ABSTRACTS

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A CROSS-SECTIONAL, MULTI-CENTRIC, EPIDEMIOLOGICAL STUDY OF DIABETIC NEUROPATHY AND ASSOCIATED CO-MORBIDITIES IN TYPE 2 DIABETIC PATIENTS IN INDIA

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Objectives: Diabetic neuropathy, one of the most common microvascular complications affects nerves due to hyperglycemia in patients with type 2 diabetes (T2DM). This cross-sectional study was aimed to understand the clinical presentation of diabetic neuropathy; types of neuropathies; associated co-morbidities and risk factors; and treatment patterns for T2DM and diabetic neuropathy in India.

Methods: This was a single-visit, cross-sectional, multi-centric, epidemiological study conducted at 363 centres. Adult T2DM patients with neuropathy were included. Patients with any other neurological disorder that could mimic symptoms of neuropathy; pregnant or lactating women and those with significant pain were excluded. Data collection included demographics, lifestyle habits, medical history, treatment regimens for diabetes and neuropathy, concomitant medications and laboratory investigations.

Results: A total of 7172 patients were enrolled with mean age of 52.8 ± 8.04 years, majority being males (58%). The prevalence rates of painful and painless diabetic neuropathy were 49.1% and 50.9%, respectively. The median duration of T2DM was 6 years (range 0.1 to 35 years) and neuropathy was about 2 years (range 0.1 to 30 years). The most common types of neuropathies reported were acute sensory neuropathy (32.3%) and chronic sensorimotor neuropathy (31.4%). Reported symptoms ranged from numbness (30.7%), to paraesthesia (29.2%), and burning sensation (28.0%). Majority of the patients had uncontrolled glucose parameters (Fasting plasma glucose [>100mg/dL]: 90.1%, post-prandial plasma glucose [>140 mg/dL]: 90.5%, glycosylated hemoglobin [>7%]: 69.8%) and lipid profile (low density lipoprotein cholesterol [>100 mg/dL]: 65.5% and triglycerides [>150 mg/dL]: 61%). Hypertension was the most prevalent co-morbid condition reported in 15.9%. Almost two-thirds (61.3%) were treated with metformin as monotherapy or in combination with other anti-diabetic drugs. More than half (52.3%) received mecobalamin for treatment of diabetic neuropathy. Higher proportions of patients with painful neuropathy were prescribed pregabalin as compared to painless (32.18% vs 19.79%).

Conclusion: In conclusion, diabetic neuropathy is painful in almost half of the Indian patients with T2DM. Acute sensory neuropathy occurs in most of the patients. Onset of diabetic neuropathy could be much earlier than expected and hence, routine screening is recommended. Poor glycemic control and hypertension are the potential risk factors for diabetic neuropathy. Metformin and mecobalamin are commonly prescribed for the treatment of diabetes and diabetic neuropathy, respectively. Pregabalin is a preferred treatment option for painful diabetic neuropathy.

TRIPLE ORAL FIXED DOSE COMBINATION OF GLIMEPIRIDE, METFORMIN AND LOW DOSE (7.5 MG) PIOGLITAZONE IN THE TREATMENT OF UNCONTROLLED TYPE 2 DIABETES

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Background: There is paucity of data on triple drug combination containing low dose (7.5 mg) pioglitazone in Indian type 2 diabetes patients (T2DM).

Objective: Comparative evaluation of efficacy and safety of glimepiride, metformin (GM) plus low dose pioglitazone fixed dose combination (FDC) in T2DM.

Material and Methods: In this open label study, 75 insulin naïve T2DM subjects inadequately controlled on GM oral therapy were randomized into Group A: FDC of G 1mg + M 500 mg SR + Pioglitazone 7.5 mg; Group B: FDC of G 2mg + M 500 mg SR + Pioglitazone 7.5 mg or Group C: Insulin 70/30 Mix + M 500mg SR. The primary outcome measure was reduction in HbA1c at 180 days. The secondary end points included reduction in fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and change in lipid parameters and weight.

Results: At baseline mean age, weight, HbA1c, body weight, FPG, PPG, C peptide level, LDL-C, triglyceride and HDL-C were similar in three groups. All treatments resulted in significant reduction in mean HbA1c. At the end of 180 days, reduction in HbA1c was 1.49%, 1.51% and 1.11% in Group A, B and C respectively. The difference in HbA1c reduction between groups was not statistically significant. At the end of 180 days, the mean reduction

in FPG was –66.72 ± 27.12 mg/dl, –79.68 ± 23.87 mg/dl and –69.60 ± 25.34 mg/dl in Group A, B and C respectively. The difference in the reduction of FPG and PPG was not significant between the groups at day 30, 90 and 180. Significant reduction in LDL-C, TG and increase in HDL-C was observed in all groups without significant difference between the groups. No hypoglycemic episodes requiring hospitalization were observed in any group. Change in weight was comparable between groups.

Conclusion: Metformin, glimepiride plus low dose pioglitazone FDC is equally efficacious and well tolerated compared to insulin plus metformin in uncontrolled T2DM. This combination may help in postponing insulin therapy.

SAFETY, FEASIBILITY AND SHORT TERM COMPLICATION FOLLOWING LSAGB (LAPAROSCOPIC SINGLE ANASTOMOSIS GASTRIC BYPASS), RESULTS IN THE FIRST 277 CASES

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Background: In the past 10 years, laparoscopic single anastomosis Gastric Bypass(LSAGB) procedure has been gaining popularity among bariatric surgeons who showed excellent short and long term results. The combination of restriction and some degree of malabsorption seems to improve the long term results in addition to the markrd improvement in comorbidities. Database from the first 277 patient was retrospectively studied including telephone calls.

Results: Mean age was 41.84 ±12.46 years (range, 13–72), preoperative BMI was 42.17 ± 6.47 kg/m^2 (range, 21.63–78.91), mean preoperative weight was 117.33 ± 22.9 kg (range, 54–235), 174 (62%) were females and 104 (38%) males. Length of stay for primary vs. revisional MGB was 2.28 ± 1.11 days vs. 2.43 ± 1.35 days. 7 patients (2.5%) were reoperated within 7 days of surgery, 2 patients (0. 7%) due to stapler line bleeding, 2 patients (0.7%) due to stapler line leakage, 3 patients (1%) due to anastomotic ostruction .most of these reopeations were during the learning curve. No mortality or severe morbidity.

Results: LASGB is feasible and safe even in revisional surgery ,most complications occurred during the learning curve.

LIPOPROTEIN(A) SERUM LEVELS AND ITS RELATIONSHIP TO THE SEVERITY OF RETINOPATHY IN TYPE 2 DIABETES MELLITUS

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Background: Atherogenic lipoproteins, such as total cholesterol, LDL cholesterol, oxidized low density lipoprotein, and triglycerides, are associated with progression of retinopathy.

Aim: To evaluate the relationship between lipoprotein(a) and retinopathy in patients with type 2 diabetes mellitus. Materials and Methods. We enrolled 90 diabetic consecutive patients (57 females, 33males; mean age 55.30 ± 7.99 years, mean duration of diabetes 9.98 ± 1.32 years,). Presence and severity of retinopathy were evaluated. Serum lipid profile, including Lp(a) level, was assessed.

Results: serum lipoprotein(a) levels, were higher in patients with DR compared with those without DR (55.8 ± 11.35 vs. 31.7 ± 6.9 mg/dl, P<0.001). lipoprotein(a) levels ≥30 mg/dl. have been observed in 35 (77.8%) diabetic subjects with DR. Lp(a) levels were high in 12 (26.7%) patients without retinopathy. Patients with PDR had significantly higher serum lipoprotein(a) levels as compared to patients with NPDR (74.11 ± 13.14 vs 51.23 ± 20.63 P<0.001). In patients with retinopathy, a positive correlations were observed between serum lipoprotein(a) levels and Total cholesterol, Serum triglycerides and Serum LDL-C (r = 0.52 p <0.001, r = 0.55 p <0.001and r = 0.68 p <0.001, respectively). Logistic regression analysis showed that diabetic neuropathy, high serum Lp(a) level, high systolic and diastolic blood pressure were the most significant independent factors that are associated with higher incidence of DR and that high serum lipoprotein(a) level and high blood pressure were the most significant factors that associated with high incidence of PDR (p <0.01 and p <0.02, respectively).

Conclusions: Lp(a) levels are increased in a significant percentage of patients with retinopathy, especially PDR, compared to diabetic patients without retinopathy.

ASSOCIATION OF SERUM FERRITIN WITH INSULIN RESISTANCE IN OFFSPRINGS OF TYPE 2 DIABETES MELLITUS

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Background: Type 2 diabetes is prevalent worldwide. Insulin resistance is a main player in pathogenesis of type 2 diabetes. Previous studies suggested a link among iron, insulin resistance and sensitivity.

