: Predicted LNBG (mg/dL) = 127.4-0.836 × Age (y) + 0.119 × FBG (mg/dL) + 0.717 × BID (U/day) (adjusted $R^2$ 0.35, SEC 17.2 mg/dL, SEP 31.0 mg/dL). By the validation of formula using 29 data sets of the FV group (age 65.7 ± 13.4 y, FBG 130.3 ± 37.0 mg/dL, TID 29.3 ± 22.2 U/day, BID 13.5 ± 9.7 U/day, actual LNBG 102.4 ± 33.2 mg/dL), SEP was calculated at 27.2 mg/dL. Moreover, all predicted values fell within zones A (no effect on clinical action) and B (little or no effect on clinical outcome) on Parkes error grid.

Conclusions: LNBG levels were predictable with SMBG data. This prediction may be helpful for prevention of NH through earlier intervention.

## 2238-PUB

### Impact of Sitagliptin on Hypoglycemia in Elderly Subjects with T2DM Treated with Insulin

R. RAVI SHANKAR, JIANMIN LONG, LEI XU, EDWARD A. O'NEILL, SAMUEL S. ENGEL, *Kenilworth, NJ*

Hypoglycemia (HYPO) is uncommon with sitagliptin (SITA) treatment but occurs more frequently when SITA is added to insulin (INS) due to insulin's ability to cause hypoglycemia. HYPO is of special concern in elderly INS-treated patients. To assess the effect of SITA on glycemic control and event rates (ERs) of HYPO in the elderly treated with INS compared to younger (<65 years) subjects, data from two 24-week studies that compared the addition of SITA with PBO in subjects with T2DM on INS ± metformin were pooled (N=1299, 320 elderly; INS dose held stable in one, intensively titrated in the other) and treatment effect and event rates of HYPO were analyzed. We also examined ERs of HYPO by subgroups characterized by selected baseline characteristics.

Reductions in A1C were similar in both age groups (Table). In general, elderly subjects had similar or lower ERs of HYPO compared to younger subjects. ERs of symptomatic HYPO and nocturnal HYPO were lower with SITA compared with PBO (Table) in both younger and elderly. In subgroups evaluated by baseline A1C, eGFR and duration of T2DM, ERs of HYPO were lower with SITA compared with PBO in both age groups.

In this pooled analysis of SITA vs. PBO added to INS, SITA provided similar improvement in glycemic control and reductions in event rates of HYPO in both elderly and younger patients.



For author disclosure information, see page A751.

**Table.**

| Parameter | <65 years N = 979 | | ≥65 years N = 320 | |
|---|---|---|---|---|
| **A1C (%)** | **Sitagliptin** *n* = 487 | **Placebo** *n* = 492 | **Sitagliptin** *n* = 164 | **Placebo** *n* = 156 |
| Baseline | 8.76 (0.96) | 8.78 (1.00) | 8.48 (0.85) | 8.56 (0.97) |
| Week 24 | 7.77 (1.17) | 8.28 (1.28) | 7.57 (0.95) | 8.16 (1.10) |
| Change from baseline[1] | -0.98 (-1.08, -0.89) | -0.51 (-0.60, -0.41) | -0.91 (-1.05, -0.78) | -0.36 (-0.50, -0.22) |
| Sita vs. placebo[2] | -0.48 (-0.61, -0.34) p<0.001 | — — | -0.55 (-0.74, 0.36) p<0.001 | — — |
| **Event rate of hypoglycemia** (events/subject year) | **Sitagliptin** *n* = 487 | **Placebo** *n* = 492 | **Sitagliptin** *n* = 164 | **Placebo** *n* = 156 |
| Symptomatic[3] | 1.32 | 2.18 | 1.50 | 1.65 |
| Severe[4] | 0.05 | 0.10 | 0.04 | 0.01 |
| Nocturnal (CT)[5] | 0.66 | 0.89 | 0.38 | 0.90 |

Values are mean ± standard deviation unless otherwise noted. [1] Least squares (LS) mean (95% CI). [2] Difference in LS mean changes from baseline (95% CI). [3] Symptoms consistent with hypoglycemia. [4] Hypoglycemia requiring assistance, or with marked loss of consciousness or seizures. [5] Hypoglycemia occurring between 11 PM and 6 AM.

*Supported By: Merck & Co., Inc.*

## 2239-PUB

### Analysis of National EMS Information System (NEMSIS) of Emergency Responses in 2013 for Treatment and Transportation of Hypoglycemic Patients

BETH D. MITCHELL, DAVID R. NELSON, MICHAEL KAUFMANN, *Indianapolis, IN*

National estimates and management of hypoglycemia outside the emergency department are unknown. This study evaluated patient characteristics, treatment, and transport by emergency medical services (EMS) for hypoglycemia using NEMSIS. Analysis included 180,561 patients (0.8% of all records) dispatched for "diabetes" with primary or secondary provider's impression of hypoglycemia. Primary symptom recorded was "change in responsiveness" (69,053 [38.2%]). Treatments for "change in responsiveness" included intravenous (IV) dextrose (26.2%), glucagon (5.7%), or none/oral glucose (68.2%)/(6.8%). "Change in responsiveness" increased odds of glucagon ([odds ratio: 95% CI]: 2.19; 2.08-2.30) or IV dextrose (2.77; 2.70-2.84) use. Venous access failure also increased odds of glucagon use (9.88; 9.40-10.38). Variables with higher odds of transport included: primary symptoms of diarrhea/fever/nausea/vomiting (4.62; 4.41-4.84); nursing home (4.44; 4.24-4.66); organ system complaints including pulmonary/renal/cardiovascular (4.43; 4.04-4.86); African-Americans (1.30; 1.26-1.33); and call from a rural setting (1.25; 1.20-1.31). Approximately, 43.3% (77,678) of patients who called EMS were not transported and those receiving IV dextrose had lower odds of transport (0.41; 0.40-0.42). This is the first U.S. EMS report for hypoglycemia.

**Table.** Patient Characterstics According to Treatment.

| Characteristics[a] | Glucagon (N=10,215) | IV dextrose (N=47,240) | None/oral glucose (N=123,106) |
|---|---|---|---|
| Age (mean, years) | 57.2 | 59.8* | 56.5 |
| Female | 5468 (53.5) | 20,834 (44.1)* | 60,713 (49.3)* |
| Whites | 4702 (46.0) | 26,711 (56.5)* | 63,161 (51.3)* |
| African-Americans | 3780 (37.0) | 10,671 (22.6)* | 33,182 (26.9)* |
| **Patient Disposition** | | | |
| No treatment required | 59 (0.6) | 290 (0.61)* | 5226 (4.2)* |
| Refused care | 1191 (11.7) | 9783 (20.7)* | 20,993 (17.1)* |
| Treated, released | 1669 (16.3) | 15,462 (32.7)* | 18,903 (15.4)* |
| Treated, EMS transported | 7073 (69.2) | 20,464 (43.3)* | 69,049 (56.1)* |

*p<.0001 vs glucagon; [a]Values shown are for n (%) unless otherwise noted

*Supported By: Eli Lilly and Company*

## 2240-PUB

## WITHDRAWN

## 2241-PUB

### Temporal Changes in Inpatient and Outpatient Hypoglycemia among Patients Treated with Sulfonylureas or Dipeptidyl Peptidase-4 Inhibitors in the U.S.

YUEXIN TANG, JINAN LIU, SWAPNIL RAJPATHAK, SAMUEL S. ENGEL, HAKIMA HANNACHI, *North Wales, PA, Rahway, NJ, Lebanon, NJ*

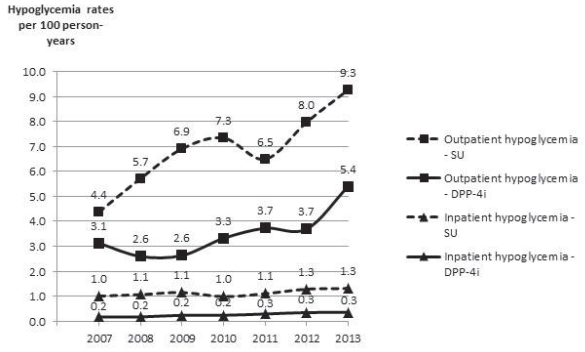
Objective: Recent evidence suggests hypoglycemia rates, mainly in inpatient setting, have not changed much in recent years. Less is known about hypoglycemia in other healthcare settings and by treatment groups with known differential hypoglycemia risk. This real world study aimed to assess changes in annual rates of both inpatient and outpatient hypoglycemia among patients either on sulfonylureas (SU) or dipeptidyl peptidase-4 inhibitors (DPP-4i) during 2007-2013.

Methods: This retrospective cohort study using MarketScan Commercial Claims included adult type 2 diabetic patients using either SU (n=230,556) or DPP-4i (n=133,768) (mono- or combination therapy with other drugs, excluding insulin). Hypoglycemia, defined by ICD-9 diagnosis codes, was assessed during 12-month follow-up period after drug initiation.

Results: Outpatient hypoglycemia rates (100 person-years) increased from 2007 to 2013: 4.4 to 9.3 in SU; 3.1 to 5.4 in DPP-4i. Inpatient hypoglycemia rates ranged 1.0-1.3 in SU; 0.2-0.3 in DPP-4i (Figure 1).

Conclusion: There was apparent increase outpatient hypoglycemia rate in recent years in both SU and DPP-4i, which might be related to improved awareness and coding/reporting. Changes in inpatient hypoglycemia overtime were relatively small. In both settings, hypoglycemic events were consistently higher among SU than DPP-4i users.

**Figure 1.** Inpatient and outpatient hypoglycemia rates in SU and DPP-4i users.
Notes: SU: sulfonylurea; DPP-4i: dipeptidyl peptidase-4 inhibitor.
SU group: N = 230,556; age=51.9 years, female=43.2%, Charlson Comorbidity Index=1.49;
DPP-4i group: N = 133,768; age=52.6 years, female=45.3%, Charlson Comorbidity Index=1.55.
Poisson models were used to generate 95% confidence interval (CI) for hypoglycemia rates:
•Outpatient hypoglycemia rates from 2007 to 2013: 4.4 (95% CI: 4.1-4.7) to 9.3 (95% CI: 8.8-9.8) in SU; 3.1 (95% CI: 2.8-3.5) to 5.4 (95% CI: 5.0-5.9) in DPP-4i;
•Inpatient hypoglycemia rates from 2007 to 2013: 1.0 (95% CI: 0.9-1.2) to 1.3(95% CI: 1.1-1.5) in SU; 0.2(95% CI: 0.1-0.3) to 0.3 (95% CI: 0.2-0.5) in DPP-4i.




*Supported By: Merck & Co., Inc.*

For author disclosure information, see page A751.

## 2242-PUB

**Impact of an Electronic Hypoglycemia Risk Calculator on Primary Care Practice**

MICHAEL WEINER, JONATHAN CUMMINS, ANNASWAMY RAJI, SUSAN OFNER, KRISTY IGLAY, EVGENIA TEAL, XIAOCHUN LI, SAMUEL S. ENGEL, KRISTINA KNAPP, SWAPNIL RAJPATHAK, JAROD BAKER, ARNAUB CHATTERJEE, LARRY RADICAN, *Indianapolis, IN, Kenilworth, NJ*

Studies indicate that hypoglycemia (HG) occurs in 20% to 60% of patients with diabetes mellitus (DM) each year. Our objective was to implement an informative tool about HG in an electronic health record system, and determine the tool's effect on clinical practice and outcomes. An alert tool was created based on a multivariable model of HG. Based on a patient's characteristics, the tool provided information about HG risk, including display of each contributing factor, and estimated current risk of HG. We piloted the tool by randomizing outpatient primary-care providers (PCPs) in an urban academic medical practice, to see, or not see, the alert upon viewing patients' records. Patients were assigned to intervention or control according to the first PCP seen during 4 months. During 5-month follow-up, we assessed patients' characteristics, prescriptions and diagnostic testing, and HG. Categorical variables with more than 2 values were compared by multinomial model with fixed effect for treatment group and random intercept for PCP. Binary variables were compared by logistic model. Continuous variables were compared by linear model with similar independent variables. Intervention (N=3365) and control (N=3415) patients visited 198 PCPs. Intervention PCPs (N=99) were shown 18,653 alerts about HG. Patients' mean age was 55 years, with 61% female, 49% black, 27% white, and 49% with Medicaid. Mean A1c (8.7) and body mass index (35.2) were similar at baseline between groups. During the follow-up period, the intervention group had more prescribing actions (new, changed, or refilled) per 100 patients, on average, for long-acting insulin (52 vs. 22), non-long-acting insulin (38 vs. 18), sulfonylurea (25 vs. 12), and potentially HG-inducing antibiotics (25 vs. 14). Frequency of A1c testing and HG events was unchanged. Drug discontinuation could not be assessed. Displaying patients' risk of HG to PCPs led to more prescribing actions (new, changed, refilled) of common DM medications. This may reflect greater awareness of HG.

## 2243-PUB

**Hypoglycemia Awareness and the Risk of Severe Hypoglycemia in the Global HAT Study of 27,585 Patients with Type 1 and Type 2 Diabetes**

ULRIK PEDERSEN-BJERGAARD, RONNIE ARONSON, HELGE GYDESEN, JESPER BARNER LEKDORF, KAMLESH KHUNTI, *Hillerød, Denmark, Toronto, ON, Canada, Søborg, Denmark, Leicester, United Kingdom*

Impaired awareness of hypoglycemia (IAH) is the most important predictor for, and is associated with increased incidence of, severe hypoglycemia, particularly in type 1 diabetes (T1D). IAH and its effects are largely unknown outside Europe and North America. The global Hypoglycemia Assessment Tool (HAT) study (NCT01696266) assessed hypoglycemia incidence and awareness in patients with T1D and type 2 diabetes (T2D) in 6-month retrospective and 1-month prospective periods in Northern Europe, Canada, Eastern Europe, the Middle East, Latin America, South East (SE) Asia and Russia. Hypoglycemia awareness was assessed at baseline using a validated method based on the question: "Do you have symptoms when you have a low sugar level?" The answers "always," "usually," "occasionally" and "never" indicated increasing degrees of IAH. In patients with T1D, higher estimated annual incidence rates (IRs) for severe hypoglycemia corresponded with a greater degree of IAH (retrospective IRs: always 1.87; usually 2.00; occasionally 3.39; never 3.58; prospective IRs: always 4.30; usually 4.79; occasionally 6.46; never 10.49). The association between severe hypoglycemia and IAH was most pronounced in Eastern Europe (retrospective IRs: always 1.36; usually 1.71; occasionally 2.18; never 3.08), but an inverse association was uniquely observed in SE Asia (retrospective IRs: always 2.90; usually 1.92; occasionally 0.91; never 0.27). In T2D patients, the IRs for severe hypoglycemia in the retrospective period decreased as impairment increased, but no association was present in the prospective period. These results show that incidence of severe hypoglycemia increases with a greater degree of IAH in T1D with large regional differences, but not in T2D. Further research into the reasons for these large regional differences in IAH and severe hypoglycemia is needed.