Aim of Work: To study serum ferritin level in non-diabetic offspring of diabetic subjects with and without impaired glucose tolerance and its relation to insulin resistance. Subjects and methods: Cross sectional case control study included 25 completely healthy subject as control group, and 50 offspring of type 2 diabetes; which divided into normal and impaired glucose tolerant offspring subgroups after glucose tolerance test. All of them underwent thorough clinical examination, routine laboratory investigation including complete blood count, liver and kidney function tests, as well as measuring fasting and postprandial blood glucose, serum ferritin, fasting insulin by ELISA and calculation of BMI and HOMA-IR.

Results: Significant increase in mean value ± SD of serum ferritin, fasting insulin, HOMA-IR, fasting and postprandial blood glucose in impaired glucose tolerant offspring subgroup as compared to both control group and normal glucose tolerant offspring subgroup. Significant positive correlation was found between serum ferritin versus each of BMI, fasting insulin, fasting, postprandial blood glucose, and HOMA-IR in impaired glucose tolerant offspring subgroup.

Conclusion: Elevated serum ferritin in non diabetic with impaired glucose tolerance off spring may play a role in pathogenies of insulin resistance state which may progress to type 2 diabetes. Early detection and management of hyperferritinemia may help to delay the development of diabetes in the offspring.

RELATION OF MEAN PLATELET VOLUME WITH SERUM PARAOXONASE-1 ACTIVITY AND IN DIABETIC PATIENTS WITH RESPECT TO OBESITY AND DIABETIC COMPLICATIONS

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Background: Relation of mean platelet volume with serum paraoxonase-1 activity and in diabetic patients with respect to obesity and diabetic complications.

Objective: To evaluate the relation of mean platelet volume (MPV) levels with serum paraoxonase-1 activity and brachial artery diameter and intima media thickness in diabetic patients with respect to obesity and diabetic complications.

Methods: A total of 201 diabetic patients grouped with respect to obesity [obese (n = 89) and non-obese (n = 112) and diabetic complications [with (n = 50) or without (n = 150) microvascular complications and with (n = 91) or without (n = 108) macrovascular complications] groups were included. Data on demographic and lifestyle characteristics of patients, anthropometric measurements, diabetes related microvascular and macrovascular complications, serum levels for MPV, and serum paraoxonase and arylesterase activities were recorded. Correlation of MPV values to paraoxonase and arylesterase activities.

Results: Mean (SD) paraoxonase and arylesterase values were 119.8 (37.5) U/L and 149.0 (39.9) U/L, respectively in the overall population, with no significant difference with respect to obesity and macrovascular diabetic complications, whereas significantly lower values for paraoxonase 107.5 (30.7) vs. 123.9 (38.8) U/L, p=0.007) and arylesterase (132.1 (30.2) vs. 154.7 (41.2) U/L, p=0.001) were noted in patients with than without diabetic microvascular complications. Mean (SD) MPV values were 9.10 (0.87) fL in the overall population, with no significant difference with respect to obesity and diabetic complications. No significant correlation of MPV values to paraoxonase and arylesterase activities.

Conclusion: In conclusion, our findings revealed a significant decrease I PON-1 activity in diabetic patients with microvascular rather than macrovascular complications, whereas regardless of obesity and diabetic complications, no increase in thrombogenic activity and no relation of thrombogenic activity with PON-1 activity.

EFFECTS OF L-CARNITINE IN SODIUM NITROPRUSSIDE (SNP) INDUCED RAW 264.7 MACROPHAGES

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L-carnitine has a crucial role in the transport of long chain fatty acids into mitochondrial matrix. It acts as a very effective reactive oxygen species scavenger. Sodium nitroprusside (SNP), a NO donor, has been recognized as an inducer of apoptosis in various cell lines. In this study we investigated the effects of L-carnitine on SNP induced RAW 264.7 cells. For this purpose, conventional MTT (thiazolyl blue tetrazolium bromide) reduction assay was performed. When the cells were incubated with different concentrations (0.5-4mM) of SNP, it was observed that SNP decreased cell viability in dose dependent manner. To determine the effect of L-carnitine on SNP induced cell viability, cells were preincubated with different concentrations of L-carnitine (0.5-10mM) for 1 hour and then cells were incubated with 1mM SNP. 1mM SNP decreased cell viability about %60 and pretreatment with L-carnitine (0.5-2mM) increased cell viability to %75, %76, %71 respectively ($p<0.001$). 5mM and 10mM L-carnitine could not restore the anti proliferative effect of SNP and synergically decreased cell viability with SNP. These results show that low concentrations of L-carnitine prevented SNP induced cell viability. However, high concentrations of L-carnitine (higher than 5mM) enhances antiproliferative effect of SNP.

DIABETES ONE REGISTRY THE NATIONAL DIABETES REGISTRY IN INDIA

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Objectives: Currently available data is limited in estimating/understanding the demography of diabetes patients across India. This registry was planned to create a database of diabetes across India to understand the diabetes profile, the associated complications, comorbidities, treatment paradigms and socio-economic impact aspects across India. Secondary objectives were to assess different aspects involved in the management of diabetes and glycemic indices in Indian diabetics.

Methods: A multicenter, observational, non-interventional, 6-month follow-up registry was conducted in 26 states across India involving 2944 male and female patients with type-2 diabetes mellitus between 18-75 years of age. Detailed medical history, profile of patients, diet patterns and lifestyle methods were captured. The laboratory parameters like hemoglobin (Hb), fasting blood glucose (FBG), post-prandial blood glucose (PPBG) and glycosylated hemoglobin (HbA1C) were captured at enrolment, 3 months and 6 months. Descriptive analysis was performed on data for all patients.

Results: Out of total 2944 patients, data of 2849 (96.77%) patients were considered for analysis. The mean age of patients with diabetes was 52.9 years with mean diabetes duration of 5.8 years. Majority (81%) of the patients were from Tamil Nadu (13.1%), Kerela (12.3%) and Maharashtra (11.6%). About one in four diabetics are hypertensive (24.05%) and majority were from the upper middle socio-economic strata (42.6%). About 15.8% patients were never advised lifestyle modifications and non-pharmacological interventions during the physician interaction. Metformin was the most commonly used oral hypoglycemic drug (58.53%) followed by glimepiride (35.87%); whereas a combination of metformin and glimepiride was used in 16.98% patients. Triple drug therapy is used in 4.86% patients and insulin in 9.21% patients. Good glycemic control (HbA1c<7%) is observed only in 20.8% and 23.4% patients at month-3 and month-6 respectively. Non-compliance to diabetic diet is found in 8% individuals. The most common cause of non-compliance is lack of motivation (5.54%), lack of information (2.28%), busy job schedules (1.94%) and financial reasons (1.56%).

Conclusions: The one diabetes registry helps in understanding the patient flow, comorbid conditions, and compliance to therapy from Indian perspective.

A CROSS-SECTIONAL, MULTI-CENTRIC, EPIDEMIOLOGICAL STUDY OF DIABETIC NEUROPATHY AND ASSOCIATED CO-MORBIDITIES IN TYPE 2 DIABETIC PATIENTS IN INDIA

Praveen Raj[*] ; Dr. Shailesh Pitale[1]; Dr. Anil Batra[2]; Dr. Muklesh Gupta[3]; Dr. Rajeshwar Singh[4]; Dr. Ashish Dengra[5]; Dr. S. Suneetha[6]; Dr. Harmesh Aggarwal[7]; Dr. Soumayabrata Roy Chaudhuri[8]; Dr. Sudarshan Chakraborty[9]; Dr. J.S. Shekhawat[10]; Dr. Mirju Mori[11]; Rahul Balip[12]

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Objectives: Diabetic neuropathy, one of the most common microvascular complications affects nerves due to hyper-

glycemia in patients with type 2 diabetes (T2DM). This cross-sectional study was aimed to understand the clinical presentation of diabetic neuropathy; types of neuropathies; associated co-morbidities and risk factors; and treatment patterns for T2DM and diabetic neuropathy in India.

Methods: This was a single-visit, cross-sectional, multicentric, epidemiological study conducted at 363 centres. Adult T2DM patients with neuropathy were included. Patients with any other neurological disorder that could mimic symptoms of neuropathy; pregnant or lactating women and those with significant pain were excluded. Data collection included demographics, lifestyle habits, medical history, treatment regimens for diabetes and neuropathy, concomitant medications and laboratory investigations.