*Supported By: Novo Nordisk*

## 2244-PUB

**WITHDRAWN**

## 2245-PUB

**WITHDRAWN**

## 2246-PUB

**Patient Web Portal in Type 2 Diabetes Mellitus**

KALYANI MURTHY, HANNAH CALDWELL, NEIL MINKOFF, JENNIFER BRAIMON, MARY BETH HODGE, LEIGH TAYLOR, VIOLETA RISTIC, JESSICA SPEISER, JOSEPHINE NORQUIST, *Burlington, MA, Maynard, MA, Peabody, MA, Kenilworth, NJ*

Background: Patient-Reported Outcome (PRO) portals can capture key health information. Documenting hypoglycemia (HG) in type 2 diabetes mellitus (T2D) is important as episodes may impact medication compliance and quality of life. We conducted a pilot study in T2D patients new to sulfonylurea and/or insulin to compare HG events reported on EmpiraMed™ PRO Portal™ Platform (portal) vs. paper surveys.

Methods: A 6-month prospective pilot was conducted. Participants completed in-clinic paper surveys at baseline and follow-up (f/up) and received portal access. We compared paper and portal responses on HG reports (with built-in alerts), symptoms, and number of events.

Results: 100 participants [67 males, mean age 61 y] consented and completed baseline paper surveys. 90 registered on the portal [mean T2D duration 97 months]; 40 made portal diary entries and 82 completed f/up paper survey. Reports on presence of HG somewhat concurred between methods at baseline or f/up (kappa=0.67). 12 participants with multiple HG values triggered alerts to study staff. There was a lower rate of skipped responses on portal vs. f/up paper survey for impact on daily life (0% vs. 14%) and timing (0% vs. 8%). 42% of participants completing f/up paper survey reported logging some or all of their HG events on the portal. Among patients who reported no low glucose values, HG symptoms were still reported by 52% and 26% on the portal and paper survey, respectively.

Conclusions: Our study highlights potential applications of portals in T2D care. The low concurrence between the two methods regarding presence of HG symptoms could be multifactorial, including event recall and clinical status at time of report. Analysis showed the portal captured descriptive data such as symptom timing and impact. Alerts enabled timely management. More participants without HG reported symptoms on the portal, potentially demonstrating capture of pseudohypoglycemia. Future studies should evaluate feasibility of incorporating portals as an adjunct in clinical practice.

*Supported By: Merck & Co., Inc.*

## 2247-PUB

**Hypoglycaemia in Cystic Fibrosis**

NATASHA ARMAGHANIAN, TANIA P. MARKOVIC, JENNIE C. BRAND-MILLER, CARMEL P. MORIARTY, PETER T.P. BYE, KATE S. STEINBECK, *Sydney, Australia*

Hypoglycaemia in cystic fibrosis (CF), in the absence of diabetes or glucose lowering medication, is an increasingly recognised phenomenon in oral glucose tolerance tests (OGTT) and continuous glucose monitoring. However empirical data relating to both the patient experience and the mechanistic cause of hypoglycaemia are limited. The aims of this study were to review patient electronic medical records (EMR) in order to 1) describe patient characteristics of a university teaching hospital cystic fibrosis CF clinic, 2) determine the prevalence of hypoglycaemia on OGTT and explore associations with demographic and clinical characteristics, and 3) explore patient reported symptoms suggestive of hypoglycaemia documented in the EMR. All adults who attended the CF clinic between January 2009 to April 2016 were included in the study. The prevalence of hypoglycaemia on OGTT and reported symptoms suggestive of hypoglycaemia documented in the EMR were recorded. These patients were compared to age and sex matched pre-transplant controls selected from the CF clinic that did not have diabetes or liver disease. Hypoglycaemia during OGTT was detected in 22 out of 146 patients. These patients were heavier, less likely to have pancreatic insufficiency and more likely to have normal glucose tolerance than age and sex matched controls. Another 13 patients also reported symptoms suggestive of hypoglycaemia in their EMR. These patients had lower BMI, greater abnormality of lung function, and were also more likely to have a higher insulin response during OGTT. This study found two different presentations of hypoglycaemia occur in different clinic sub-populations. OGTT related and symptomatic hypoglycaemia is not uncommon in CF, however the aetiology remains to be elucidated.

## 2248-PUB

**WITHDRAWN**

## 2249-PUB

**WITHDRAWN**

## 2250-PUB

**Vision, Insulin-Usage Skills, and Food Insecurity Increase Hypoglycemia**

DAVID C. ZIEMER, CATHERINE S. BARNES, JANE M. CAUDLE, PAYAL SHAH, LAUREN L. HOYER, *Atlanta, GA*

Hypoglycemia (HYPO) complicates diabetes management; for prevention plans in a public hospital setting we assessed potential causal pathways—focusing on vision, socio-demographics and self-management education (DSME).

Primary care diabetes patients at increased risk of hypoglycemia (81) reported hypoglycemia risk factors and 58 insulin users demonstrated drawing up 17 U of insulin with 50 U syringe; results recoded as difference from 17 U. Visual acuity (Va) with correction was measured with Rosenbaum eye chart.

For author disclosure information, see page A751.

ADA-Supported Research

Population had mean age 58 years and was 65% female, 94% African American, and 96% non-Hispanic. The majority (72%) reported completing high school or more. Using 2 question survey, 48% reported food insecurity. Va was worse than 20/40 in 23% of subjects. Severe HYPO (ER/EMS/hospital admission or BG<50 mg/dL) in the prior year was reported by 24%. Sixteen percent reported having insulin usage problems (PROB_INS). When asked to draw up 17 units of insulin, 58 insulin using participants drew up, on average, 17.1 units; only 62% drew up the correct amount.

Severe HYPO was associated with Va, PROB_INS, degree of food insecurity, and in insulin using population trend for having ever had DSME. No associations seen with hypoglycemia unawareness or REALM score. In a multivariable model severe HYPO was associated with Va, PROB_INS (both p=0.001) and somewhat with degree of food insecurity (p=0.078). PROB_INS was associated with age and actual insulin measurement error (IME) in multivariable model. IME was in turn associated with Va and somewhat with DSME.

Thus, probable causative factors for hypoglycemia in a public hospital setting include visual acuity, self-reported insulin usage problems, and age. Other potential factors include food insecurity and lack of diabetes self-management education. Visual acuity screening and correction, insulin training and screening for food insecurity are crucial, modifiable steps to prevent hypoglycemia and improve glycemic control.

*Supported By: American Diabetes Association (7-12-HYPO-11 to D.C.Z.)*

## 2251-PUB

**Lumacaftor/Ivacaftor (Orkambi) Not Quite a Cure for Cystic Fibrosis-Related Diabetes (CFRD)**

MARINA LITVIN, JOAN ZUKOSKY, DANIEL ROSENBLUTH, *St. Louis, MO*

Cystic Fibrosis (CF) is the most common autosomal recessive disease. The affected gene codes for cystic fibrosis transmembrane conductance regulator (CFTR), and is present in multiple organs, including airways and pancreas. As patients with CF live longer, pancreatic function declines and diabetes emerges. Up to 50% of patients ≥18 years old develop Cystic Fibrosis Related Diabetes (CFRD). Poorly-controlled CFRD has been associated with increased exacerbations, worse lung function, lower BMI and higher mortality. Aberrant CFTR predisposes to bronchiectasis and infections, and can lead to exocrine and endocrine pancreatic insufficiency. In 2015, FDA approved lumacaftor/ivacaftor (Orkambi), a CFTR corrector/potentiator, for patients homozygous for F508 del mutation. The drug improves lung function, and may affect insulin secretion. We report a case of an insulin-requiring patient with CFRD, who discontinued insulin therapy, and then had a reduced insulin requirements after starting Orkambi.

A 37 year old man with CFRD complicated by microalbuminuria, treated with insulin for 4 years, total daily insulin doses ≥30 units, developed recurrent hypoglycemia 9 months after starting Orkambi, leading to discontinuation of insulin. Labs showed normal TSH and AM cortisol, and negative Celiac Disease antibodies. A1c at 5 weeks off insulin was 6.9%, similar to prior. OGTT showed abnormal fasting glucose of 101 (< 100) and abnormal 2 hr glucose of 211 (< 200). C-peptide was detectable, and increased from baseline of 0.92 to 3.48 at 2 hrs (1.19-6.0ng/mL). Insulin was restarted for hyperglycemia after 5 weeks, but insulin requirements remained 30% less than prior to Orkambi, at 20 u per day, without changes in weight.

Little data exist on effects of CFTR therapy on pancreatic beta cells. Patients with CFRD receiving such therapy require close glucose monitoring, and possible insulin down-titration to prevent hypoglycemia. Monitoring for off-target effects of new therapeutics should be considered.

# COMPLICATIONS—MACROVASCULAR—ATHEROSCLEROTIC CARDIOVASCULAR DISEASE AND HUMAN DIABETES

## 2252-PUB

**WITHDRAWN**

## 2253-PUB

**Characteristics of Metabolic Inflammatory Syndrome among Type 2 Diabetes Patients in China**

RENMING HU, RUMEI LI, BIN LU, YING XIE, QIANG LI, FENGLING CHEN, LIANXI LI, JI HU, YING HUANG, QIN LI, WEIWEI YE, ZHAOYUN ZHANG, LINUO ZHOU, MIN HE, JIE WEN, LILI CHEN, YEHONG YANG, YIMING LI, HONGYING YE, YANGANG WANG, GUIJUN QIN, WEIWEI ZHANG, QING SU, JUN ZHU, YANCHENG XU, HONGWEI JIANG, WANG XINJUN, KEQIN ZHANG, DONGFENG GU, DAIMING FAN, *Shanghai, China, Guangzhou, China, Harbin, China, Suzhou, China, Qingdao, China, Zhengzhou, China, Wuhan, China, Luoyang, China, Haikou, China, Beijing, China, Xi'an, China*

Background: The clinical value of clustering metabolic diseases that are linked by a common pathogenesis, metabolic inflammation, has not been clarified. We propose a new concept, metabolic inflammatory syndrome (MIS), including the following four components: atherosclerosis, T2D, nonalcoholic fatty liver disease (NAFLD), and overweight/obesity.

Methods: MIS was studied in 8344 participants with T2D from 10 medical centers in China. The detection rate of MIS was calculated, and its association with the risk of coronary heart disease (CHD) as compared with the risk associated with metabolic syndrome (MS) was determined using a binary logistic analysis.

Results: In the T2D patients, the detection rate of MIS was much higher than that of MS (93.6% vs. 53.2%). The most common combination of MIS was with all 4 components, with a constituent ratio of 30.9%. According to the odds ratios (ORs), MIS was a better predictor of CHD than MS, especially after adjustment for age, gender, smoking, and alcohol consumption (MIS: adjusted OR:3.083; 95% CI, 2.030-4.683; P<0.001; MS: adjusted OR: 1.515; 95% CI, 1.327-1.729; P<0.001).

The presence of more components of MIS was associated with a higher detection rate of CHD (P<0.001). Among all the components of MIS and MS, atherosclerosis, the most commonly detected (71.9%), had the greatest OR, after adjusting for age, gender, smoking, and alcohol consumption (after adjustment, OR: 1.787; 95% CI, 1.490-2.143; P<0.001).

Conclusions: The detection rate of MIS among T2D patients was high, and MIS appeared to be an independent risk factor for CHD. Among all the components of MIS, atherosclerosis, with the highest detection rate, was the best predictor of CHD (highest OR) and a critical component of MIS. The concept of MIS is not only conducive to the early screening of atherosclerosis but also to the understanding of metabolic diseases from the perspective of holistic integrative medicine.

*Supported By: National Natural Science Foundation of China (81030014, 81270902, 81471057)*

## 2254-PUB

**WITHDRAWN**

## 2255-PUB

### Medical Resource Use and Costs in Patients with Type 2 Diabetes Mellitus during the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

SHELBY D. REED, YANHONG LI, JOSE LEAL, FELICIA GRAHAM, JOAKIM ALFREDSSON, ALASTAIR M. GRAY, JOHN B. BUSE, JENNIFER B. GREEN, KEITH D. KAUFMAN, AXEL RIEFFLIN, SHAILAJA SURYAWANSHI, FRANS VAN DE WERF, ERIC D. PETERSON, RURY R. HOLMAN, TECOS STUDY GROUP, *Durham, NC, Oxford, United Kingdom, Linköping, Sweden, Chapel Hill, NC, Kenilworth, NJ, Husby, Germany, Leuven, Belgium*

Background: TECOS, a cardiovascular safety trial, randomized 14,671 participants from 38 countries to sitagliptin or placebo, added to usual care, who were managed to achieve individualized glycemic control, equally in both groups. Sitagliptin was non-inferior to placebo for the primary composite cardiovascular outcome. Secondary and tertiary objectives were to compare medical resource use and costs between treatment groups.

Methods: Medical resource use data were collected from randomization to study end. Medical services and medications were valued using U.S. Medicare payment rates and wholesale acquisition costs, respectively. Hierarchical generalized linear models (HGLM) were used to account for variable practice patterns by country.

Results: Mean and median follow-up was 3.0 years in both groups. Resource use and costs were similar (Table). Sitagliptin-treated patients had 5 fewer hospitalizations per 100 patients (p=0.16). Total costs, exclusive of sitagliptin, were $11,937 vs. $12,409 for sitagliptin vs. placebo. Mean sitagliptin costs were $9,978 per patient. When adding study medication costs, total costs in the sitagliptin group averaged $21,915.

Conclusions: In a trial designed to achieve glycemic equipoise between groups, small reductions in hospitalizations rates with sitagliptin slightly offset treatment costs.

**Table.** Medical Resource Use and Costs *HGLM Did Not Converge.

| Mean (SD) | Sitagliptin (n=7332) | Placebo (n=7339) | Difference (95% CI with bootstrap method) | P-value |
|---|---|---|---|---|
| Hospitalizations | 0.66 (1.29) | 0.70 (1.43) | -0.049 (-0.095 to -0.008) | 0.16 |
| Inpatient days | 5.50 (16.38) | 5.74 (16.54) | -0.243 (-0.768 to 0.241) | 0.99 |
| Outpatient care visits | 19.42 (17.36) | 19.43 (17.35) | -0.008 (-0.520 to 0.583) | 0.86 |
| Inpatient costs | $6947 (19,935) | $7377 (20,066) | -430 (-1109 to 168) | * |
| Outpatient costs | $1465 (1413) | $1464 (1364) | 1 (-39 to 50) | 0.85 |
| Diabetes medication costs | $3524 (7644) | $3567 (7623) | -43 (-269 to 216) | 0.26 |
| Total costs, excluding sitagliptin | $11,937(22,265) | $12,409 (22,283) | -472 (-1193 to 247) | 0.59 |

*Supported By: Merck & Co., Inc.*

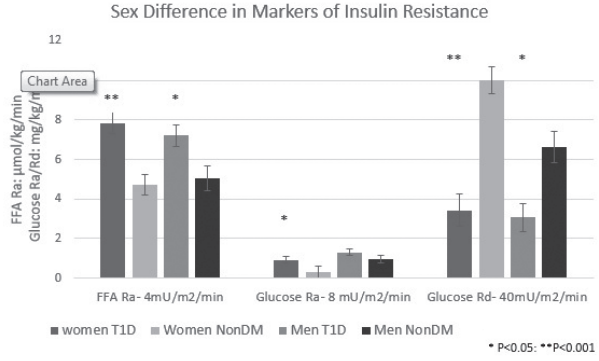
## 2256-PUB

### Tissue-Specific Insulin Resistance Differs by Sex in Type 1 Diabetes

RICHARD MILLSTEIN, LAURA PYLE, BRYAN C. BERGMAN, IRENE E. SCHAUER, JANET K. SNELL-BERGEON, *Aurora, CO*

People with type 1 diabetes (T1D) are more insulin resistant (IR) than those without diabetes (NonDM), and IR is associated with cardiovascular disease (CVD). Women with T1D have a greater relative increase in CVD risk than men with T1D when compared to people without diabetes, and so we examined if there are also sex differences in IR in T1D. Three-stage hyperinsulinemic-euglycemic clamps (4, 8, 40mU/m$^2$/min, testing adipose, hepatic and skeletal muscle IR respectively) were performed on 41 T1D and 47 NonDM adults (mean±SD age 46±8). There was no difference in age by T1D status in either in men or women. BMI did not differ by T1D status among either women (TID:25.8±4.3 vs. NonDM: 25.2±4.3, p=0.621) or men (T1D:28.5±4.2 vs. NonDM:27.2±3.6, p=0.414). Analysis of Palmitate and Glucose isotope tracers was used to determine FFA rate of appearance (Ra), glucose Ra, and glucose Rate of disappearance (Rd) in 52 of these participants (25 M and 27 W). As shown in the Figure, FFA Ra and glucose Rd were significantly higher in both men and women with T1D compared to NonDM men and women, and there were significant sex by T1D interactions for both. Glucose Ra was significantly higher in women with T1D than NonDM women but did not differ in men by T1D status, but there was no significant sex by T1D interaction for glucose Ra. We found that T1D affects adipose and skeletal muscle IR in women to a greater extent than in men, perhaps explaining part of the sex difference in CVD.

**Figure.**




*Supported By: National Heart, Lung, and Blood Institute (R01HL113029, R01HL61753, R01HL79611); Diabetes & Endocrinology Research Center (P30DK57516); JDRF (17-2013-313); Building Interdisciplinary Research Careers in Women's Health; National Institutes of Health (M01RR00051); Clinical and Translational Science Award (UL1TR001082)*

## 2257-PUB

### Possible Clinical Prognostic Meaning of Glucose Variability Indexes in Type 2 Diabetes (T2D) with Lower-Limb Neuropathic and Neuroischemic Lesions—Italian Leukemia Association Treviso Section Project

MARIA SAMBATARO, ANDREA TURA, LUISA SAMBADO, ENRICA TREVISIOL, ELENA SEGANFREDDO, ELISABETTA DURANTE, MATILDE CACCIATORE, GIOVANNI PACINI, AGOSTINO PACCAGNELLA, *Treviso, Italy, Padova, Italy*

Diabetic foot is marker of limb amputations and cardiovascular mortality. One possible link between diabetic peripheral and heart disease is glucose variability action on bone marrow derived circulating endothelial progenitor cells with distal limb and coronary neuroischemia. We studied in 74 T2D with neuropathic foot lesions without (30 N1) or with (44 N2) critical limb ischemia ($pO_2$ <30 mm Hg): bone marrow BMPC and peripheral blood PePC precursor cells CD34+; BMEP and PeEP endothelial progenitor cells CD34+KDR+ by flow cytometry. We considered retrospective 12 years data for mathematical indexes of HbA1c variability: Stability (SI) and Lability (LI), Standard Deviation (SD), Coefficient of Variation (CV), CONGA, and prospective 5 years data for death. BMPC/PePC ratio and PeEP alone were significant higher in N1 vs. N2. SI correlated with BMPC and BMPC/PePC ratio (p≤0.007). In N2 alive vs. 5 dead : SD 6.3 [8.7] vs. 11.0 [21.4] (median [IQR]), p=0.04; CV 10.2 [10.5] vs. 17.0 [29.4], p=0.02; CONGA 5.6 [7.9] vs. 20.8 [33.5], p=0.004; LI 8.1 [23.1] vs. 93.1 [259.3], p=0.0008. We demonstrated that temporal glucose load affects progenitor cells repair function in neuroischemic T2D with diabetic foot. Mathematical indexes have good prognostic value

For author disclosure information, see page A751.

for cardiac death. We hypothesize that at diabetes onset bone marrow is a sensible euglycemic setting where vascular cellular homeostasis is prematurely lost with irreversible regeneration impairment.

*Supported By: Italian Leukemia-Lymphoma-Myeloma ONLUS Association, Section of Treviso*

## 2258-PUB

**Association between Triglyceride Glucose Index and Coronary Artery Calcification in Korean Adults**

JI HONG YOU, JUNG HYE KIM, KAHUI PARK, YU SIK KIM, DA WOON HAN, BOMIN KOH, SU JEONG PARK, HO SEON PARK, SANG BAE LEE, JI SUN NAM, JONG SUK PARK, CHUL WOO AHN, KYUNG RAE KIM, *Seoul, Republic of Korea*

Objective: Insulin resistance is well known risk factor of cardiovascular disease. Recently, triglyceride glucose (TyG) index is considered a simple surrogate marker of insulin resistance. However, few studies have investigated the relationship between TyG index and coronary artery calcification (CAC), thus we investigated the association between TyG index and CAC in healthy Korean Adults.

Methods; A total of 4,463 participants underwent cardiac computed tomography in health promotion center were enrolled. Anthropometric profiles and multiple cardiovascular risk factors were measured. TyG index was calculates as ln[fasting triglycerides (mg/dl) X fasting glucose (mg/dl)/2]. Multi-detector CT was used to measure coronary artery calcium score (CACS) and CACS>0 was defined as the presence of CAC.

Results: All subjects were stratified into four groups according to TyG index. There were significant differences in cardiovascular parameters among the groups and the prevalence of CAC significantly increased with TyG index levels. In the logistic regression analysis after adjusted for multiple risk factors, the odds ratios (95% CI) for the prevalence of CAC were 1.0, 1.03 (0.72-1.45), 1.23 (0.85-1.74), 1.68 (1.15-2.44) for increasing TyG index level ($p<0.05$).

Conclusion: There was a significant association between TyG index and prevalence of CAC. TyG index, a simple measure reflecting insulin resistance, might be useful to the indicator of atherosclerosis. TyG index is even simple to calculate and seems a useful marker of atherosclerosis, and reflect cardiovascular risk.

## 2259-PUB

**Relationship between Hyperuricemia and Atherosclerotic Lesions in Hospitalized Chinese Patients with Type 2 Diabetes Mellitus**

ZHU CHAOYU, XIAO YUANYUAN, WEI LI, *Shanghai, China*

Objective: The association of hyperuricemia with atherosclerosis remained controversial. The goal of this study was to investigate the relationship between hyperuricemia (HUA) and atherosclerotic lesions in type 2 diabetes.

Methods: This study was performed with a sample of 1926 Chinese patients with type 2 diabetes. Hyperuricemia was defined as a serum uric acid (UA) level ≥420μmol/L for men and ≥360μmol/L for women. Both carotid and lower limb atherosclerotic lesions including atherosclerotic plaque and stenosis were assessed by Doppler-ultrasound. The association of hyperuricemia with atherosclerotic lesions was analyzed by logistic regression analyses. The chi-square test was used to compare the prevalence data.

Results: A fully adjusted multiple logistic regression analysis revealed that hyperuricemia was associated with Body Mass Index (BMI), triglycerides (TG), glomerular filtration rate (GFR) in male patients (OR=1.112,1.027, 0.969, respectively, P<0.001), and also was associated with triglycerides (TG) and glomerular filtration rate (GFR) in female (OR=1.205, 0.955, respectively, P<0.001). Carotid atherosclerotic lesions was associated with age, hyperuricemia, HDL, LDL, SBP, NAFLED (OR=1.071,1.033, 0.388,1.052,1.006,1.122, respectively, P<0.001); lower limb atherosclerotic lesions was associated with age and hyperuricemia (OR=1.097,1.309, respectively, P<0.001). Moreover, from the comparison of atherosclerotic lesions between patients with or without hyperuricemia, we found that both the prevalence of carotid (55.55% vs. 47.165, P=0.014) and lower limb (69.49% vs. 57.15%, P=0.007) atherosclerotic lesions were significantly increased in the hyperuricemia patients with type 2 diabetes.

Conclusions: Hyperuricemia increased the risk of atherosclerotic lesions in Chinese patients with type 2 diabetes, although atherosclerosis does not affect the prevalence of hyperuricemia.

## 2260-PUB

**Association between Diabetic Nephropathy and Acute Ischemic Stroke Severity and Outcome**

KONSTANTINOS TZIOMALOS, STELLA BOUZIANA, MARIANNA SPANOU, STAVROULA KOSTAKI, STELLA-MARIA ANGELOPOULOU, KONSTANTINOS CHRISTOU, ARETI SOFOGIANNI, TRIANTAFYLLOS DIDANGELOS, CHRISTOS SAVOPOULOS, APOSTOLOS HATZITOLIOS, *Thessaloniki, Greece*

Introduction and Aims: Patients with diabetic nephropathy have comparable cardiovascular morbidity and mortality with patients with established cardiovascular disease. However, it is unclear whether diabetic nephropathy is related with the severity and outcome of acute ischemic stroke. The aim of the present study was to evaluate this association.

Patients and Methods: We prospectively studied 922 consecutive patients admitted for acute ischemic stroke (42.2% males, age 79.6±6.9 years). Stroke severity was evaluated at admission with the National Institutes of Health Stroke Scale (NIHSS). Outcome was evaluated with functional dependency at discharge (modified Rankin scale between 2 and 5) and with in-hospital mortality. Diabetic nephropathy was defined as estimated glomerular filtration rate <60 ml/min/1.73m$^2$ based on the Modified Diet in Renal Disease equation in patients with a history of type 2 diabetes.

Results: 11.9% of patients had diabetic nephropathy. The NIHSS did not differ between patients with diabetic nephropathy and those without (9.6±9.3 and 8.7±9.1, respectively; p=NS). However, rates of functional dependency showed a trend for being higher in patients with diabetic nephropathy than in those without (69.1 vs. 59.6%, respectively; p=0.075). In-hospital mortality did not differ between the two groups (8.2 and 9.6%, respectively; p=NS).

Conclusions: Diabetic nephropathy does not appear to affect the severity of acute ischemic stroke but appears to be associated with worse functional outcome in patients with acute ischemic stroke.

## 2261-PUB

**Preclinical Morphofunctional Alterations of Large Arteries in Children and Adolescent with Type 1 Diabetes Mellitus: Preliminary Data**

ROSALIA ROPPOLO, GIUSEPPE MULE', VIOLETTA DI PIETRANTONIO, ORIANA BOLOGNA, MARIA C. CASTIGLIONE, GIUSYELISA GALIONE, ANNA M. TRANCHIDA, GIOVANNI CORSELLO, FRANCESCA CARDELLA, *Palermo, Italy*

Background: Children and adolescent with type 1 diabetes mellitus (T1DM) are considered one of the pediatric populations at highest cardiovascular risk.

Aim: This cross-sectional study was aimed to assess in children and adolescents with T1DM, the clinical correlates of early morphofunctional changes of the large arteries.

Methods: Children and adolescents with T1DM treated with basal-bolus insulin therapy were included in the study if they had a disease duration of at least 5 years. The following parameter were examined: waist circumference, waist/height ratio (W/H), BMI, blood pressures, lipid profile, microalbuminuria, insulin dose, HbA1c, carotid intima-media thickness (c-IMT) and the difference between the observed and 95th percentile of age and height c-IMT distribution (Δc-IMT), aortic pulse wave velocity (Ao PWV) and the difference between the observed and 90th percentile of age Ao PWV distribution (ΔPWVAo). The study population was divided into two groups, on the basis of a value of W/H < or > 0.5.

Results: A total of 45 (20 males and 25 females) children and adolescents were included in the study. Their mean age was 14.0±2.7 years, their disease duration 6.2±3.5 years. Significant correlations were found between W/H and age Δc-IMT (p= 0.009), height Δc-IMT (p= 0.008), and mean c-IMT (p= 0.015). AoPWV correlated with HbA1c values (p= 0.012), diastolic blood pressures (p=0.014), triglycerides (TG) (p= 0.009) and with microalbuminuria (p= 0.017). Subjects with W/H > 0.5 have higher values of mean c-IMT (p= 0.03), age ΔcIMT (p=0.02) and height ΔcIMT (p= 0.02).

Conclusion: In children and adolescents with T1DM morphofunctional changes of the large arteries are associated with different clinical features, including the waist/height ratio. It showed a stronger correlation with c-IMTA than other indices of adiposity. Its simple measurement may allow to better assess the cardiovascular risk of T1DM pediatric patients.

## 2262-PUB

**Pleiotropic Effects of Ranolazine in Diabetic Patients Undergoing Percutaneous Coronary Intervention: Preliminary Results of an Observational, Prospective Study**

ANGELO LAURIA PANTANO, ANNUNZIATA NUSCA, ROSSELLA DEL TORO, ERNESTO MADDALONI, ERMELINDA BORRELLI, LUCA ZAPPIA, CLAUDIO PROSCIA, ROSETTA MELFI, SILVIA MANFRINI, GERMANO DI SCIASCIO, PAOLO POZZILLI, *Rome, Italy*

Background: Recent studies highlighted the prognostic role of glycemic variability (GV) on short and long-term outcome of patients with diabetes mellitus (DM) and coronary artery disease (CAD). Ranolazine has been demonstrated to reduce oxidative stress, improve endothelial function and glycemic control attenuating HbA1c levels in ischemic patients, beyond its antianginal effect. Thus, the aim of our study was to investigate the "pleiotropic effects" of this drug in a cohort of patients undergoing percutaneous coronary intervention.