Results: A total of 7172 patients were enrolled with mean age of 52.8 ± 8.04 years, majority being males (58%). The prevalence rates of painful and painless diabetic neuropathy were 49.1% and 50.9%, respectively. The median duration of T2DM was 6 years (range 0.1 to 35 years) and neuropathy was about 2 years (range 0.1 to 30 years). The most common types of neuropathies reported were acute sensory neuropathy (32.3%) and chronic sensorimotor neuropathy (31.4%). Reported symptoms ranged from numbness (30.7%), to paraesthesia (29.2%), and burning sensation (28.0%). Majority of the patients had uncontrolled glucose parameters (Fasting plasma glucose [>100mg/dL]: 90.1%, post-prandial plasma glucose [>140 mg/dL]: 90.5%, glycosylated hemoglobin [>7%]: 69.8%) and lipid profile (low density lipoprotein cholesterol [>100 mg/dL]: 65.5% and triglycerides [>150 mg/dL]: 61%). Hypertension was the most prevalent co-morbid condition reported in 15.9%. Almost two-thirds (61.3%) were treated with metformin as monotherapy or in combination with other anti-diabetic drugs. More than half (52.3%) received mecobalamin for treatment of diabetic neuropathy. Higher proportions of patients with painful neuropathy were prescribed pregabalin as compared to painless (32.18% vs 19.79%).

Conclusion: In conclusion, diabetic neuropathy is painful in almost half of the Indian patients with T2DM. Acute sensory neuropathy occurs in most of the patients. Onset of diabetic neuropathy could be much earlier than expected and hence, routine screening is recommended. Poor glycemic control and hypertension are the potential risk factors for diabetic neuropathy. Metformin and mecobalamin are commonly prescribed for the treatment of diabetes and diabetic neuropathy, respectively. Pregabalin is a preferred treatment option for painful diabetic neuropathy.

GENE POLYMORPHISM IN ESSENTIAL HYPERTENSION & ITS RELATION TO ENVIRONMENTAL FACTORS IN NORTH INDIANS

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Aim: We aimed to determine genotype and allele frequencies of angiotensinogen (AGT) and alpha adducing (ADD1) polymorphisms in patients with essential hypertension.

Methods: We recruited total 205 subjects. In which 105 were essential hypertensive and 100 were Healthy controls. DNA samples for each individual were isolated from peripheral blood by standard phenol/chloroform method analyzed by polymerase chain reaction & enzymatic digestion. Lipid profile was analyzed by vitros ˚250 Dry Biochemistry Fully auto-analyzer (Gonson & Gonson Company). Electrolytes (in serum & urine) were measured by ion-selective electrodes (Roche Hitachi modular, Hitachi Ltd) in Clinical lab of Biochemistry.

Results: The distribution for each ADD1 genotypes were 61.96% for GG (69), 33.51% for GT (21) and 4.53% for TT (11) in the essential hypertensive group; 82.72% for GG (91), 16.46% for GT (9) and 0.82% for TT in the control group. The distribution of AGT genotypes was found significantly different between groups ($x^2 = 10.00$: df = 2; P = 0. 006). The frequencies for each of the AGT genotypes were found as 44.66% for MM (43), 44.33% for GT (49), and 11% for TT (9) in essential hypertensive group; 64% for MM (66), 32% for GT (36), and 4% for TT (3) in healthy control group. The distribution of AGT genotypes did not highly significant as compared to AGT between the groups. We suggest that AGT and ADD1 gene polymorphism play a role for development of essential hypertension ($x^2 = 9.767$: df = 2; P = 0.007).

Conclusion: Patients with essential hypertension exhibited higher levels of Serum cholesterol, LDL Cholesterol & TG than in control subjects. Taken together the genotype and biochemical parameters & considering the restrictive selection criteria used, the present results suggest a relationship between these gene polymorphism and essential hypertension in North Indians.

ASSOCIATION OF HYPERTRIGLYCERIDAEMIA WITH GESTATIONAL DIABETES AND ADVERSE PREGNANCY OUTCOMES

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Background: Plasma lipids and lipoproteins increase during pregnancy, but the mechanism is not completely understood, but appears to be partly caused by elevated oestrogen, progesterone and human placental lactogen. We aimed to determine whether high plasma triglyceride levels in the second trimester of pregnancy are associated with adverse pregnancy outcomes including, pre-eclampsia, preterm birth, gestational diabetes mellitus, and high uterine artery pulsatility index.

Methods: This was a prospective cohort study between 2008 and 2010. Plasma levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride were measured after 8 hours of overnight fasting. We compared the outcomes of 45 pregnant women who had high triglyceride levels (≥195 mg/dl) with 135 pregnant women with triglyceride levels <195 mg/dl.

Results: The incidence of gestational diabetes (20% vs. 5.9%, $p = 0.03$), Preterm birth (24.4% vs. 5.9%, $p<0.0001$), and Pre-eclampsia (17.8% vs. 3.7%, $p = 0.004$), in the high triglyceride group was significantly higher than that in the control group. The incidence of Increased pulsatility index in women with high triglyceride levels was higher than in women with low triglyceride levels but was not significant (17.8% vs. 3.7%, $p = 0.6$).

Conclusion: There is a positive relation between hypertriglyceridaemia and pre-eclampsia, preterm birth, and gestational diabetes.

INSULIN RESISTANCE AND HYPERTENSION IN NON DIABETIC ASIAN INDIAN ADULTS

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Background: There is a growing evidence showing a relationship between Insulin resistance and hypertension. Human as well as experimental studies have indicated the importance of reduced insulin sensitivity in etiopathogenesis of hypertension in some cases of essential hypertension. This study was performed to review the existing hypothesis that hypertension is an insulin resistant state irrespective of the diabetic status in Asian Indian adults.

Methods: One year cross sectional study was conducted on 180 non diabetic adults of Asian Indian ethnicity who were grouped as normotensives(60), prehypertensives(60) and hypertensives(60) according to JNC 7 classification. Insulin resistance was calculated as fasting Homeostatis Model Index(HOMA) using fasting plasma Insulin levels and was compared with blood pressure in all three groups with relevant statistical methods.

Results: Normotensives had a mean HOMA index 2.17 ± 0.66,Prehypertensives had a mean HOMA index 2.91 ± 1.27 and hypertensives had mean HOMA index 4.59 ± 1.87.Scheffe test for intergroup variability and One Way ANOVA was performed for HOMA index which showed a highly significant correlation with $p<0.001$.

Conclusion: These results suggest that Insulin resistance is independently linked with blood pressure in non diabetic Asian Indian adults. We suggest lower intervention threshold and development of newer therapeutic strategies to combat insulin resistance irrespective of the diabetic status.

IMPACT OF METABOLIC SYNDROME TARGETED LIFESTYLE MODIFICATION COUNSELLING IN THE MANAGEMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETICS

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Background: Non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome (MS) stem from insulin resistance and the former is the hepatic manifestation of MS. NAFLD is a common co-morbidity in type 2 diabetics with deleterious health outcomes. There is meagre data on the impact of MS targeted lifestyle modification counselling in the management of NAFLD in type 2 diabetics.

Objective: To determine the impact of MS targeted lifestyle modification counselling in the management of NAFLD in type 2 diabetics.

Methods: Outpatient type 2 diabetics with NAFLD were randomly allocated into intervention arm (n=30, lifestyle

modification counselling plus standard care) and control arm (n = 30, standard care). Data on lifestyle factors, biochemical parameters and abdominal ultrasound was conducted at baseline and at the end of four months of intervention.

Results: Systolic blood pressure (145.2 to 128.1mmHg, P 0.000) triglycerides (138.7 to 121.5mg/dl, P 0.031), high sensitivity C reactive protein (4.6 to 3.4mg/l, P 0.024) and liver span (173.5 to 16.4mm, P 0.037) declined and the HDL-C increased with the intervention (47.2 to 52.2mg/dl, P 0.000) and became higher from controls (52.2 vs. 46.7mg/dl, P 0.049). Prevalence of MS declined from 76.7% to 53.3% (P 0.06) with the intervention. The prevalence of NAFLD declined with the intervention (100% to 63.3%, P 0.0002) and became lower from controls (63.3% vs. 96.7%, P 0.0013).

Conclusion: MS targeted lifestyle modification counselling that reversed NAFLD in 36.7% of the type 2 diabetics, can be an effective strategy to ameliorate and manage NAFLD in type 2 diabetics.

CS6253 ABCA1 AGONIST TREATMENT OF APOE4 DRIVEN ALZHEIMERS'S DISEASE

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Apolipoprotein E (apoE4) is the strongest genetic risk factor for Alzheimer's disease (AD) and apoE4 AD is characterized by vascular engagement including Amyloid beta (Aβ) accumulation in the cerebral vessels and disrupted blood brain barrier (BBB) integrity including micro-bleeds. ApoE4 AD disease may thus have vascular origin and be linked to systemic and brain apoE lipoprotein metabolism. Human and animal model studies suggest that apoE4 is hypolipidated in AD. The ATP-binding cassette transporters A1 (ABCA1) is a key lipidating protein. CS6253 is a potent and selective ABCA1 agonist with anti-atherosclerosis and anti-diabetic properties. To assess CS6253's therapeutic potential in apoE4 AD we treated apoE4 target replacement (TR) mice previously characterized to show prototypical AD phenotype development including cognition deterioration, contrasting them to apoE3 TR mice known to not develop AD phenotype. Read-outs were serum lipids, AD brain phenotype and cognition.