Methods and Results: We enrolled 19 patients with DM type 2 with stable or unstable coronary syndromes: 11 treated with ranolazine and 8 representing the control group. At baseline and after 12 weeks we measured HbA1c levels and oxidative stress (using the Plasma Antioxydant Test); we also performed Continuous Glucose Monitoring by iProTM2 and flow-mediated dilatation (FMD) assessment. After 12 weeks a significant improvement in FMD values was observed in patients treated with ranolazine compared with baseline (p= 0.026). Oppositely no significant difference was shown in the control group (p=0.215). Moreover, an important attenuation of oxidative stress was measured in ranolazine-treated patients. Finally, in ranolazine group, lower levels of HbA1c and MAGE (Mean Amplitude Glycemic Excursions) was found after 12 weeks of drug therapy, whereas, no difference in glycemic parameters was observed in the control arm.

Conclusions: In patients with CAD and DM, adding ranolazine to the standard medical therapy, regardless of its anti-ischemic effect, may produce a significant improvement in glycemic variability, endothelial dysfunction and oxidative stress.

## 2263-PUB

**Efficacy of IDF and Japanese New Guidelines on the Prevention of Diabetic Complications in 9.2-Year Study of 4,014 Diabetic Patients, Including 1,016 Elderly Older than 75 Years**

TOSHIO HAYASHI, KOUTARO YOKOTE, KOICHIRO INA, MITSUHIKO NODA, *Nagoya, Japan, Chiba, Japan, Moroyama, Japan*

Background: Elderly diabetic individuals are drastically increasing, and their guidelines were proposed by IDF and Japan Diabetes Society. However, the efficacy has not been determined. Further, elderly's stroke risk is not well known.

Methods: We performed a prospective cohort study. 4,014 type 2 diabetics (67.4±9.5 years, ≥75years, n=1,016) were recruited from 40 Japanese hospitals in 2004. Lipids, glucose and other risk factors were investigated annually.

Results: 218I HD cases and 138 CVAs (7.8 and 5.7/1,000/year) occurred over 9.2 years. 134 patients died. Hemoglobin A1c (HbA1c) on registration was correlated with IHD in patients <75years, LDL-C in patients <65 and >75 years, and HDL-C in all. HDL-C and HbA1c were correlated with CVA in patients <75 years. For severe nephropathy and proliferative retinopathy, FPG and HDL-C were risk for >75 years. Guidelines by IDF was applied. The patient controlled of their blood glucose within IDF guideline significantly decreased IHD between 65 and 75 years and stroke older than 65 years, however there are no evident effect for IHD older than 75 years. The results on JDS is almost same as IDF.

Conclusion: IHD and CVA in elderly diabetics were predicted by LDL-C or HDL-C. HDL-C also affects microangiopathies in elderly. These age-dependent differences in risk and the guideline by IDF and/or JDS are important to prevent diabetic complications. Trial Registration: UMIN-CTR: UMIN00000516.

*Supported By: Japan Agency for Medical Research and Development*

## 2264-PUB

**Predictors of Ventricular Arrhythmias and Myocardial Ischemia in Patients with Type 2 Diabetes**

ALEXANDER AMETOV, SR., EKATERINA ERMAKOVA, *Moscow, Russian Federation*

Background and Aims: Evaluate the effect of glycemic control on cardiovascular system.

Materials and Methods: The study involved 85 patients with type 2 diabetes, coronary heart disease aged 43-79 years. All patients underwent simultaneous monitoring of blood glucose levels and the Holter monitoring.

Results: In assessing the impact of daily glycemia on the occurrence of ventricular arrhythmias it has been show that an increase index hypoglycemia and glycemia variability increase risk of arrhythmia. We had found significant association between the frequency of ventricular arrhythmias and hypoglycemia index (r=0,38 P=0,03). Was found direct significant correlation between SD (r=0,53, P=0,05), MAGE (r=0,52, p=0,02) and number PVCs (ventricular arrhythmias). Has been found depend effects short-term fluctuations of glycemia on heart rate variability from average blood glucose level on which drop occur.

When analyzing the effect on glycemic parameters of myocardial ischemia, it was revealed that the only chronic glucose toxicity affects the occurrence of ischemia. Patients with episodes of ischemia had significant higher HbA1c than patients without ischemia (p=0,006). While the average level of blood glucose, glycemia variability, index of hypoglycemia did not affect the incidence and duration of ischemia.

Conclusion: Founded glycemic thresholds (less than 4,2 mmol\l and above 15 mmol\l) under which increases the likelihood of developing cardiac arrhythmias.

High glycemic variability (MAGE more than 5 mmol\l) is associated with increased risk dangerous ventricular arrhythmias.

## 2265-PUB

## WITHDRAWN

For author disclosure information, see page A751.

## 2266-PUB

**WITHDRAWN**

## 2267-PUB

**Volitional Exercise Reverses Western Diet-Induced Vascular Stiffness and Impaired Vascular Relaxation in Female Mice**

ANNAYYA AROOR, GUANGHONG JIA, JAVAD HABIBI, VINCENT DEMARCO, JAUME PADILLA, FRANCISCO I. RAMIREZ-PEREZ, BRADY BARRON, DONGQING CHEN, ZHE SUN, GERALD MEININGER, LUIS MARTINEZ-LEMUS, JAMES R. SOWERS, *Columbia, MO*

Prevalence of cardiovascular disease is increasing in part because of the rising epidemic of obesity. Premenopausal obese women lose cardiovascular protection that is seen in premenopausal lean women. Obese premenopausal women also exhibit arterial stiffness which is emerging as an independent risk factor for cardiovascular disease. We have shown that volitional exercise can prevent the development of vascular stiffness in obese female mice. In this study we tested the hypothesis that volitional exercise would also reverse western diet induced vascular stiffness in female mice. Four-week old C57BL/6 mice were randomized into control diet, sedentary (i.e., caged confined, n=5) or western diet sedentary (i.e., caged confined, n=5) for 26 weeks. All mice were singly housed fed control diet or a WD containing high fat (46%), high sucrose (17.5%), and high fructose corn syrup (17.5%). At 26 weeks, WD fed mice were either remained sedentary or subjected to volitional exercise (i.e., access to running wheels, n=5) conditions for 10 weeks. Compared to control diet fed mice, WD fed mice exhibited increased endothelial cortical stiffness in aortic explants as assessed by atomic force microscopy that was revered by volitional exercise. This effect of exercise on endothelial cortical stiffness was also accompanied by improvement in WD induced relaxation of the aorta to acetylcholine but not nitroprusside suggesting improving nitric oxide mediated vasorelaxation by exercise. Together, these data demonstrate for the first time that regular volitional aerobic exercise reverses endothelial cortical stiffness and improves nitric oxide mediated vasorelaxation in the setting of diet induced obesity.

## 2268-PUB

**WITHDRAWN**

## 2269-PUB

**Factors Affecting Circulating Endothelial Progenitor Cells (EPCs) and Endothelial Microparticles (EdMPs) in Patients with Type 2 Diabetes**

LAURA GIUSTI, DANIELA LUCCHESI, MONIA GAROFOLO, VERONICA SANCHO BORNEZ, GIUSEPPE DANIELE, ANGELA DARDANO, ROBERTO MICCOLI, STEFANO DEL PRATO, GIUSEPPE PENNO, *Pisa, Italy*

EdMPs and EPCs contribute to vascular health in type 2 diabetes (T2D). We aimed at identifying factors affecting circulating EdMPs and EPCs in T2D. EdMPs ($CD42^-/CD31^+$) and EPCs ($CD34^+/CD133^+/KDR^+$) were quantified by FACS (M±SD) in 196 T2D (age 62±9 yrs, DD 28±12 yrs, BMI 30.8±6.1 kg/m$^2$, HbA1c 7.3±1.2%) on multiple glycemic and metabolic treatments and 20 controls (C, age 52±9 yrs, BMI 24.1±1.8 kg/m$^2$, HbA1c 5.5±0.3%). Compared to C, stem cells ($CD34^+$ and $CD34^+CD133^+$) were similar in T2D (2193±707 and 967±30 vs. 2212±1261 and 1067±797 cells/ml) whereas EPCs ($CD34^+CD133^+$ and $CD34^+CD133^+KDR^+$) were lower (878±354 and 435±227 vs. 408±338 and 222±207; both p<0.001). EdMPs were marginally increased in T2D (11261±15979 vs. 7903±2501 n/ml) while EdMP/EPC ratio was higher than in C (85.2±148.5 vs. 21.6±13.2; p=0.02). Based on diabetes duration (DD: <10 yrs, n. 69, 10-19 yrs, n. 92 and ≥20 yrs, n. 35) there was no difference in $CD34^+$ and $CD34^+CD133^+$ cells, while $CD34^+KDR^+$ (343±260, 426± 379, and 487±343, p=0.054) and $CD34^+CD133^+KDR^+$ cells (186±152, 231±237 and 266±208, p=0.07) increased with DD. EdMPs did not differ by DD and EdMP/EPC decreased (p=0.064). Age increased by DD while total- and LDL-C and eGFR decreased. There was no difference in gender, HbA1c, BMI, BP, HDL-C, triglycerides, creatinine, uric acid, and A/C ratio. Smoking was more common in DD <10 and 10-19 yrs, ex-smokers in DD ≥20 yrs (p=0.035) who also had more retinopathy and CVD (p=0.04 or less). Use of incretin-mimetics was similar in DD groups, while statins, BP-lowering agents, and RAS-blockers (all p≤0.006) increased with DD. By logistic regression, higher than median $CD34^+CD133^+KDR^+$ cells and lower than median EdMP/EPC ratio were independently associated with statins and RAS-blocker (OR: 2.429, 95% CI 1.353-4.363, p=0.003 and OR: 0.579, 95% CI 0.285-1.046, p=0.067). EPCs and EdMPs are altered in T2D though their number and ratio can be favorably affected by statins and RAS-blocker.

*Supported By: Regione Toscana (D55E11002680005)*

## 2270-PUB

**Sarcolipin Silencing Enhanced Electrophysiological Stability of High-Glucose Incubated Myocytes**

ZHONGWEI LIU, JUNKUI WANG, GONGCHANG GUAN, *Xi'an, China*

Background and Objective: Our previous investigation showed that knocking-down expression of sarcolipin attenuated ventricular arrhythmias in diabetic cardiomyopathy rat model. This study was aimed to investigate the molecular and electrophysiological mechanisms.

Methods: High-glucose incubation was administrated to cultured H9c2 cells. Expression levels of intracellular sarcolipin was knocked down by specific siRNA. Real-time PCR and Western blotting were used to assess the expression level of sarcolipin. A colorimetric method was used to determine the activity of SERCA2a. Confocal laser scanning microscopy was employed to observe the calcium sparks. The early depolarization (EAD) and triggered activities (TA) were recorded by whole cell patch clamp.

Results: Expression of sarcolipin was increased in high-glucose incubated H9c2 cells. As a result, the activity of SERCA2a was suppressed which further increased the frequencies of spontaneous calcium sparks, EAD and TA. However, in H9c2 cells transfected with siRNA against sarcolipin, the activity of SERCA2a was found recovered which reduced the frequencies of spontaneous calcium sparks, EAD and TA.

Conclusions: High-glucose condition would induce disturbance of calcium homeostasis which cause instability of electrophysiological condition in cardiomyocytes. Increased sarcolipin mediated SERCA2a activity loss was supposed to play a critical role.

*Supported By: National Natural Science Foundation of China*

## 2271-PUB

**WITHDRAWN**

## 2272-PUB

**WITHDRAWN**

## COMPLICATIONS—NEPHROPATHY—BASIC AND EXPERIMENTAL SCIENCE

## 2273-PUB

**Delineating Mechanisms for Effects of High Free Fatty Acids on Autophagy, ER Stress, and Apoptosis in Human Kidney Epithelial Cells**

GUO DONG LI, MUHAMMAD NURFIKRI BIN JUMA'AT, MIAN MIAN TONG, CHUI SUN YAP, YONG MONG BEE, *Singapore, Singapore*

Obesity increases the risk of type 2 diabetes, cardiovascular and kidney diseases. Excess circulating free fatty acids (FFA) may promote insulin resistance and facilitate the onset and progress of diabetic nephropathy which are attributable to chronic low-grade inflammation and lipotoxicity in a process involving autophagy, endoplasmic reticulum (ER) stress and apoptosis. We previously found that culture with high saturated fatty acid (0.5-1 mM palmitic acid; PA) reduced viability and number of human renal epithelial cells through induction of ER stress, autophagy and apoptosis. This study aims to examine the mechanisms of FFA-induced toxicity on kidney cells. Adverse effects of PA on renal cells appeared to exclude oxidative stress and protein kinase C activation. PA-induced autophagy occurred prior to ER stress and apoptosis. Inhibition of autophagy was shown to reduce PA-induced autophagy and apoptosis without affecting ER stress. Blocking apoptosis alone did not affect autophagy and ER stress. Inclusion of equal molar of monounsaturated fatty acid (oleic acid; OA) protected the cells from PA-driven cytotoxicity. The presence of OA also helps channel PA into triglyceride pools in the cells. However, preventing the formation of intracellular lipid droplets in PA plus OA-treated cells only slightly reduced the protective effect of OA. Interestingly, inhibiting acyl-CoA formation by triacsin C improved cell viability and prevented autophagy and apoptosis in PA-treated cells. In addition, attempts to block downstream protein palmitoylation also revealed an increase in cell viability in these cells, although PA-induced autophagy, ER stress and apoptosis were not inhibited. Hence, understanding the effects of PA and OA on renal cells with regards to autophagy, ER stress, apoptosis, lipid droplet formation and palmitoylation may provide insights to better management of nephropathy in obese and/or diabetic conditions.

*Supported By: National Medical Research Council of Singapore*

## 2274-PUB

**Calbindin-D28k Downregulation Aggravates AGEs-Induced Proximal Tubular Epithelial-to-Mesenchymal Transition**

CHIH KANG CHIANG, WEI HAN LIN, CHEN YUAN CHIU, SHING HWA LIU, *Taipei, Taiwan, Changhua, Taiwan*

Background: Tubulointerstitial fibrosis is a common characteristics of diabetic nephropathy. Calbindin-D28k (CB) expressed in renal distal tubular cells has been suggested to be involved in calcium reabsorption. In type 1 DM kidney, CB expression was markedly increased in whole renal tubules. However, the role of CB in diabetic nephropathy remains unclear, esp. in the proximal tubule. Advanced glycation end-products (AGEs) have been suggested to contribute to the development of diabetic nephropathy. Here, we investigated the role of CB in AGEs-induced renal fibrosis in the proximal tubules.

Methods: Human renal proximal tubular cells (HK-2) were treated with AGEs (10-100 μg/ml) for 48 h with or without CB siRNA transfection. In some experiments, the db/db diabetic mice were used. The protein expressions were determined by Western blot or immunohistochemistry.