Prolonged i.p. injection of CS6253 (20 mg/kg/48h, 6 weeks) to apoE4 and apoE3 TR mice confirmed the apoE4 driven AD phenotype and resulted in the following changes;

a) Serum; apoE4 FPLC distribution to smaller lipid particles, in line with what is observed for apoE3 or apoE2 FPLC distribution.
b) PK; penetration of CS6253 to the brain and co-localized with astrocytes in hippocampus.
c) Target engagement; decreased ABCA1 protein levels in apoE4 native mice and upregulation of ABCA1 protein concentrations in the brain by CS6253 treatment.
d) PD effect; increased apoE4 lipidation in the brain.
e) AD phenotype; apoE4 driven brain pathology was reversed resulting in lower Aβ42 and phosphorylated tau in hippocampal neurons and increased levels of VGluT1 and apoER2.
f) Cognition; reversal of cognitive deficits in the apoE4 mice (novel object recognition test and the Morris water maze).

Conclusion: We find that the impaired lipidation of apoE4 and the associated brain and cognitive impairments can be counteracted in vivo by CS6253, a potent and selective ABCA1 agonist. Further studies are needed to delineate the down-stream effects of the improved ABCA1-apoE4 lipidation mediating the therapeutic benefit, involving vascular and non-vascular factors. These findings have important clinical ramifications and suggest that ABCA1 is a promising target for anti-apoE4 treatment of AD and related vascular and neurodegenerative disease states.

SLEEP DEPRIVATION AND COFFEE CONSUMPTION INDUCED CHANGES IN BMI, BLOOD PRESSURE AND BLOOD GLUCOSE IN MALE WISTAR ALBINO RATS

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Intentional restriction of sleep is progressively high and common among those experiencing environmental/psychological stress due to work demands, abnormal working hours and psychiatric/physical disorders in developing and developed industrialized societies. Deficiency of sleep have its several concerns, amongst which include increased prevalence of disease risks and mortality. 30 adult rats were randomly divided into six groups with sleep deprivation (SD) (using multiple platform method) and coffee administration for 30 days after 2 weeks of acclimatization: A (control), B (SD only), C (416.75ml/kg coffee), D (833.50ml/kg coffee), E (SD + 416.75ml/kg coffee) and E

(SD + 833.50ml/kg coffee). Blood pressure was determined by cannulation of carotid artery using pressure transducer and a polygraph. Glucose concentration was determined after enzymatic oxidation and BMI calculated using rat weights' and lengths'. Mean arterial pressure (MAP) was significantly increased in groups B, D, E and F compared to control. Blood glucose demonstrated a significant reduction in groups B, C, D, E and F compared to control. SD rats had a significant decrease in BMI compared to control while groups C, D, E and F were significantly increased compared to B. Reduction in glucose across the treatment groups could indicate an improved glucose tolerance, no insulin resistance. Also, increased energy expenditure, may explain the reduction in BMI in high and low doses of coffee + SD groups and increase in MAP. SD + coffee induced stress may aide in the prevention of obesity, type 2 diabetics although the significant increase in MAP.

PREDICTING 10-YEAR RISK OF DIABETES INCIDENCE IN MIDDLE-AGED AND ELDERLY: THE BLSA STUDY

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Background: It remains unknown whether sub-distribution hazards model perform better to risk prediction for diabetes incidence than Cox proportional hazards model among the middle-aged and older adults.

Methods: Data were collected by the Beijing Longitudinal Study of Aging (BLSA) between August 1992 and December 2012. Diabetes was diagnosed as a self-reported history of diabetes diagnosis, taking antidiabetic medicine, or having FPG ≥7.0 mmol/L (126mg/dl) at any of the periodic examinations. Sub-distribution hazards model and Cox proportional hazards model were used to evaluate the risk of developing a first diabetes event. Receiver operating characteristic (ROC) curve, areas under the ROC curves (AUC), and calibration plots were used to evaluate the discrimination and calibration ability of the both methods.

Results: 144 cases of 1857 participants were documented for diabetes incidence with a median 10.9 (Interquartile range: 8.0-15.3) years follow-up period. The incidence density was 7.908/1000 person-years. Cumulative incidence function of diabetes was 11.60% after adjusting for the competing risks of non-diabetes deaths. AUCs were 0.74 (95% *CI*: 0.70-0.78) and 0.70 (95% *CI*: 0.66-0.75) in sub-distribution hazards model and Cox proportional hazards model, respectively. Sensitivity, specificity, and Youden index of the sub-distribution hazards model was 0.81, 0.52, and 0.67, and that of Cox proportional hazards model was 0.84, 0.42, and 0.63.

Conclusion: A multivariable sub-distribution hazards model was developed, after accounting for non-diabetes death, which performed better than Cox proportional hazards model to risk prediction for 10-year incident diabetes among middle-aged and older adults.

THE ROLE OF URIC ACID IN IMPAIRMENT OF THE GLOMERULAR FILTERATION RATE IN NONPROTEINURIC PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Background: Increased uric acid levels were associated with increased risk of development of hypertension, cardiovascular disease and progression of chronic kidney disease.

Objective: Measurement of serum uric acid(SUA), HBA1c, total cholesterol and C-reactive protein and their relationship to the estimated GFR (by using Cockcroft – Gault formula).

Subjects: This cross sectional study consisted of 100 subjects (64 males and 36 Females). To all, history taken , anthropometric and laboratory measurements were assessed.

Research Design and Methods: We study our patients for The Role of Uric Acid in Impairment of The GFR in Nonproteinuric Patients with Type 2 Diabetes Mellitus.

Results: Our study included 100 Type 2 DM patients; range of age was 32-67 years, SUA range was 4.4-10.3 mg/dl, e-GFR range was 42-151 ML/min. - SUA is statistically positively correlated with the duration of DM, body weight, BMI and age (r=0.14 P>0.05, r=0.43 P<0.001, r=0.26 P<0.05, r=0.1 P>0.05 respectively). Also, statistically positive correlation were observed between SUA and

HBA1c, Total cholesterol and CRP (r=0.22 P<0.05, r=0.22 P<0.05, r=0.3 P>0.05, respectively). A positive correlation were observed between e-GFR and body weight, BMI, HBA1c, cholesterol (r=0.6 P<0.001, r=0.3 P<0.05, r=0.3 P<0.05, r=0.1 P>0.05, respectively) and a negative correlation were observed with age and CRP (r=-0.4 P<0.001, r=–0.4 P<0.05, respectively). A negative statistically significant correlation were observed between e-GFR and SUA (r=–0.1, P<0.05).In the patients with SUA <7 mg/dl we found; the e-GFR was 101.56 ± 23.893 mL/min, FBS was 175.074 ± 29.51mg/dl and HBA1c was 7.242 ± 0.5489, In patients with SUA 7-8 mg/dl; the e-GFR was 95.75 ± 24.263 mL/min, FBS was 160.221 ± 22.22 mg/dl and HBA1c was 7.008 ± 0.3106 and in the patients with SUA > 8 mg/dl; the e-GFR was 91± 23.635 ml/min, FBS was 148.01 ± 27.10mg/dl and HBA1c was 7.592 ± 0.7840.

Conclusions: Increased serum uric acid is considered as impact factor and play a significant role in impairment of estimated GFR in non- proteinuric patients with type 2 DM. Uric acid is considered as a novel marker of inflammation and remodelling within the arterial vessel wall and hyperuricaemia caused renal microvascular disease; and seems to be an independent risk factor for the development of incident chronic kidney disease .

INSULIN RESISTANCE IN PHEOCHROMOCYTOMA

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Introduction: Pheochromocytoma are rare neuroendocrin tumors. The incidence of pheochromocytoma is 2 to 8 per million persons per year. Ninety percentage arise from adrenal medulla and it is often associated with hyperglycemia. Catecholamines are important counterregulatory hormone to insulin. It is cause of insulin resistance. Impaired glucose tolerance is present in pheochromocytoma 25-75 %.

Methods: We evaluated 44 patients. The patient were diagnosed pheochromocytoma between 2014 and 2016. We used Homeostasis Model Assessment (HOMA-IR) to estimate insulin resistance. It was calculated according to the formula, HOMA-IR = fasting insulin (μU/L) x glucose (mmol/L) / 22.5.

Results: The 44 pheochromocytoma patients were enrolled study to the (34 women and 10 men). The mean age of the patients was 54.16 ± 12.06, HOMA-IR 3.19±1.20. Twentynine of patients were noted have insulin resistance (65.9%).

Conclusion: In patients with pheochromocytoma the prevalence of insulin resistance was 65.9 %, according to the HOMA-IR measurement. This finding is similar to the literature. Epinephrine is a more potent catecholamine in producing hyperglycemia because of its higher affinity to the ß2 adrenergic receptors, probably by inducing glucagon secretion. It increases transient glycogenolysis in the liver. And inhibits insulin secretion mostly by stimulating α2 adrenergic receptor.

SYSTEMIC LEVELS OF ANGIOGENESIS AND ANGIOSTASIS CXC CHEMOKINES ARE DIFFERED IN NEONATES DELIVERED MOTHERS SUFFERING GESTATIONAL DIABETES MELLITUS AND THEIR NEONATES

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Gestational diabetes mellitus is amongst the most frequent metabolic disorders in pregnancy, affecting 1–10% of all pregnancies. Several regulators including cytokine and chemokine network are considered as crucial agents in pregnancy Therefore, the present study was aimed to determine systemic levels of CXCL1, CXCL9, CXCL10 and CXCL12 in GDM mothers and their neonates, as recruiters of immune cells. In the present cross- sectional study, we recruited 54 pregnant women suffering GDM in the third trimester of pregnancy and 54 healthy normal pregnant women. Peripheral blood specimens were collected from both GDM and controls and subjected to serum isolation. Cord blood samples were also obtained from neonates of GDM mothers and normal pregnant women. The serum and cord blood levels of CXCL1, CXCL9, CXCL10 and CXCL12 were measured by ELISA in studied groups. Statistical analysis of differences between groups was carried out using the statistical package for the Social sciences. Data were analyzed using chi-squared test and *t*-test between two groups. The *P*-values <0.05 were considered significant. Our results showed that CXCL1 and CXCL9 were increased in GDM patients in compare to control but CXCL10 and CXCL12 remind unchanged. While the serum levels of CXCL1, CXCL9, CXC10 and CXCL12 were significantly differed in neonates delivered from GDM patients when compared to neonates who were delivered by normal pregnant women. According to the results of this work, it could probably be concluded that in GDM the expression of CXC chemokine is related with the balance between angiogenesis / angiostasis phenomenon associ-

ated with pregnancy and follows a pattern of inflammatory response in pregnant women.

NT-PROBNP LEVELS CAN PREDICT HEART DYSFUNCTION IN DIABETIC SENESCENT PATIENTS

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Brain natriuretic peptide (NT-proBNP) levels are known to be elevated in patients with cardiovascular disease (CVD), but to what extent it can be used prospectively to predict abnormal heart function in diabetic patients remains to be seen. We aimed to test if BNP levels are associated with increased risk of cardiovascular disease in diabetic senescent patients and can be used as a biomarker of cardiac disease and associated pathologic states. Blood samples were obtained from senescent patients (74.4 ± 5.68 years), with CVD (group I) and group II – diabetic patients with CVD, both compared with control group. NT-proBNP levels were measured by ELISA immunoassay with spectrophotometric detection at 450 nm. Our data showed a 46.93% increase of BNP levels for group I vs. control and a 65.52% increase for group II vs. control. Between the two groups of patients, those with diabetes (group II) have higher BNP values than group I with only CVD (28.92 ± 36.06 vs. 18.79 ± 16.87). We found the secretion of BNP increased in diabetic patients and this suggests the association of diabetes and BNP in CVD with higher prevalence. Thus, BNP may serve as a screening tool to diagnose patients with complex symptomatology especially diabetic patients where the risk of cardiac disease exists. BNP analysis would greatly assist to identify patients with diabetes and CVD, to a further examination and optimization of drug therapy.

DIFFERENCES IN PHYSIOLOGIC AND METABOLIC OUTCOMES IN AN INTENSIVE WEIGHT REDUCTION PROGRAM FAVOR PARTICIPANTS ON PRESCRIPTION DIABETES MEDICATION

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Given the prevalence of American adults with Type 2 Diabetes (T2D), it is important to understand how prescription treatment may affect weight loss. For the first time, we present data collected over the past 18 months from the 20Lighter Program (T20LP), a 3-phase (9wk) intensive weight reduction program. This abstract focuses on data from participants taking/not taking prescription diabetes medications over the first 2 phases (6wk) between Jan 2015- June 2016.

602 participants completed the first 6wk of T20LP by July 31, 2016; 59 reported taking at least one prescription diabetes medication (oral and/or injectable). Baseline age, comorbidities, history and prescription medications were similar between groups (T2D, non-T2D), and typical of metabolic syndrome. From initial baseline to 6wk, each group (T2D and non-T2D) showed statistically significant ($p<0.05$) and clinically meaningful reductions in body weight (**A**, 27.9 ± 1.2; 25.1 ± 0.35), Body Mass Index (BMI) (**B**, 4.1±0.15; 3.8±0.05), body fat (**C**, 4.9 ± 0.40; 4.0±0.14), visceral fat (**D**, 4.0 ± 0.28; 3.1 ± 0.09), basal metabolic rate (**E**, 111.5 ± 11.3; 119.2±4.4), metabolic age (**F**, 8.3 ± 1.35; 10.3±0.42), and increases in body water (**G**, 2.3±0.22; 2.0±0.09). When comparing mean changes between T2D and non-T2D groups we found a statistically significant difference in reduction of BMI (**H**, $p<0.05$), and a trend in reduction of body fat % (**I**, $p=0.0501$) favoring the T2D group. Data reported as: (Figure, T2D; Non-T2D) and shown as mean ± SEM.

Improvements from baseline were significant for all outcomes in both T2D and non-T2D groups. Interestingly, when comparing the mean changes between groups we found BMI and body fat reductions favored the T2D group.

FRAMINGHAM RISK SCORE AND ESTIMATED 10- YEAR CARDIOVASCULAR DISEASE RISK CAN BE REDUCED BY A SHORT-TERM YOGA-BASED LIFESTYLE INTERVENTION

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Introduction: Yoga-based lifestyle interventions seem to reduce the cardiovascular risk. However, this benefit in terms of cardiovascular risk reduction has been seldom measured using a validated and reliable tool such as Framingham Risk Score (FRS). This study evaluated the efficacy of a short-term yoga-based lifestyle intervention program on FRS, and estimated 10-year cardiovascular risk.

Methods: Single arm, pre-post interventional study included data from a historical cohort with low-to-moderate risk for cardiovascular diseases (CVD). Subjects attended one of the pretested short-term yoga-based lifestyle intervention at a tertiary care center. This included *asanas* (physical

postures), *pranayama* (breathing exercises), meditation, relaxation techniques, stress management, group support, nutrition awareness program, and individualized advice. Primary endpoints were changes in FRS, and estimated 10-year CVD risk. A gender-based subgroup analysis was also done, and correlation between changes in FRS and cardiovascular risk factors was evaluated.

Results: Data for 554 subjects was screened, and 386 subjects (252 females, 134 males) were included in the analysis. There was a significant reduction in FRS ($p < 0.001$), and estimated 10-year cardiovascular risk ($p < 0.001$) following the short-term yoga-based intervention. There was a strong positive correlation between reduction in FRS and serum total cholesterol ($r = 0.60$, $p < 0.001$). There was a moderate positive correlation between reduction in FRS and LDL-cholesterol ($r = 0.58$, $p < 0.001$), weak, but positive, correlation between reduction in FRS and triglycerides ($r = 0.26$; $p = < 0.001$), serum VLDL-cholesterol ($r = 0.29$, $p < 0.001$), and SBP ($r = 0.20$; $p = < 0.001$.

Conclusions: This yoga-based lifestyle intervention program significantly reduced the CVD risk as shown by lower FRS, and estimated 10-year CVD risk.

THE EFFECT OF DUAL PEG INCRETIN AGENTS ON IMPROVEMENTS OF METABOLIC SYNDROME IN DIO CYNOMOLGUS MONKEYS

Changqing Zhang

WuXi Apptec

14 DIO (diet induced obesity) Cynomolgus monkeys (7/sex) with BMI ≥35 were selected in this study. Vehicle control group had 2 animals (1/sex), each treatment group (low, middle, high) had 4 animals (2/sex). Dose frequency was once/4 days, total 8 times. Control group animals received saline; treatment group animals received Dual PEG Incretin Agents at low, middle and high dose, respectively. IVGTT, food intake, body weight and serum chemistry were determined at pre-treatment and after treatment. Food intake of the treatment groups decreased, and control group nearly no change. Body weight (BW) of the treatment groups decreased, and vehicle control group increased. The body fat composition (FC) and waist circumference (WC) of the treatment groups decreased, and control group nearly no change. Fast plasma glucose (FPG) decreased for treatment groups, and increased for vehicle control group. Fast plasma insulin (FPI) increased in both treatment groups and vehicle control group, but control group increased much more than treatment group. The clearance of glucose (K-value) for control group decreased, but treatment groups increased except high dose group.The triglyceride (TG) value of treatment groups decreased, and nearly no change in vehicle control group. The total cholesterol (TCHO) and free fatty acid (FFA) values of treatment group increased, but vehicle group decreased.