For author disclosure information, see page A751.

Results: The protein expressions of AGEs, fibronectin, connective tissue growth factor (CTGF), and CB were markedly increased in db/db diabetic mouse kidneys as compared with db/m control kidneys. Non-cytotoxic concentrations of AGEs up-regulated the expressions of CB, fibronectin, CTGF, receptor for AGEs (RAGE), vimentin, pSmad2/3, and Snail, and down-regulated E-cadherin expression in HK-2 cells, which could be reversed by RAGE neutralizing antibody, but be enhanced by CB knockdown.

Conclusion: These results demonstrate for the first time that epithelial-to-mesenchymal transition contributes to AGEs-RAGE axis-induced fibrotic transition, which could be aggravated by CB knockdown in the proximal tubular cell. These findings suggest that increased CB may play a protective role in decreasing the rate of AGEs-induced renal fibrosis in diabetes.

*Supported By: Taiwan Ministry of Science and Technology*

## 2275-PUB

### Uric Acid Itself Activated NLRP3 Inflammatory Pathway of Human Renal Tubular Epithelia in the Case of In Vitro Hyperglycemia

JIANMIN RAN, PEIYANG LI, PING ZHU, RUYI ZHANG, RONGSHAO TAN, YAN LIU, *Guangzhou, China*

Background: Hyperuricemia is an independent risk factor for diabetic kidney disease (DKD). Studies had established a close link between uric acid (UA) and chronic kidney disease by its ability of activating kidney NLRP3 inflammasome. Yet it remains unclear whether hyperglycemia could directly lead to DKD by promoting the UA activation of this inflammasome.

Methods: Human renal tubular epithelial cells (HK-2) were cultivated. The experiment was designed according to a 2×4 multifactorial style. Two glucose concentrations (5.5MM and 25MM) crossed with four escalated UA concentration (Blank, 0.2MM, 0.4MM, and 0.8MM respectively), totally 8 cultivation groups were set up in the study. All cell groups were standardly cultivated for 72 h. Gene and protein expressions of pivotal factors involved in NLRP3 inflammasome pathway including NLRP3, ASC, caspase-1, IL-1β, IL-18, were measured.

Results: 1) The intact effects: Either in low or high glucose concentration, escalated UA concentrations overall increased gene expressions of 5 factors in a dose-dependent manner, except that 0.8MM of UA remarkably inhibited those expressions ($P<0.05$). There is an obvious synergistic interaction between UA and glucose concentration levels on gene expressions of 5 factors ($P<0.05$). 2) Individual effects: Gene expressions of NLRP3, Capase-1 and IL-18 were significantly increased in the high glucose concentration ($P<0.05$), while gene expressions of Capase-1 and IL-18 were significantly increased along with the escalated concentrations of UA until the inhibited effects with 0.8MM of UA ($P<0.05$). 3) Expressions of IL-1β and IL-18 protein were significantly increased in the high glucose concentration ($P<0.05$).

Conclusions: In the case of a vitro hyperglycemia, UA significantly upregulates expressions of 5 key factors involved in the NLRP3 pathway in human renal tubular epithelial cells, despite that those effects are individualized for each factor.

*Supported By: Guangzhou Science and Technology Project Fund (201300000181, 2014J4100076); Guangzhou Scientific Fund for Clinical Study and Translational Medicine (2014Y2-00549); Guangzhou Specific Scientific Fund for Key Laboratory (2014SY000015)*

## 2276-PUB

### miR-433: A Potential and Newly Biomarker For Diabetic Kidney Disease

LIHUA ZHANG, JUNYI HE, YING SHENG, YANAN WU, RONG LI, *Kunming, China*

We have previously shown that TGF-β/Smad3-dependent microRNAs are key mediators in renal fibrosis. Here we report that miR-433 is a new biomarker for diabetic kidney disease (DKD) and is a potential therapeutic target for DKD in vitro and in vivo.

Expression of miR-433 was examined in rat mesangial and tubular epithelial cell lines after high glucose treatment, diabetic kidneys from db/db mice and patients with T2DM. The functional role and therapeutic potential of miR-433 in diabetic kidney disease were examined in vitro in a rat NRK52E tubular epithelial cell (TEC) line and mesangial cell (MC) line, by overexpressing or down-regulating of miR-433 and in vivo a mouse model of T2DM by an ultrasound- microbubble-mediated anti-miR-433 gene transfer.

Renal miR-433 was significantly increased in NRK52E and MC cells after high glucose stimulation and in the diabetic kidneys. Findings that knockdown of miR-433 suppressed, but overexpression of miR-433 enhanced collagen I expression revealed a functional importance of miR-433 in diabetic conditions. More importantly, ultrasound-microbubble-mediated gene transfer of miR-433 knockdown plasmid into mouse kidneys was capable of preventing renal fibrosis, demonstrating a therapeutic potential for DKD by targeting miR-433. Furthermore, we also found that miR-433 expression was elevated both in diabetic kidney and serum of patients with T2DM. Although, statistic of miR-433 expression in serum of DKD patients was not significant due to the limited patient enrollment in the study, miR-433 might be a potential and new biomarker of DKD.

MiR-433 is a key mediator of DKD and a new biomarker and a potential therapeutic target for diabetic kidney disease.

*Supported By: National Natural Science Foundation of China (81560126)*

# COMPLICATIONS—NEPHROPATHY—CLINICAL AND TRANSLATIONAL RESEARCH

## 2277-PUB

### Risk Factors for Progression of Chronic Kidney Disease in Individuals with Diabetes

KAITLYN S. MAGUIRE, VINCENT WOO, *Winnipeg, MB, Canada*

This is a retrospective study assessing risk factors for chronic kidney disease (CKD) progression using estimated glomerular filtration rate (eGFR) in individuals with diabetes (DM). The study included 393 individuals with eGFR <60 ml/min/1.73m$^2$ and/or albumin/creatinine ratio >2.0 mg/mmol, with eGFR values taken at 6 month intervals. Renal progression was defined as 50% decline from baseline eGFR. Individuals were followed for a median of 4.6 ± 0.8 years. Baseline characteristics include 62.3% males, 76.1% with type 2 DM, 46.3% with microalbuminuria, 21.9% with overt proteinuria, and mean eGFR of 73.5 ± 27.2 ml/min/1.72m$^2$. At last visit, 77.1% were on ACEi/ARBs, mean A1c was 8.1 ± 1.5%, mean systolic blood pressure (BP) was 126.7 ± 15.0 mm Hg, mean diastolic BP was 73.2 ± 24.4 mm Hg, mean LDL-C was 1.8 ± 0.8 mmol/L and mean age was 65.2 ± 12.0 years. The mean cumulative decline in eGFR was 2.62 ± 4.06 ml/min/1.73m$^2$/yr. In those with renal progression, the mean decline in eGFR was 8.93 ± 1.58 ml/min/1.73m$^2$/yr. At 5 years, 6.4% of patients lost 50% of their baseline eGFR, serum creatinine had doubled in 4.6% and 2.5% had progressed to end-stage renal disease. Only 1.5% improved their baseline eGFR by 30%. The likelihood of progression was significantly increased with overt proteinuria, use of diuretics, and later stages of CKD (Table 1). A1c, BP, ACEI/ARBs use, age, microalbuminuria, sex, and elevated lipids did not affect progression.

**Table 1.** Association of Risk Factors with Likelihood of Progression to 50% of Baseline eGFR.

| Risk factor | Relative risk | 95% Confidence interval |
|---|---|---|
| Macroalbuminuria | 4.51 | 2.13 - 9.58 |
| Use of diuretics | 2.99 | 1.22 - 7.34 |
| CKD initial stage of 3, 4 or 5 | 2.32 | 1.08 - 4.96 |

## 2278-PUB

### Chronic Kidney Disease in Individuals with Diabetes: A Retrospective Analysis of Cardiovascular Risk

KAITLYN S. MAGUIRE, VINCENT WOO, *Winnipeg, MB, Canada*

This is a retrospective study that describes individuals with diabetes mellitus (DM) with chronic kidney disease (CKD). Individuals were included when their estimated glomerular filtration rate (eGFR) was <60 ml/min/1.73m$^2$ and/or albumin/creatinine ratio (ACR) was ≥2.0 mg/mmol, and had been taking consistent anti-hypertensive medication (HTN meds) for the previous 6 months. This study describes the demographics, presence of proteinuria and hypertension, use of HTN meds and lipid-lowering meds, and assesses whether targets for cardiovascular (CV) risk factors have been met. Of the 431 individuals included, 46.2% had an eGFR <60 ml/min/1.73m$^2$ and 86.1% had albuminuria indicated by ACR >2.0 mg/mmol. The mean age was 64.7 ± 12.3 years, 61.0% were males, 80.0% had type 2 DM and 8.5% were smokers. Of the 199 individuals with reduced eGFR, 29.7% had normoalbuminuria (<2.0 mg/mmol), 40.2% had microalbuminuria (2 mg/mmol to 20 mg/mmol), and 30% had overt proteinuria (>20 mg/mmol). At last visit, 33.2% of individuals had a systolic blood pressure (BP) >130 mm Hg and 12.3% had a systolic BP >140 mm Hg. Individuals averaged 2.0 ± 1.2 HTN meds, with 37.6% taking ≥ 3 HTN meds, 75.0% on angiotensin system inhibitors (ACEI/ARBs) and statins used by 79.7%. This population with high risk for CV disease shows further efforts are required to reach target levels for A1c, BP, LDL and non-HDL to order to minimize CV risk (Table 1).



For author disclosure information, see page A751.

**Table 1.** Descriptors Including Cardiovascular Risk Indicators and Percent of Individuals at Target Levels.

| | Mean | Percent of individuals at target |
|---|---|---|
| A1c | 8.1 +/- 1.6% | 23.7% at <7% |
| Systolic blood pressure / diastolic blood pressure | 126.9 +/- 14.9 mm Hg / 73.1 +/- 23.6 mm Hg | 66.8% at </= 130 mm Hg (systolic) |
| LDL levels | 1.9 +/- 0.8 mmol/L | 61.1% at </= 2 mmol/L |
| non-HDL levels | 2.7 +/- 1.1 mmol/L | 51.5% at </= 2.6 mmol/L |
| A1c, systolic blood pressure and LDL levels | | 10.6% on target for all 3 risk factors |

## 2279-PUB

### SGLT2-Inhibitor Shows a Kidney-Protection Effect through Ketone Body Increase

TOMOE KINOSHITA, MASASHI SHIMODA, JUNPEI SANADA, YOSHIRO FUSHIMI, MOMOYO NISHIOKA, SHINTARO IRIE, ATSUSHI OBATA, TOMOHIKO KIMURA, HIDENORI HIRUKAWA, KENJI KOHARA, FUMINORI TATSUMI, SHINJI KAMEI, SHUHEI NAKANISHI, TOMOATSU MUNE, KOHEI KAKU, HIDEAKI KANETO, *Okayama, Japan, Kurashiki, Japan*

In subjects with diabetes mellitus (DM), reabsorption of glucose in proximal tubule is increased and consequent increase of ATP consumption easily brings out tissue hypoxia. In addition, such hypoxia leads to the change of tubulointerstitium. Sodium-glucose co-transporter 2 (SGLT2) inhibitor reduces glucose reabsorption and thereby ameliorates glucose metabolism. Furthermore, the possibility of organ protection effect with ketone body has attracted much attention recently. The aim of this study was to examine the effects with SGLT2 inhibitor for proximal tubule in Japanese subjects with type 2 DM (T2DM). We enrolled a total of 82 subjects with T2DM who newly started taking SGLT2 inhibitor after September 1, 2014 in Kawasaki Medical School in Japan. The study subjects were divided into two groups: urinary N-acetyl-beta-D-glucosaminidase (U-NAG) reduction group (n=37) and non-U-NAG reduction group (n=45). When U-NAG was reduced after the initiation of SGLT2 inhibitor, we divided the subject into U-NAG reduction group. When the subjects were divided into 3 groups; U-NAG before medication <5, 5-15 and >15U/g.Cr, U-NAG was significantly decreased only in a group with >15U/g.Cr. Three months after starting SGLT2 inhibitor, eGFR and visceral fat area (VFA) were reduced in U-NAG reduction group compared to non-U-NAG reduction group (both, $p<0.05$). Plasma 3-Hydroxybutyric acid (3-HBA) levels tended to be increased ($p=0.07$) and percentage of subjects using ARB tended to be higher in U-NAG reduction group. Finally, to elucidate which are independent factors determining U-NAG reduction, we performed multivariate regression analyses including age, gender, $\Delta$eGFR, $\Delta$VFA, $\Delta$3-HBA, use of ARB as independent variables. As the results, age, $\Delta$eGFR and $\Delta$3-HBA were independent factors contributing to U-NAG reduction (OR: 1.11, 0.90, and 1.01). These data suggest the possibility that SGLT2 inhibitor reduces renal tubular disorder through improvement of hyperfiltration in glomerulus and increase of ketone body.

## 2280-PUB

**WITHDRAWN**

## 2281-PUB

**WITHDRAWN**

## 2282-PUB

### Halting CKD Progression in Diabetes with Virtual Interactions: A Five-Year Retrospective Analysis

JOTHYDEV KESAVADEV, ARUN SHANKAR, GEETHU SANAL, LAKSHMY RAMACHANDRAN, GOPIKA KRISHNAN, SUNITHA JOTHYDEV, *Trivandrum, India*

Background: Diabetic Kidney Disease (DKD) once developed, has a natural progression which could effectively be halted in its early stages with optimal control of blood glucose, blood pressure (BP), lipids and lifestyle modifications. In routine clinical practice, it is seldom possible to reassess customized targets and address the huge inter-day and inter-day variations.

Aim: DKD being a complication with serious physical, emotional and economic consequences, we explored the possibility of using simple technologies aided with telemedicine program to sustain individualized lifestyle and metabolic targets to slow down progression of DKD.

Methods: Clinical profiles of T2DM patients with Stage 3 DKD as of January-December 2010 were de-identified. Patients who had optimal follow-up (once weekly virtual consultations via Diabetes Tele Management System, DTMS® and physical visits every 3 months) and adherence to therapies and lifestyle advice were selected. Their 5-year retrospective data were analysed.

Results: In 166 T2DM patients, age 61.83±9.15, duration 23.5±10.2, 76% male, no significant changes were observed in any of the parameters viz. Creatinine, eGFR, BP, Spot microalbumin, HbA1c and Hb even after 5 years of CKD development.

Conclusions: Our results reveal that implementation of dose alterations, education and motivation through virtual consultations can successfully halt the progression of DKD.

For author disclosure information, see page A751.

**Table.** Impact of Successful Diabetes Management in Halting CKD Progression.

| Parameter | Baseline | At 5th year | Change from baseline | p-value |
|---|---|---|---|---|
| Creatinine (mg/dL) | 1.42±0.39 | 1.38±0.33 | -0.039 | 0.7014 |
| eGFR (mL/min/1.73m²) | 54.8±12.8 | 55.49±14.07 | 0.69 | 0.8622 |
| Systolic BP (mmHg) | 137.9±18.67 | 140.3±17.68 | 2.40 | 0.6289 |
| Diastolic BP (mmHg) | 73.61±8.5 | 68.78±7.08 | -4.83 | 0.1046 |
| Spot microalbumin (mg/L) | 73.05±65.6 | 160.8±227.1 | 87.75 | 0.1102 |
| Hb (gms%) | 12.38±1.66 | 12.47±1.49 | 0.09 | 0.7766 |
| HbA1c (%) | 7.76±1.61 | 8.32±1.52 | 0.56 | 0.2578 |

## 2283-PUB

### Effect of Intravenous and Oral Therapy with Sulodexide on Diabetic Nephropathy

HAI LI, WEIJIAN KE, JUAN LIU, XIAOYING HE, JR., LIEHUA LIU, YANBING LI, *Guangzhou, China*

Introduction: Diabetic nephropathy may be effectively treated by strict metabolic control and administering AECI/ARB. However, many of the patients undergoing AECI/ARB treatment continue to show persistent microalbuminuria. This study was to compare the effect of oral vs. sequential therapy of sulodexide (vessel) in reducing albuminuria in Chinese type 2 diabetic patients.

Methods: A total of 40 microalbuminuric and macroalbuminuric type 2 diabetic patients with serum creatinine ≤1.5 mg/dL and stable BP and metabolic control were recruited. They were randomly allocated to one of two groups: oral group treated with 1000 LSU sulodexide daily, or sequential group treated with 1200 LSU sulodexide daily intravenously for 2 weeks following 1000 LSU sulodexide daily orally. Both groups were treated for 3 months.

Results: After 3 months treatment, albumin excretion rate was significantly reduced in both groups (-32.26±3.08ug/min, -58.71±5.03ug/min, respectively, both $p<0.05$). But there was no difference in inducing percent reductions in AER between two groups (24.3% vs. 28.5%, $p>0.05$).

Conclusion: Intravenous or oral administration sulodexide significantly improves albuminuria in type 2 diabetic patients, but intravenous with oral sequential administration is not necessarily better than the effect of orally administered.

## 2284-PUB

### Liraglutide in Patients with Type 2 Diabetes and Stage 3 Chronic Nephropathy

MARIA DOLORES GARCIA DE LUCAS, BEATRIZ AVILES, JULIO OLALLA, *Malaga, Spain*

Chronic kidney disease limits treatment in type 2 diabetes mellitus patients. We evaluate liraglutide treatment in overweight diabetic patients with stage 3 chronic nephropathy (estimated glomerular filtration rate, eGFR, between 59 and 30 ml/min/1.73 m² by CKD-EPI formula).

Aims: To assess the liraglutide efficacy and safety in this population after 28 weeks or treatment. To improve their glycemic control, BMI and hypoglycemic episodes. This study includes 20 diabetic patients 69 ± 8,5 years old with stage 3 chronic nephropathy, HbA1c > 7-10% and BMI > 30 Kg/m². 25% had previous cardiovascular disease and 35,2% basal albuminuria. The dose of liraglutide was 1.2 mg/day. We discontinued all previous oral antidiabetic medication. Results are expressed in medians and IQR. We withdraw liraglutide in 3 patients (15%) due to gastrointestinal intolerance (similar incidence is described in patients with normal renal function). We did not observe symptomatic hypoglycemic episodes. After 28 weeks of treatment with liraglutide, showed a statistically significant decrease of their BMI, basal glycemic and HbA1c controls, needs of insulin, and less hypoglycemic episodes. Their eGFR remained stable. The albuminuria improved although without sigificacion and disappeared in a patient. The use of liraglutide in this population seems to be safe and effective, it could open new therapeutic options.

# COMPLICATIONS—NEUROPATHY

## 2285-PUB

### Prediction Model of the Number of Remaining Teeth Using Foot Examination in Type 2 Diabetes

HIROTO SASAKI, YURIA NAMIKI, YUYA TAKANO, HIKARU TAKAMINE, KOJI INAZUMI, YUKO MUROHASHI, URU NEZU OSADA, *Yokohama, Japan*

Periodontal disease is a major complication of type 2 diabetes (T2D). However, reports on the association with neuropathy are limited. We investigated the association between the number of remaining teeth and the common foot examination of peripheral perception. From our inpatient database from 2015 to 2016, we extracted T2D patient who's number of remaining teeth (NRT) was counted by orthopantomograph. In foot examination, the sensation loss threshold (SLT) at plantar surface was tested by 10-g monofilament and vibration perception threshold (VPT) was tested by 128-Hz tuning fork. In result, totally 302 patients were 64.0±13.5 years in age, diabetes duration was 10.5±9.3 years, BMI was 25.8±4.9 kg/m² and HbA1c (NGSP) was 9.8±2.0%. In foot examination, median SLT was 4.31 and mean VPT was 9.9±4.0 seconds. Mean NRT were 18.5±9.9. SLT and VPT showed negative ($r=-0.18$, $p=0.006$) and positive ($r=0.29$, $p=<.0001$) correlation with NRT. In stratified analysis according to NRT cut off value by 20, NRT <20 group (n=122) showed significantly worse peripheral perception compared to NRT≧20 group (n=180). In specific, SLT was 4.2±0.1 vs. 3.9±0.1 ($p=0.0002$) and VPT was 8.6±0.4 vs. 10.7±0.3 ($p=<0.0001$) in each NRT subgroups. In multivariate logistic model adjusted with duration of diabetes, gender, smoking history, BMI, between-meal snack and government welfare support, SLT (odds ratio 2.39, 95% CI 1.45-4.14) and VPT (odds ratio 0.87, 95% CI 0.80-0.93) were significant and independent risk factors of NRT<20. In prediction of NRT<20, the optimal cut off of SLT was 3.61 (sensitivity 0.71, specificity 0.66, AUC 0.71) and that of VPT was 8 seconds (sensitivity 0.61, specificity 0.76, AUC 0.72).

In summary, our results indicate that the progression of diabetic neuropathy is the significant risk of periodontal disease. Moreover, our prediction model revealed that the mild abnormality in foot examination may already be associated with clinically undesirable tooth loss.

## 2286-PUB

### Pulse Pressure Amplification and Autonomic Dysfunction in Type 2 Diabetes

IOANNA ELEFTHERIADOU, ANASTASIOS TENTOLOURIS, GIORGOS DROSOS, STAMATINA CHOREPSIMA, GIORGOS KONSTANTONIS, ATHANASIOS PROTOGEROU, NIKOLAOS TENTOLOURIS, *Athens, Greece*

Pulse pressure amplification (PPA) is expressed as the ratio of peripheral PP to central PP and has emerged as a new hemodynamic marker for the assessment of cardiovascular risk. Recent studies suggest that PPA is increased in individuals with diabetes when compared with nondiabetic patients, but this difference disappears after adjustment for heart rate. Cardiac autonomic dysfunction (AD) is a chronic complication of diabetes and altered heart rate variability (HRV) is found early. In this study we examined the association of PPA with AD in diabetes. A total of 142 patients with type 2 diabetes were included. All participants underwent assessment of central PP using pulse wave analysis. Cardiac autonomic nervous system activity was determined by measurement of parameters of HRV, while baroreflex sensitivity (BRS) was measured using the spontaneous sequence method. Univariate linear regression analysis showed that PPA was significantly associated with age, male gender, height, waist circumference, heart rate, augmentation index, central BRS, total power, low frequency power of HRV and use of b-blockers, while there was a trend for association with diabetes duration and high frequency power. No association was observed with smoking, arterial hypertension, dyslipidemia, HbA1c and renal function. Multivariate analysis, after adjustment for age, diabetes duration, waist, use of b-blockers and central BRS, demonstrated that male gender [standardized regression coefficient ($\beta$) =0.171, $p=0.007$], heart rate ($\beta=0.336$, $p<0.001$), augmentation pressure ($\beta=-0.550$, $p<0.001$), and total power of HRV ($\beta=-0.149$, $p=0.015$) were associated independently with PPA. In patients with diabetes, PPA is associated with cardiac autonomic activity irrespective of known factors related to pressure pulsatility, such as age, gender, heart rate, wave reflections and traditional cardiovascular risk factors. AD may attenuate pressure wave reflections and contribute to higher PPA observed in patients with diabetes.



For author disclosure information, see page A751.

## 2287-PUB

**WITHDRAWN**

## 2288-PUB

### Screening and Early Detection of Diabetic Neuropathy in Newly Diagnosed Type 2 Diabetes Mellitus

MITRA TAVAKOLI, ENA-CLAHRC GREATER MANCHESTER NEUROPATHY STUDY GROUP, *Exeter, United Kingdom*

Aim: Screening for presence and severity of Diabetic Peripheral Neuropathy with using Corneal Confocal Microscopy (CCM) in a cohort of newly diagnosed type 2 diabetic patients.

Method: 450 diabetic patients as part of national eye screening programme have been assessed by CCM.

Results: 80% of patients had no retinopathy. 15.3% of patients had symptoms of diabetic neuropathy. There was significant alterations in corneal nerves morphological parameters in patients compare to control subjects including CNFD (P<0.001); CNBD (P=0.007); CNFL (P<0.001), and size of beading along c-nerve fibres (P<0.001). CNFD and CNFL were reduced in 15.5%, and 18.8% of the diabetes patients, respectively. There was no correlation between neuropathy symptoms and severity of alterations of corneal nerves. No correlation has been also found for retinopathy and neuropathy.

Discussion: This study showed the significant level of nerve damage and presence of DPN in newly diagnosed type 2 diabetic patients. As part of screening programme, feasibility and acceptability of using CCM alongside retinopathy screening have been established.

*Supported By: National Institute for Health Research, UK*

## 2289-PUB

### Heart-Rate Variability and Metabolic Syndrome in an Adult Chinese Population

KARA MIZOKAMI-STOUT, JORDAN UEBERROTH, MAMTA JAISWAL, LYNN ANG, BRIAN CALLAGHAN, EVA L. FELDMAN, LEILI GAO, YUFENG LI, RODICA POP-BUSUI, LINONG JI, *Ann Arbor, MI, Lansing, MI, Peking, China*

Recent evidence suggests that metabolic syndrome (MetS) is a risk factor for the development of neuropathy in patients without diabetes mellitus. Cardiovascular autonomic neuropathy (CAN) is a serious complication with increased mortality risk. We evaluated the association between CAN, assessed by heart rate variability, and MetS in a cohort of 4,000 adult Chinese subjects in the Pinggu region. Subjects were diagnosed with MetS if they met the modified NCEPT ATPIII criteria for individuals of Asian descent. In this cohort, 892 participants (22%) met criteria for MetS. Time-domain indices of heart rate variability (HRV) including standard deviation of the R-R intervals (SDNN) and root mean square of successive differences (RMSSD) were derived from resting ECG recordings using ImageJ software. Preliminary HRV data was available for an initial 92 healthy controls (HC) and 81 age-matched MetS subjects. MetS subjects had higher fasting glucose (133 ± 50 vs. 118 ± 51 mg/dL), higher systolic blood pressure (147 ± 20 vs. 135 ± 18), and higher triglycerides (292 ± 177 mg/dL vs. 108 ± 45 mg/dL) vs. HC. However, neither SDNN (16.5 vs.13.2 msec, p= 0.27) nor the RMSSD (15.9 vs. 13.7 msec, p=0.4) were different between MetS and HC respectively. No consistent correlations were found between indices of HRV and components of the MetS in this initial cohort. Analyses further evaluating CAN and MetS associations are ongoing in the entire larger cohort to better understand the relationship between CAN and the MetS in this population.

## 2290-PUB

### The Application of SUDOSCAN for Screening Diabetic Peripheral Neuropathy in Chinese Patients

JIEWEN JIN, TIANWEI GU, WEI CHEN, WEIMIN WANG, YAN BI, DALONG ZHU, *Nanjing, China*

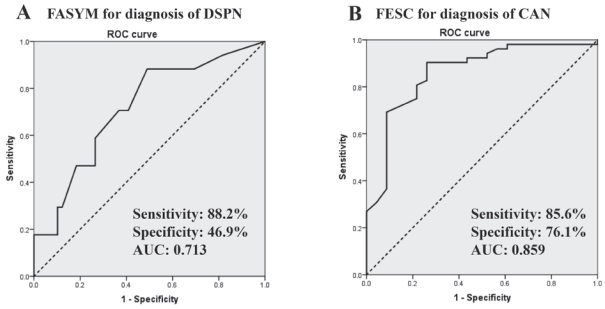
Background: Diabetic peripheral neuropathies (DPN) are the common chronic complications of diabetes, but the diagnosis is insensitive by physical examination in busy outpatients. Here we evaluated the performance of SUDOSCAN in screening DPN in Chinese type 2 diabetic patients.

Methods: The study enrolled 180 Chinese type 2 diabetic patients for annually screening. All patients underwent nerve conduction studies to evaluate diabetic sensorimotor polyneuropathy (DSPN) and Ewing tests to evaluate cardiovascular autonomic neuropathy (CAN). SUDOSCAN was evaluated by electrochemical skin conductance in hands (HESC) and feet (FESC), asymmetry ratio in hands (HASYM) and feet (FASYM) and predicted cardiac neuropathy (PCN).

Results: Patients enrolled had an average age of 56.1 years, 9.8 years of diabetic duration, and the average HbA1c of 9.07%. DSPN(+) patients showed lower FESC and higher FASYM compared with DSPN(-). FASYM >12% had 88.2% sensitivity and 46.9% specificity in diagnosing DSPN. CAN(+) patients showed lower HESC and FESC and higher FASYM and PCN compared with CAN(-). FESC <65μS had 85.6% sensitivity and 76.1% specificity in diagnosing CAN (Figure).

Conclusions: SUDOSCAN is a sensitive test to detect DPN in Chinese patients and could be used as an effective screening tool in busy outpatients.

**Figure.**




*Supported By: National Natural Science Foundation of China (81570737, 81570736, 81500612); Key Discipline of Medicine of Jiangsu Province of China (XK201105); Key Research and Development Program of Jiangsu Province of China (BE2015604)*

## 2291-PUB

### The Influencing Factors for Albuminuria: A Real-World, Cross-Sectional Survey of Chinese Adult Patients

QIAN REN, LINONG JI, CHANGSHENG MA, JIGUANG WANG, XIAOHUI GUO, ATTEND INVESTIGATORS, *Beijing, China, Shanghai, China*

Objective: In order to investigated influencing factors for albuminuria in a real-world, cross-sectional survey of China adult patients.