The liver enzyme Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) decreased in treatment groups and increased in control group. G-glutamyltransferase (GGT) and Alkaline Phosphatase (ALP) decreased in both treatment groups and control group.

ASSOCIATION OF LIPID PROFILE AND LIVER FIBROSIS AMONG ADULTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) UNDERGOING ROUTINE EXECUTIVE CHECK-UP IN MAKATI MEDICAL CENTER

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Non-alcoholic fatty liver disease (NAFLD) is regarded as the most common cause of chronic liver disease in the world and an emerging epidemic, Many non-invasive scoring systems have been formulated and validated to act as surrogate to liver biopsy, one of which is the NAFLD Fibrosis Scoring (NAFLD-FS or NFS). In this study, the prevalence of those with, or at risk, for advanced liver fibrosis among those with NAFLD in adult patients who underwent routine executive health check-up in our institution.. A total of 284 adult were patients identified with NAFLD by liver ultrasound were included in the analyses. The mean age of the subjects was 50 ± 10.89 years old, predominantly male (60.92%), and obese (78%). A portion of patients with Type 2 Diabetes Mellitus (20%) and Metabolic Syndrome (38%) were identified. Using the NFS, majority (80%) of the 284 subjects had no liver fibrosis (negative NFS), only two patients (0.70%) had liver fibrosis, and 54 (19%) were classified as indeterminate. Using Fisher's exact test, a negative association between NFS liver fibrosis category and LDL ($p < 0.009$). However, only 5% of the total variation in NFS is being explained by LDL which is very small and hence insignificant. Hence, using the NFS most of our patients were found to have negative NFS or no liver fibrosis.

IN VITRO THERAPEUTIC ASSESSMENT OF FIVE HERBAL PRODUCTS USED IN THE TREATMENT OF DIABETES MELLITUS IN KWAZULU-NATAL, SOUTH AFRICA: INSULIN SECRETION, GLUCOSE UTILIZATION AND MINERAL CONTENT

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Artemisia afra, Bulbine natalensis, Bulbine fructescens and Aloe arborescence have been long recommended in South Africa folk medicine for the treatment of diabetes but the therapeutic targets have not yet been defined. The insulin secretory effects of these botanicals on isolated mouse islets and MIN6 β-cells were measured by radioimmunoassay following static incubation in the absence and presence of extracellular calcium. Their glucose utilization potential was determined by the glucose oxidase method in liver Huh-7 cells. The concentration of minerals known to ameliorate diabetes mellitus in the plant samples was determined using atomic absorption spectrometer. All the plant extracts significantly stimulated insulin secretion from MIN6 β-cells at 100 μg/ml (2mM glucose: 4.82 ± 0.25ng/30000 cells/h ranging from 11.16 ± 2.13 to 17.55 ± 5.83, $P < 0.05$) without compromising membrane integrity/cell viability. Further stimulatory effects were obtained in MIN6 β cells with 1mg/ml of plant extracts ranging from 13.72 ± 5.38 to 19.91 ± 5.25. The plant extracts at 1mg/ml also increased insulin secretion from mouse islets. The insulin secretagogue effects of plant extracts in MIN6 β-cells were abolished in the absence of extracellular Ca^{2+} (all $P > 0.2$ vs 2mM glucose). The extracts also increased glucose utilization in Huh-7 cells when used at 12.5 μg/ml. All the plant extracts contained varying degree concentration of mineral components which may contribute significantly to the enhanced insulin secretion. This study has revealed that extracts from these botanicals directly stimulate insulin secretion from mouse islets and MIN6 β-cells at least in part as a consequence of Ca^{2+} influx, and they also enhance glucose utilization.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM PATHWAY GENE POLYMORPHISMS AND RISK OF CORONARY ARTERY DISEASE IN ASIAN INDIANS: SYNERGISTIC EFFECTS OF GENE-GENE AND GENE-ENVIRONMENT INTERACTIONS

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The genetic variations in renin-angiotensin-aldosterone system (RAAS) pathway genes have been implicated as risk factors for the development of coronary artery disease (CAD) in different populations with inconsistent results, possibly due to heterogeneity among various genetic and environmental factors. The aim of this study was to investigate the possible association of polymorphisms in RAS genes: ACE (ID), AT1R (A1166C) and AGT (M235T) with CAD and their synergistic effects on coronary risk in an Asian Indian population. In addition, we studied the interactions amongst the socioeconomic, demographic and lifestyle risk factors and RAAS polymorphisms on development of CAD. In total, 868 participants (452 healthy controls and 416 CAD patients) aged 25-85 years were recruited from north Indian population. The socioeconomic, demographic, anthropometric and biochemical measurements were done. The genotyping of SNPs in ACE, AT1R and AGT genes were done using PCR-RFLP method. The results demonstrates a significant difference between CAD patients and control subjects in respect of socio-economic status, Alcohol consumption and smoking, physical activity and hypertension. Abdominal obesity as evident from significantly higher WHR and waist circumference along with dyslipidemia was predicted as the major risk factors. The reduced HDL-cholesterol and elevated creatinine values observed in CAD patients may have contributed to the pathophysiology of CAD and renal dysfunction in this study subjects. Logistic regression analysis of data demonstrate that DD genotype of ACE gene was associated with 1.6 fold increased risk of development of CAD (OR = 1.6; 95% C.I. = 1.077-2.313; p = 0.019). However, no significant association was observed with AT1R gene (OR = 1.8; 95% C.I. = 0.586 - 3.89; p = 0.115) and AGT genes (OR=1.55; 95% C.I. = 0.87 - 2.74) p=0.133) in north Indian population. In conclusion, abdominal obesity, dyslipidemia, low SES alcohol consumption and smoking are the independent cardiovascular risk factors in our population. Our report indicates ACE (ID) gene polymorphisms associated with the increased risk of CAD in Indian population.

EFFECTS OF CANAGLIFLOZIN VERSUS GLIMEPIRIDE ON SERUM LEPTIN AND ADIPONECTIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS (T2DM)

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Background: In a 52-week study of patients with T2DM on background metformin, the SGLT2 inhibitor canagliflozin demonstrated superiority (300 mg) in lowering A1C versus glimepiride, and greater reduction in body weight (BW) primarily via loss of fat mass. We examined the effects of canagliflozin versus glimepiride on the adipokines leptin and adiponectin as markers of impaired adipose tissue function associated with insulin resistance, to determine whether weight loss with canagliflozin resulted in improved adipose tissue function.

Methods: This post hoc analysis was based on serum samples from randomly selected patients enrolled in the overall study (n = 1450) receiving canagliflozin 300mg (n = 100) or glimepiride (n = 100). Change from baseline to Week 52 in serum leptin and adiponectin was compared between groups and correlated with change in A1C, BW, and lipids (HDL-C, LDL-C, TG).

Results: Among patients with biomarker assessments, ΔA1C at Week 52 was –0.99% with canagliflozin and –0.91% with glimepiride (baseline = 7.7-7.8%). ΔBW was –4.1kg with canagliflozin and 0.7kg with glimepiride (baseline = 90-91kg). These results were similar to the overall cohort. At Week 52, canagliflozin decreased serum leptin and increased serum adiponectin compared with glimepiride. ΔLeptin was correlated with ΔBW ($r \geq 0.35$) only; Δadiponectin was not correlated with ΔA1C, ΔBW, or Δlipids.

Conclusion: The observed effects of canagliflozin on serum leptin and adiponectin suggest improvements in adipose tissue function/insulin sensitivity, which have been associated with cardiometabolic health. The canagliflozin-related decrease in leptin and increase in adiponectin were independent of glycemic benefit, and the increase in adiponectin was independent of weight loss in this study.

EFFICACY AND SAFETY OF CANAGLIFLOZIN IN PATIENTS WITH TYPE 2 DIABETES BASED ON HISTORY OF CARDIOVASCULAR DISEASE OR CARDIOVASCULAR RISK FACTORS

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Background: Treatment of patients with type 2 diabetes mellitus (T2DM) and a history of cardiovascular (CV) disease or CV risk factors may present clinical challenges due to the presence of comorbid conditions and use of concomitant medications. Canagliflozin (CANA), an SGLT2 inhibitor, has been shown to improve glycemic control, body weight, and blood pressure (BP) with a favorable tolerability profile in a broad range of patients with T2DM. This post hoc analysis assessed the efficacy and safety of CANA in patients with T2DM based on CV disease history/risk factors.