Methods: All of the 2510 subjects in ATTEND study were enrolled in this study, including patients seen for hypertension in cardiology (n=1330) or for diabetes mellitus in endocrinology (n=1180). A standardized questionnaire was used to collect information on medical history. BP and anthropometry were measured. Fasting plasma glucose, HbA1c, serum lipids, routine urine test and urinary albumin-to-creatinine ratio were measured in all the subjects.

Results: Among the 2510 subjects, the average age was 58.3±11.57 years old, and there are 1181 male patients (47.1%). A total of 1515 subjects finished urinary tests, and 17.8% patients had albuminuria (14.3% and 3.5% for micro-albuminuria and macro-albuminuria, respectively). The incidence of micro-albuminuria was slightly higher in patients seen in endocrinology than in patients seen in cardiology (16.1% and 13.0% respectively). In endocrinology, the incidence of micro-albuminuria was significantly higher in patients with both hypertension and diabetes than diabetes only (17.6% and 13.7% respectively, p=0.008), and similarly rates in cardiology (18.1% and 10.7%

For author disclosure information, see page A751.

respectively, p=0.0002). Multivariate logistic analysis of albuminuria rate by demographic and baseline disease characteristics showed that HbA1c increased by 0.5%, the albuminuria rate increased by 16% (OR=1.16, 95% CI 1.11-1.21, P<0.001), and SBP increased by 5mmHg, the albuminuria rate increased by 14% (OR=1.14, 95% CI 1.10-1.19, P<0.001).

Conclusion: HbA1c and SBP were the independent influencing factors for albuminuria in patients with diabetes and/or hypertension. Cautious should be taken in using ACR to diagnose diabetic nephropathy.

*Supported By: Sanofi China*

## 2292-PUB

**Neurohumoral Regulation of Tissue Reparation In Diabetes**

EKATERINA ARTEMOVA, ZERA ABDULVAPOVA, GAGIK GALSTYAN, ALEKSANDR BERDALIN, ANNA GORBACHEVA, EKATERINA KLOCHIHINA, ALLA TOKMAKOVA, SVETLANA GAVRILOVA, *Moscow, Russian Federation*

Introduction: Diabetic neuropathy is one of the most common late complications of diabetes, as well as the main reason for the formation of DFU. Damage to the integrity of the skin leads to activation of keratinocytes, triggers a cascade of reactions that contribute to changes in the phenotype of the epidermal cells lead to their migration and proliferation.

Materials and Methods: 14 patients with DF neuropathic ulcers (ulcer group) and 9 diabetic patients without ulcers (control group) were included. DF patients were underwent to standard treatment including debridement, dressing, offloading with removable total contact cast, antibacterial therapy in some cases. Measurement of ulcer size and punch ulcer biopsy samples were done to conduct Hematoxylin/Eosin and immunohistochemical analysis on 0 and 10 days of treatment. All patients underwent an evaluation of neurologic signs and symptoms according to the disability NDS, CCM for estimation of corneal nerve fibre density (CNFD) and fibre length (CNFL).

Results: The average size of DF ulcers before and on 10th day of treatment was of 5.56 cm2 and 4,29 cm2, respectively (p<0,004). Severity of neuropathy according to NDS was significantly greater in ulcer group compared to the control group. CCM in group with ulcers showed a significant reduction in CNFD (12.8±7.4 vs. 23.1±4.1no/mm2, p<0.0001) and CNFL (16.1±4.7 vs. 27.3±2.7 mm/mm2, p <0.0001). Corneocyte cells comprising the top layer of the epidermis express primarily $\alpha$7nAChR. Immature (basal) keratinocytes located within the base layer of the epidermis express primarily $\alpha3\beta2$. All keratinocyte cells appear to express $\alpha$9nAChR.

Conclusions: Peripheral nervous system plays an important role in keratinocytes cycle and tissue repair. Identifying common signaling pathways that contribute to cutaneous inflammation and immune function will facilitate better scientific and therapeutic strategies in patients with DFU.

*Supported By: Russian Science Foundation (16-15-10365)*

## COMPLICATIONS—RETINOPATHY

## 2293-PUB

**The Ten-Year Real-World Population-Based Study in Diabetes Retinopathy in Type 2 Diabetes Mellitus—Based on the Diabetes Case Management Program 2001, Taiwan**

MARTIN M.T. FUH, PEI CHIN CHEN, CHIA ING LI, *Taichung, Taiwan, Hsinchu, Taiwan*

Background and Aims: In order to evaluate the retinopathy in T2DM in usual clinical care and ensuing development of personalized preventive program.

Materials and Methods: From Jan. 2005 to Dec. 2015, 14713 diabetes beneficiaries were randomly and cumulatively recruited in DCMP 2001 via outpatient clinic visit. Accordingly, the lifestyle measurements, total daily caloric intakes, macronutrient consumptions and corresponding recommendations were tri-monthly recorded. The annual eye examination was routinely performed in patient enrolled in DCMP 2001 within one month by using the digital retinal photography. From this cohort, there were 222 cases without taking any anti-diabetes medication except lifestyle intervention as Group I whereas, 14491 cases with diabetes drugs including insulin classified as Group II and III. Matching with age, sex, duration of diabetes and A1c levels and with 1: 4 ratio of case number, there were 67 cases with A1c (%) (Mean± SD) 6.89± 1.12 in Group I, 268 cases in Group II with A1c 7.09± 1.01 and Group III with A1c 8.54± 1.39 respectively in last 10 years. Comparison of the occurrence of retinopathy among Groups, log-rank test was used.

Results: The baseline data among these 3 well-matched. There were no statistically significant difference of all bio-metabolic measures among 3 Groups except FBG and A1c of Group III that were significantly higher than Group I and II. The accumulating probability of diabetes retinopathy amid these 3 Groups were totally identical and no statistically significant difference identified in 10-year time interval.

Conclusions: The aforementioned results clearly indicated that the risk factors of diabetes retinopathy rather than anti-diabetes medications including insulin, duration of disease and even long-term glycemic control would be considered in this T2DM population-based cohort.





## DIABETIC DYSLIPIDEMIA

## 2294-PUB

**Empagliflozin Moderately Increases LDL-Cholesterol Levels Only under Dyslipidemia and Chronic Treatment, and Does Not Change LDL Particles Size in Golden Syrian Hamsters**

FRANCOIS BRIAND, ISABELLE URBAIN, EMMANUEL BROUSSEAU, THIERRY SULPICE, MICHAEL MARK, ERIC W. MAYOUX, SR., *Labège, France, Biberach, Germany*

We previously showed that chronic SGLT2 inhibition with empagliflozin in dyslipidemic hamsters leads to moderate increase in plasma LDL-cholesterol (LDL-C) and ketones levels. We tested whether this effect could be also observed in normolipidemic or dyslipidemic hamsters after a single dose of empagliflozin, compared to chronic treatment. We also tested whether the LDL-C increase may alter LDL size. Hamsters were treated with vehicle or with 30mg/kg empagliflozin, as a single dose or for 2 weeks. LDL particles size was assessed by Lipoprint analysis. Empagliflozin, 8 hours after single dosing, significantly reduced blood glucose (-30%) and raised plasma ketone bodies by up to 32%, in both fasted normolipidemic and dyslipidemic hamsters. No change in plasma LDL-C and LDL particles size was observed. After a 2-week chronic treatment, empagliflozin significantly reduced fasting blood glucose levels by 37%, raised the plasma levels of ketone bodies by 57% and free fatty acids (FFA) by 34% in normolipidemic hamsters (both p<0.01 vs. vehicle). In dyslipidemic hamsters, the reduction of fasting blood glucose and the increase of plasma FFA were similar (-37% and +32% respectively vs. vehicle, both p<0.01), while the elevation of plasma ketones levels was more pronounced (132% higher vs. vehicle, p<0.001). Empagliflozin increased plasma LDL-C levels by 28% only in dyslipidemic hamsters (p<0.05 vs. vehicle), without modifying the proportion of large and small dense particles which represented ~85% and ~15% of the LDL fraction, respectively.

In conclusion, empagliflozin increased LDL-C only in dyslipidemic hamsters after 2-week chronic treatment, indicating that alteration in cholesterol homeostasis requires time and depends on dyslipidemia, in contrast to ketone pathway activation. Meanwhile, despite the increase in LDL-C levels, there is no change in the proportion of small dense atherogenic LDL particles.

## 2295-PUB

## WITHDRAWN

## 2296-PUB

**Relationships between ApoC-II, ApoC-III, and Metabolic Parameters In Type 2 Diabetes**

MARINA HARADA, TADASHI YAMAKAWA, KENICHIRO TAKAHASHI, HIROSHI KAMIYAMA, HITOSHI OUKI, RIE FUJII, YASUO TERAUCHI, *Yokohama, Japan*

Dyslipidemia in type 2 diabetes is characterized by an excess of triglyceride-rich lipoproteins (TRLs), decreased HDL-C, and an accumulation of LDL-C particles. Modifications of ApoC-II and ApoC-III levels may play an important role in the mechanisms, although the data supporting these roles are scarce and inconsistent. To assess the relationship between these two apolipoproteins and other metabolic parameters, we retrospectively analyzed data for 418 patients with type 2 diabetes during 2011-2016. The sample had the following characteristics: average age, 59.7 ± 14.4 years; sex ratio (M/F), 275/143; average BMI, 25.3 ± 5.1 kg/m2. Blood measurements resulted in the following average values: TG, 169.9 ± 161.8 mg/dL; LDL-C, 126.8 ± 83.5 mg/dL; non-HDL-C, 155 ± 46.2 mg/dL; HDL-C, 47.5 ± 13.2 mg/dL; HbA1c, 9.9 ± 2.3%. Our study showed a parallel increase in ApoC-II and ApoC-III levels; both significantly increased with increasing TG levels, as reported in a previous study. We also observed a relationship with obesity; with increasing BMI, ApoC-II significantly increased from 8.6 mg/dL (BMI <20) to 10.7 (BMI ≥20 and <25), and ApoC-III significantly increased from 4.2 mg/dL (BMI <20) to 4.9 (BMI ≥20 and <25). Furthermore, with increasing BMI, lipoprotein lipase (LPL) levels significantly decreased from 47.7 ng/mL (BMI <20), to 45.1 (BMI ≥20 and <25) and 38.2 (BMI >30). We suggest that overweight and high TG levels increase the levels of these two apolipoproteins despite opposite effects on LPL activity. However, there was no relation between the C-peptide response-index, insulin sensitivity, HbA1c, and ApoC levels. Multivariate analysis showed that ApoB and LDL-C levels were independently associated with ApoC-II levels, and TG levels were independently associated with ApoC-III levels in terms of the relationships with other lipid markers.

In conclusion, both ApoCs were positively associated with BMI and TG levels, but differentially related with cholesterol-rich lipoproteins and TRLs.

## 2297-PUB

**Gender and Age Differences of Serum Lipids and Lipoproteins in Chinese Adults: A Retrospective Study of over 230,000 Individuals**

TIANWEI GU, JIE SUN, WEIHONG ZHOU, JING WANG, YAN BI, DALONG ZHU, *Nanjing, China*

Background: Previous national survey suggested that dyslipidemia is an increasing burden in China and more severe in urban population. In present study, we retrospectively analyzed the gender and age differences of lipids and lipoproteins in a large Chinese population in Nanjing city.

Methods: A total of 236,945 adults (≥20 years) who undertook a health check during 2009 to 2015 in our medical examination center were involved. Fasting total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride (TG) were measured by standard methods.

Results: The age-standardized estimates of TC, HDL, LDL and TG were 4.77 (4.76-4.79), 1.19 (1.18-1.19), 2.53 (2.52-2.54) and 1.74 (1.72-1.76) mmol/L in males (n=130954), and 4.79 (4.78-4.80), 1.46 (1.45-1.46), 2.44 (2.43-2.45) and 1.21 (1.19-1.22) mmol/L in females (n=105991), respectively. The prevalence of borderline high and high TC/LDL showed an inverse U-shaped relationship with age in males, and peak at the age of 40-59 years, earlier as compared to females. In addition, LDL levels showed an increased trend across 7 years in both males and females.

Conclusion: The dyslipidemia is an increasing epidemic in China, characterized by a rising trend of LDL. Prevention and intervention of dyslipidemia should be a top public health priority in china, especially in middle-age men and postmenopausal women.

**Figure 1A.** Age-Specific Proportion of Subjects With Borderline High and High Total Cholesteraol and LDL Cholesterol.

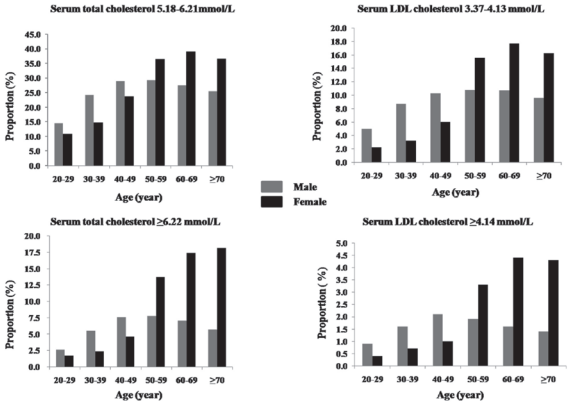
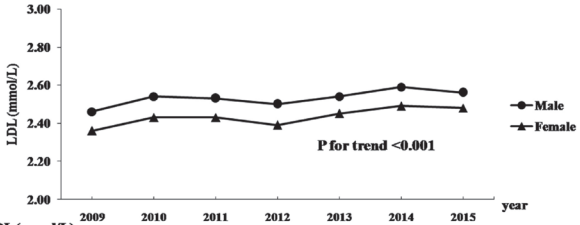



**Figure 1B.** The Trend of Age-Standard Estimated LDL Levels in Males and Females Over 7 Years, 2009-2015.




| LDL (mmol/L) | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |
|---|---|---|---|---|---|---|---|
| Males | 2.46 | 2.54 | 2.53 | 2.50 | 2.54 | 2.59 | 2.56 |
| Females | 2.36 | 2.43 | 2.43 | 2.39 | 2.45 | 2.49 | 2.48 |

*Supported By: National Natural Science Foundation of China (81570737, 81570736, 81500612); Key Discipline of Medicine of Jiangsu Province of China (XK201105); Key Research and Development Program of Jiangsu Province of China (BE2015604)*

## 2298-PUB

**The Effect of Glycated Low Density Lipoprotein on Expression of Hypoxia Inducible Factor 1α and VEGF in Osteoblast**

LIN CHEN, BINGYU ZHANG, RUIXIANG ZENG, XIAOLIANG SHU, TAO LEI, *Shanghai, China*

Objectives: Research that different levels of glycated low density lipoprotein (glyLDL) impact on osteoblast proliferation and metabolism and discuss the possible mechanism.

Methods: Different concentrations (4.97% and 8.24%) of glyLDL were cultured with mouse osteoblasts (MC3T3 E1) for 48 hours, normal LDL (nLDL) group and the blank control group were as control group. the mRNA expression of hypoxia inducible factor 1α (HIF 1α) and VEGF were measured by real time PCR and the protein expression of HIF 1 alpha by SDS PAGE. Meanwhile, the influence of proliferation and metabolism of glyLDL on osteoblast were determined by CCK8 and ELISA.

Results: The cell survival rate of nLDL group, 4.97% glyLDL group and 8.24% glyLDL group were 95.6%, 57.1% and 71.2%, respectively. Osteocalcin content of experimental groups were significantly lower than control group, and the higher glycated level the less osteocalcin secreted. The result of real time PCR showed that, nLDL group contrasted with control group, the mRNA expression of VEGF was downregulated, and had statistical significance (P<0.05). Compared with nLDL group, the mRNA expression of VEGF in 8.24% glyLDL group was upregulated, and had statistical significance, but there's no significant difference between 8.24% glyLDL group and contol group. Furthermore, the effect of 8.24% glyLDL on osteoblast were significantly upregulated the mRNA expression of HIF 1α, and the result of Western blotting indicated that 8.24% glyLDL downregulated the protein expression of HIF 1α in osteoblast.

Conclusions: High level glycated LDL may influence the expression of HIF 1α in MC3T3 E1, which may be one of the mechanisms of the effect of glyLDL on osteoblast proliferation and metabolism.

For author disclosure information, see page A751.

## 2299-PUB

**WITHDRAWN**

## 2300-PUB

**Statin Therapy in Type 2 Diabetes Mellitus Is Associated with Increased PCSK9 Levels Independent from Liver Disease**

BERND STRATMANN, MICHAEL HAUBER, DIETHELM TSCHOEPE, *Bad Oeynhausen, Germany*

Statin therapy is common in type 2 diabetes mellitus (T2DM) to reduce LDL-cholesterol levels. Effects on circulating PCSK9 levels taking into account fatty liver disease in these patients have not been evaluated yet. EDTA plasma of 125 T2DM patients receiving statin therapy (STATIN+) vs. 103 T2DM patients not receiving statin therapy were analyzed using a commercially available PCSK9 ELISA kit recognizing free and LDL Receptor-bound PCSK9. Statistical analysis was done using GraphPad Prism 6.05, values are given as mean±SD. STATIN+ patients were older (61.1±11.4 vs. 57.5±14.0 years; p=0.035), but showed comparable values for HbA1c (9.0±2.0 vs. 9.1±2.2%), triglycerides (295.4±30.6 vs. 287.4±218.0 mg/dl), total cholesterol 190.5±60.1 vs. 202.0±46.6 mg/dl) and HDL cholesterol (43.1±12.8 vs. 42.8±15.3 mg/dl; p>0.05 for all); gender distribution was comparable with 33% being females. Patients did not differ regarding liver function parameters ASAT 39.6±25.5 vs. 45.9±31.2 U/l, ALAT 49.8±37.8 vs. 54.0±36.1 U/l; p>0.05 for all). LDL cholesterol values were significantly lower in STATIN+ patients (106.0±40.1 vs. 120.8±39.8 mg/dl; p=0.0088). PCSK9 levels were significantly elevated in STATIN+ patients (320.9±76.2 vs. 233.0±72.2 ng/ml; p<0.0001). By separating patients into subgroups with underlying liver disease (ALAT>35U/L in women, ALAT>50U/L in men) no correlation between PCSK-9 levels and ALAT could be detected. PCSK9 values were independent from elevated ALAT values on a comparable level. Only patients with elevated ALAT levels receiving statin therapy a weak but significant correlation between PCSK9 levels an total cholesterol (0.375; p<0.05) as well as triglycerides (0.326; p<0.05) was detected. Statin therapy in T2DM patients induced higher circulating levels of PCSK9 which might be a response to the increased LDL-receptor occurrence following statin therapy independently from fatty liver disease. This hypothesis warrants further clarification.

## 2301-PUB

**Study of Rab Protein in Regulating the Hepatic VLDL Transport**

LING YANG, JAMES SHEPHERDSON, HAIMING CAO, *Bethesda, MD*

The biogenesis of hepatic VLDL occurs in the lumen of the ER and exits the ER compartment in a specialized vesicle, the VLDL transport vesicle (VTV). Proteins involved in the incorporation of VLDL into VTVs and VTV-Golgi docking are not yet known. However, protein kinase A (PKA) inhibitors have been found to significantly abrogate VTV budding, indicating VTV formation might regulated by PKA. We identified a Rab protein with no known metabolic function that was up-regulated by cAMP. The induction of this Rab protein was completely abolished by dominant-negative CREB, which is activated by PKA in response to elevated levels of cAMP. Consistently, we found levels of this Rab protein to be strikingly increased in the livers of fasting mice. Furthermore, liver-specific knockdown of this Rab protein significantly reduced circulating Triglycerides (TG). Given this Rab protein is localized to both ER and Golgi, and the ARFRP1-ARL1-Golgin-Rab cascade has been suggested to play an important role in lipid trafficking in intestinal cells, we will investigate whether this Rab protein is involved in hepatic VTV transport from ER to Golgi, thereby affecting TG secretion. Functional analysis of this Rab protein is ongoing using gain- and loss-of-function approaches. Future studies are aimed at investigating the role of this Rab protein in dyslipidemia, fatty liver disease, and diabetes.

## 2302-PUB

**Eicosapentaenoic Acid Reduces Small Dense Low-Density Lipoprotein Oxidation and Human Endothelial Dysfunction In Vitro in a Manner Distinct from Docosahexaenoic Acid**

R. PRESTON MASON, SAMUEL C.R. SHERRATT, HAZEM DAWOUD, ROBERT F. JACOB, HAIDAR ALHUMAID, FARINA J. MAHMUD, TADEUSZ MALINSKI, *Boston, MA, Beverly, MA, Athens, OH*

Cardiovascular disease is accelerated in patients with elevated levels of small dense low-density lipoprotein (sdLDL), an atherogenic particle that is susceptible to hyperglycemic oxidation and a contributor to endothelial cell (EC) dysfunction. The omega-3 fatty acid, eicosapentaenoic acid (EPA), has been shown to significantly reduce levels of oxidized LDL in hypertriglyceridemic patients. In this study, we examined the comparative effects of EPA and docosahexaenoic acid (DHA) on sdLDL oxidation and resultant human EC function. sdLDL was isolated from human plasma and subjected to copper-induced oxidation for 2 hr in the absence or presence of EPA or DHA (10.0 μM). Changes in lipid oxidation were monitored by colorimetric detection of malondialdehyde (MDA). Human umbilical vein ECs (HUVECs) were exposed in vitro to the pretreated, oxidation-exposed sdLDL and assayed for nitric oxide (NO) and peroxynitrite ($ONOO^-$) release using porphyrinic nanosensors. EPA was found to inhibit sdLDL oxidation by 89% as compared to vehicle-treated control (1.2 ± 0.4 vs. 10.6 ± 0.9 μM, respectively; p<0.001) and 64% as compared to DHA (3.29 ± 0.81 μM; p<0.001). In HUVECs exposed to EPA-treated sdLDL, NO release increased by 43% as compared to vehicle (sdLDL)-treated control (320 ± 21 vs. 224 ± 9 nM, respectively; p<0.001) and 22% as compared to DHA-treated sdLDL (262 ± 13 nM; p<0.01). EPA-treated sdLDL also reduced $ONOO^-$ release by 19% as compared to control (240 ± 18 vs. 298 ± 26 nM, respectively; p<0.05) while DHA-treated sdLDL had no significant effect. The $NO/ONOO^-$ ratio, a direct indicator of EC function, increased by 77% (p<0.001) with EPA-sdLDL treatment but was not significantly improved with DHA-sdLDL treatment compared to control. These data demonstrate that EPA has distinct antioxidant properties that preserve EC function under disease-like conditions and suggest EPA as a potential strategy for managing diabetes.



For author disclosure information, see page A751.

## FOOT CARE—LOWER EXTREMITIES

### 2303-PUB

**Outcome of Chronic Diabetic Foot Ulcers Treated with Natural Honey at Primary Care Level: A Retrospective Cohort Study with Long-Term Follow-Up**

HASHIM MOHAMED, *Doha, Qatar*

Diabetic foot ulceration (DFU) is associated with increased morbidity and high cost. Although secondary and tertiary care is the ideal place to treat (DFU), treatment with natural honey at primary care level is a viable cost effective alternative. We conducted a 5-year retrospective cohort study with prospective long-term follow-up of all patients with (DFU) who presented to Umgwalinah health center, Doha, Qatar. Average follow-up was 1 year. failure of natural honey was the main outcome measure. Independent predictor variables were selected by logistic regression analysis. A total of 126 patients with diabetes were managed for various foot lesions as follows. five patients (4%) of 126 underwent immediate amputation. Natural honey treatment was successful for 91 (92.86%) of 98 neuropathic ulcers, 3 (30%) of 10 neuro-ischemic ulcer, 2 (66%) of 3 Charcot foot ulceration, 4 (100%) of 4 patients with second degree burns and 6 (100%) of 6 traumatic foot ulceration or (p<.001, chi2 for trend). Independent factors predictive of failure to heal were presence of osteomyelitis (odds ratio [or]=1.6, 95% confidence interval [CI], 1.0-1.3), increased hemoglobin a1c level (or=1.002; 95% CI, 1.2-1.3), severe peripheral vascular disease (or=1.0,95% CI,1.0-1.03), prior hospitalization for (DFU) (or=1.4; 95% CI, 1.2-1.6) and gangrenous lesion (or=1.7; 95% CI, 1.3-2.1). No side effects were reported and there was a high level of satisfaction (patients and staff). Primary care based management of (DFU) using natural honey is efficacious, safe and acceptable. These findings may lead to a substantial reduction in the cost of (DFU) in the third world. Future comparative studies utilizing randomized controlled trials must be conducted in order to accurately assess the efficacy of natural honey in managing (DFU).

### 2304-PUB

**WITHDRAWN**

### 2305-PUB

**Bedside Bone Biopsy Feasibility Performed by a Diabetologist for Suspected Diabetic Foot Osteitis**

FLORINE FERON, LAURENCE SALLE-TEYSSIÈRES, MARIE LALOI-MICHELIN, TIPHAINE VIDAL-TRÉCAN, CLARA BOUCHÉ, HERVÉ JACQUIER, EMMANUEL LECORCHE, FAIZA MOUGARI, AMANDA LOPES, DOTOHÉE CHOPIN, LAURENT RASKINE, PIERRE-OLIVIER SELLIER, JEAN-DENIS LAREDO, JEAN-PIERRE RIVELINE, FRANCK MAUVAIS-JARVIS, JEAN-FRANÇOIS GAUTIER, JEAN-PHILIPPE KEVORKIAN, *Paris, France, New Orleans, LA*

Background: Surgically or under X-ray performed, bone biopsy (BB) is the microbiologic key diagnosis reference for diabetic foot osteitis. Delay might be shortened if performed at bedside by a diabetologist.

Methods: To assess bedside BB (BBB) feasibility in a diabetes inpatient setting. Inclusion criteria: foot ulcer (area >2cm$^2$, lasting ≥4weeks), suspected osteitis (clinical and/or x-ray), no antibiotics prescribed ≥15 days. BBB through clean skin performed with trocart (MadisonTM KDP13/6) following oral and inhaled analgesia and local anaesthesia. Primary endpoint: successful BBB. Adverse events: local (provoked ulcer/inflammation/necrosis/bleeding), general (fever/positive blood cultures/pain) in the following 72 h. Assessment of pain by face appearance scale during BBB, pain reliever consumption in the following 24 h. Systematic blood culture (1/h) in the following 3 hours or in case of fever.

Results: Single center, observational study of 22 consecutive diabetics. Male: 82%, mean age: 67±12 yo, no type 1 diabetic, diabetes duration: 17±8y, HbA1c: 8,7±2%. Ulcer University of Texas scale: Grade 3: 100%, A/B/C/D respectively 18, 50, 14, 18%. International scale: Grade 3: 45%, Grade 4: 55%. Severe proximal and distal peripheral arteritis: 13% (non-significant 31%). Systolic pressure index <0,9: 23%. TcPO2 <30mmHg: 32%. BBB performed within 5 days indication. Three performers needed. Mean durations: 60±10mn. BBB sites: metatarsian (68%), proximal phalange (18%), distal phalange (5%), calcaneus (9%). Primary success: 95,5% (1,9±1 piece/patient). Contributory BBB cultures: 55%. No local complication. Secondary fever: 18%. One bacteriemia related BBB (4,5%). Per-BBB pain: 9%. Post-BBB pain: 50%.

Conclusion: BBB performed by a diabetologist is easy to learn, safe, informative, with rare major related events. It might be easily incorporated in a daily diabetologist clinical practice, shortening delay of targeted antibiotherapy for diabetic foot osteitis.

### 2306-PUB

**Comorbidities of Wound Care Patients in Heritage Valley Beaver**

JEROD S. STANLEY, COLBY S.S. COX, KIMBERLEE B. HOBIZAL, *Beaver Falls, PA*

Background: There are approximately 5.7 million patients with a chronic wound. This costs an estimated 20 billion dollars annually. There are many co-morbidities that serve as determinants for wound development, prognosis, and possibly mortality. This study aims to identify various significant factors affecting mortality rate of chronic wound patients seen in the wound care center setting.

Methods: A retrospective chart review of 100 deceased patients that were seen in the wound care center by any doctor at Heritage Valley Health Systems Beaver Campus was performed. Patient's age, sex, number and location of wounds, type of wound, duration of wound, presence of diabetes mellitus, peripheral vascular disease, coronary artery disease, chronic kidney disease, presence of infection, surgical intervention, previous amputation, resultant amputation or need for incision and drainage in the OR setting were reviewed.

Results: Life expectancy in 2013 was 78.8 years per the CDC. Average age of death of our patients was 76.4 years. 190 wounds were treated. Average ulcer duration was 56.25 weeks. Average co-morbidities at time of death were 3.32. 85% of our patients had multiple co-morbidities. Diabetes was the largest co-morbidity at 64%. Diabetic ulcers represented the largest ulcer type at 34%. Foot ulcerations were the most popular ulcer site at 51.1%.

Conclusion: This study aimed to evaluate the population of deceased patients in our wound care center. We looked at how the typical co-morbidities seen in wound care patients affect the prognosis and mortality of the patient. Oftentimes, we find ourselves treating the patient's individual wound rather than the patient as a whole. It also serves as a reminder that there are many co-morbidities that contribute to the development and prognosis of these ulcerations, as well as secondary and tertiary factors that determine the patient outcome and mortality.

For author disclosure information, see page A751.