Methods: These analyses were based on pooled data from four 26-week, placebo (PBO)-controlled, Phase 3 studies that evaluated CANA 100 and 300 mg in patients with T2DM (N = 2313; mean A1C, 8.0%; body weight, 89 kg; systolic BP [SBP], 128 mmHg). Changes from baseline in A1C, body weight, and SBP at Week 26 were assessed in subgroups of patients based on history of CV disease (Y/N), history of hypertension (Y/N), baseline statin use (Y/N), and number of CV risk factors (0/1 vs ≥2). Safety was based on adverse event (AE) reports.

Results: CANA 100 and 300 mg lowered A1C, body weight, and SBP versus PBO over 26 weeks in patients with or without CV disease history/risk factors; similar reductions were seen with CANA versus PBO across subgroups. Incidence of AEs, AEs leading to discontinuation, and serious AEs was similar across subgroups.

Conclusion: CANA was efficacious and generally well tolerated in patients with T2DM regardless of CV disease history/risk factors.

PREVALENCE OF NON-ALCOHOLIC FATTY LIVER DISEASE AND OTHER CARDIOVASCULAR RISK FACTORS IN A COHORT OF INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS AT A COMMUNITY HOSPITAL IN NEW YORK

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Background: Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease that encompasses fatty liver, non-alcoholic steatohepatitis (NASH), and NAFLD associated liver disease. The metabolic syndrome and NAFLD are closely linked by a common underlying metabolic abnormalities; insulin resistance leading to multi-organ lipotoxicity. The clinical importance of NAFLD has grown in recent years, consequent to obesity epidemics, sedentary habits and high calorie diets adopted by people of Western Countries and NAFLD has been considered the most common cause of liver disease and frequent causes of elevated aminotransferases, cryptogenic liver cirrhosis and important indication for liver transplantation.

Hypothesis: Fatty liver is a common abnormality in individuals with Type 2 Diabetes and its presence correlate with increased occurrence of other cardiovascular risk factors and elevated liver enzymes activity.

Aim: The study is aimed at finding the prevalence of fatty liver disease based on the ultra-sonographic findings compatible with fatty liver in individuals with Type 2 Diabetes and to assess the correlation with other cardiovascular risk factors.

Methods: The study is retrospective and cross-sectional in design. Electronic records of patients with diagnosed Type 2 Diabetes were reviewed. A total no of 2235 records were reviewed out of which 619 records were finally included into the study after fulfilling the inclusion criteria for the study. The study population all had ultrasound within 5 years of the study and laboratory tests done at the time of ultrasound were obtained. The data were entered into the Microsoft Excel and exported into STATA version 11.0 for final statistical analysis.

Results: The mean age of the overall study population was 56.4 years (Range 23-90). 386 (62.6%) were females and 233 (37.6%) were males.378 (61.1%) of the study population were obese. 170 (27.5%) had normal ultrasound, 431 (69.6%) had hepatic steatosis and 18 (2.9%) had evidence of fibrosis/cirrhosis. The prevalence of fatty liver disease in the diabetic population was 72.5%. The mean age of patients with fatty liver disease and patients without fatty liver disease was 55.1 ± 0.56 vs 60.0 ± 1.08 (P = 0.000*). Mean AST 37.4 ± 1.34 vs 28.3 ± 1.6 (P = 0.002*). Mean ALT 46.7±1.9 vs 29.3 ± 2.2 (P = 0.0000*). The mean BMI 32.9 ± 0.3 VS 30.3 ± 0.5 (P = 0.0000*). Mean Diastolic Blood pressure was 72.6 ± 0.49 vs 70.8 ± 0.75 (P = 0.047*). The mean HDL-C was 44.9 ± 0.53 vs 47.2 (P = 0.034*) and the mean Triglyceride was 162.8 ± 5.69 vs 126.6 ± 126.6 ± 5.13 (P = 0.002*). Logistic regression showed that ALT, BMI and TG levels statistically predicted ultrasound diagnosis of fatty liver disease.

Summary: The study showed there is a high prevalence of obesity in the diabetic population (61.1%). The prevalence of Non-alcoholic fatty liver disease based on the ultrasound diagnosis was found to be 72.5%. Patients with ultrasound diagnosis of NAFLD had higher BMI, AST, ALT, Diastolic blood pressure, triglyceride and a lower HDL cholesterol which were all statistically significant. Logistic regression showed that ALT, BMI and TG levels statistically predicted ultrasound diagnosis of liver disease.

Conclusion: Fatty liver disease is a common abnormality seen in type 2 diabetes and has a strong correlation with obesity and cardiovascular risks.

ASSOCIATION OF CORONARY HEART DISEASE RISK & LIPID PROFILE IN INDIAN WOMEN WITH POLY CYSTIC OVARIAN SYNDROME

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Background: Polycystic ovarian syndrome (PCOS) has been one of the major public health problems in India. Women with PCOS are often assumed, *a priori*, to be at increased risk for cardiovascular disease (CVD), given the high prevalence of the metabolic syndrome X among them. Lipoprotein (a) [Lp(a)] is an risk factor for development of atherosclerosis and along with dyslipidaemia may add to cardiovascular risk.

Objective: To know the lipid profile variation in Indian women with PCOS.

Materials & Methods: This cross-sectional study was conducted in West Bengal state, India. The subjects enrolled for the study included 180 women with PCOS who were compared with 95 healthy women of the control group; all of them were age and weight matched. Samples were taken after overnight fasting, and then serum lipid levels were analyzed.

Results: The mean age of subjects was 28.71 ± 4.12 years in the PCOS group and 30.14 ± 3.29 years in the control group. The lipid profile parameters were comparable between patients and control subjects. There was a statistically significant difference in the Lp(a) levels between patients with PCOS and normal controls [p = <0.0001]. There were statistically significant increased levels of total cholesterol, VLDL and LDL cholesterol (LDL-C) in PCOS group when compared with the control group (P 0.05) and decreased level of HDL cholesterol (HDL-C).

Conclusion: The changed lipid profile levels may contribute for increased cardiovascular risk in PCOS patients.

MAGNESİUM REPLACEMENT IMPROVE THE METABOLİC PROFİLE İN OBESE AND PRE-DİABETİC PATİENTS WİTH MİLD-TO-MODERATE CHRONİC KİDNEY DİSEASE: A 3-MONTH RANDOMİZED DOUBLE-BLİND PLACEBO-CONTROLLED STUDY

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Background: Magnesium is an essential mineral for many metabolic functions. There is very little information on the effect of magnesium supplementation on metabolic profile in chronic kidney disease (CKD) patients. The aim of the study was to assess the influence of magnesium supplementation on metabolic profile in pre-diabetic, obese, and mild to moderate CKD patients with hypomagnesemia.

Methods: A total of 118 hypomagnesemic, pre-diabetic and obese patients with Cockcroft clearance between 90 and 30 ml/min were enrolled in a randomized, double-blind, placebo-controlled trial. Patients in magnesium group received 365 mg oral magnesium (n=57), and control group received placebo (n=61), once daily for 3 months. Hypomagnesemia defined by serum magnesium level ≤ 1.8 mg/dL in males and ≤ 1.9 mg/dL in females; obesity defined as a BMI ≥30 kg/m2; and pre-diabetes as fasting plasma glucose ≥100 but <126 mg/dl.

Results: At the end of follow-up, changes in the mean of insulin resistance (-24.5% vs. -8.2%, p:0.007), HOMA-IR index (-31.9 vs. -3.3%, p: 0.000), HbA1c (-6.6 vs. -0.16% p:0.000), insuline (-29.6 vs. -2.66%, p:0.000), waist circumference (-4.8 vs. 0.55%, p: 0.000), and uric acid (-0.8 vs. 2.2%, p: 0.004), levels were significantly lower, and albümine were significantly higher (0.91 vs. -2.91% , p: 0.007) in patients who received magnesium compared with placebo (Fig.1). The decrease in the metabolic syndrome (-10.5 vs. -4.9%, p:0.183), obesity (-15.7 vs. -8.2%, p:0.131), pre-diabetes (-17.5 vs. -9.8%, p:0.140), systolic (-5.0 ± 14.8 vs. 0.22 ± 14.9, p:0.053) and diastolic blood pressure (-3.07±9.7 vs. 0.07±9.6, p:0.071) were not reached to a significant level after study.

Conclusion: Our data support that magnesium supplementation improves the metabolic status in hypomagnesemic CKD patients with pre-diabetes and obesity.

IMPACT OF THE METABOLIC SYNDROME ON THE CHARACTERISTICS OF VESSELS WALL, MYOCARDIUM AND EPICARDIAL FAT IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Aim: To investigate the characteristics of vessels wall, myocardium and epicardial fat in patients with heart failure with preserved ejection fraction (HF-PEF) with and without metabolic syndrome.

Materials and Methods: 59 patients with HF-PEF were included. First group – patients without metabolic syndrome (MS) (n = 29), second group – patients with MS (n = 30). Following characteristics were evaluated: arterial stiffness (stiffness index, SI), reflection index (RI), augmentation index (Alp). The function of big vessels was evaluated by phase shift (PS), of the small vessels – by the occlusion index (OI). Investigations were performed by the device "Angioscan"*. Sizes of the heart chambers and the thickness of the myocardium wall and epicardial fat thickness were evaluated echocardiographically.

Results: among the patients from both groups significant changes of the vessels wall and myocardial structure were found. (tab.1) Significant intergroup differences were found in the interventricular septum thickness: 10.3 ± 1.2 mm at the first group and 11.3 ± 1.6 mm at the second (p = 0.01); left ventricle wall thickness: 10.1 ± 1.1 mm at the first group and 11.3 ± 1.6 mm – at the second (p = 0.001); left ventricle myocardium mass: 157.75 ± 46.11 g at the first group and 201.19 ± 58.82 g – at the second (p = 0.005). The epicardial fat thickness was 14.8 ± 1.8 mm at the first group and 36.7 ± 1.7 mm – at the second group (significant, p = 0,001). Tab.1 the characteristics of vessels in patients HF-PEF with and without MS.

Conclusion: among patients with HTN and HF-PEF with and without MS significant changes in the structure of vessel wall and myocardium were found. The presence of MS lead to the more pronounced myocardial remodeling. The epicardial fat thickness is significantly higher among patients metabolic syndrome. *Angioscan diagnostic hardware–software system was used for recording the photoplethysmographic signal via optical sensors mounted on the nail bones of both hands of a subject .

SAFETY AND EFFICIENCY OF SGLT 2 INHIBITOR COMBINING WITH INSULIN IN SUBJECTS WITH DIABETES: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Objective: We aimed to assess the safety and efficiency of the novel sodium glucose co-transporter 2 (SGLT2) inhibitor in combinations with insulin for type 1 and type 2 diabetes(DM).

Methods: We searched Medline, Pubmed, Embase, and the Cochrane Collaboration Library from January 2010 to March 2016, without restriction of language. FDA data and Clinical Trials (http://www.clinicaltrials.gov) were also searched. Study selection, data extraction, evaluation of risk of bias were performed by two persons independently. We refered to the Cochrance system evaluate method to assess the risk of bias and use Q test to evaluate the heterogeneity between studies. We used random effect model to analyse the results by Revman5.3.

Result: 8 trials including 3035 patients were analyzed. Compared with control group, SGLT 2 inhibitor produced absolute reduction in HbA1c (MD –0.54%, 95% CI [–0.68 to –0.40], p=0.07) FPG (MD –0.73 mmol/L, 95 %CI [–1.73 to 0.27], p<0.0001) ,insulin dosage (MD –0.47 U/24h, 95 %CI [–0.98 to 0.05], p<0.00005), body weight MD –1.92kg, 95 %CI [–2.27 to -1.56], p<0.00001) without significant increase in the events of urinary tract infection or 1.16, 95 %CI [0.83,1.64], p=0.92 But the risk of hypoglycemia (or 1.36,95% CI [1.14,1.62],p=0.81) and genital infection with SGLT 2 inhibitors was higher than placebo plus insulin (or 4.48, 95 %CI [2.22, 9.04], p=0.07), but cases were mild and responded to the therapy. According to the subgroup analysis, SGLT 2 inhibitors had the similar effect in effective factors of both T1DM and T2DM, but the risk of hypoglycemia (T1DM or 1.82 [0.63, 5.29], P=0.27 vs. T2DM or 1.35 [1.13, 1.61], P=0.001) and GTI (T1DM or 0.27 [0.01, 7.19], P=0.43 vs. T2DM or 3.03 [0.79, 11.63], P 0.00001) mainly increased in T2DM VS. T1DM.

Conclusion: SGLT 2 inhibitors have improved the HbA1c, FPG and body weight when combined with insulin and decreased the dose of insulin without increasing the risk of UTI. However, SGLT 2 inhibitor was proved to be related to the events of hypoglycemia and GTI , despite SGLT-2 inhibitors appeared to be well tolerated. We suggest that more monitoring should be done on the blood glucose to prevent the events of hypoglycemia and more randomized controlled trials should be planned next step.

DIASTOLIC LEFT VENTRICULAR FUNCTION IN OBESE HYPERTENSIVE PATIENTS TREATED BY ACE INHIBITOR

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Background: ACE inhibition may be protective in Left Ventricular (LV) Diastolic Function that is additional to its blood pressure–lowering effect.

Aim: To evaluate changes in Left Ventricular (LV) Diastolic Function in obese patients with arterial hypertension treated with lisinopril compared with perindopril.

Methods: 72 obese (BMI 33,1 ± 5,3 kg/m2) arterial hypertension (AH) patients (age 50.6 ± 12.6 ys) were randomized to Lisinopril group (n=38) or Perindopril (n=34). All patients underwent clinical, laboratory test and echocardiography in baseline and after 3 months. All patient had normal LV Systolic Function (EF >55%). LV diastolic function was estimated by Doppler echocardiography and Tissue Doppler imaging.

Results: Before the treatment LV diastolic dysfunction was noted in every obese AH patient. 100% patients had LV DF impairment of the I type. Peak mitral filling velocities during early (E) and late (A) diastole E/A ratio = 0,69 ± 0,08, tissue Doppler E/e' ratio = 7,9 ± 0,9. Blood pressure goals were achieved in all patients validating further analysis. In 3 months' follow-up LV diastolic function was improved in the both treatment group. Increased in E/A ratio from 0.68 ± 0,08 to 0.72 ± 0,07 in Lisinopril group and from 0.70 ± 0,009 to 0.74 ± 0,087 in Perindopril group (p<0.01). Decreased in tissue Doppler E/e' ratio from 7.9 ± 0,09 to 6.7 ± 0,69 in Lisinopril group and from 7.8 ± 0,85 to 7.0 ± 0,67 in Perindopril group (p<0.01). Significant trends towards E/e' decrease were demonstrated only in Lisinopril-treated patients (ΔE/e' 1.2 Lisinopril and 0.8 Perindopril , p<0.05).

Conclusion: LV diastolic function in obese AH patients demonstrated impairment of the I type. LV diastolic function was improved in response with ACE inhibitor treatment. Both Lisinopril and Perindopril treatment improved in LV diastolic function parameters, whereas only Lisinopril treatment was more significantly associated with trends in E/e' improvement in 3 months' short-term follow-up.

EVALUATION OF THE POTENTIAL EFFECT OF POLYHERBAL FORMULATION ON INTESTINAL P-GLYCOPROTEIN IN RATS

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Aims/Background: This study was evaluated synergistic effect of Polyherbal formulation (PHF) of *Allium sativum* L., *Eugenia jambolana* Lam., *Momordica charantia* L., *Ocimum sanctum* Linn and *Psidium guajava* L on p-glycoprotein of intestine. These five herbs were traditionally used for diabetes. These herbs are commonly present in ayurvedic product as antidiabetics in India.

Methodology: PHF was prepared by five indigenous herbs. Different doses (50, 100 and 200 mg/kg/day) of was orally administered to Sprague-Dawley rats of different groups for multiple weeks except control groups. Alteration in Pgp expression was evaluated by RT-PCR and western blotting while modulation in activity of Pgp was evaluated using rhodamine 123 as transport substrate by *in-situ* absorption and everted gut sac method.

Results: In PHF pretreated group received 50, 100 and 200 mg/kg/day for seven days, mRNA level decreased by 1.75, 2.45 and 2.37 fold respectively as compared to control. Similarly when PHF at dose of 100 mg/kg/day was given consequently for four weeks maximum decrease in Pgp expression level was observed only after one week and further increase in the treatment duration did not produce significant decrease compared to first week treatment. Pgp mediated transport of rhodamine 123 was significantly decreased with everted gut sac prepared from PHF pretreated rats (one week) compared to those prepared from vehicle treated rats.

Conclusions: In conclusion, we report that PHF pretreatment down regulated the expression of intestinal Pgp and this down regulated intestinal Pgp would result in decreased functional activity. Additionally this down regulated Pgp expression might affect the bioavailability of antidiabetic Pgp substrate drugs.

EFFICACY OF BERBERINE HYDROCHLORIDE ON BIOCHEMICAL PARAMETERS IN INDIAN TYPE 2 DIABETIC PATIENTS

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Objective: To evaluate the efficacy and safety of Berberine Hydrochloride in both newly diagnosed type 2 diabetic patients and patients on oral hypoglycemic agents (OHAs).

Methodology: A randomized open-label interventional clinical study on 41 Indian type 2 diabetic patients including newly diagnosed and those already on OHAs. Study A - 15 newly diagnosed Type 2 Diabetic patients were subjected to Berberine Hydrochloride twice daily for 3 months. Study B - 26 patients with poorly controlled type 2 diabetes were subjected to Berberine HCl along with current therapy. The subjects in both the studies were of both the sexes in age group 35-71 years. Biochemical investigations included fasting blood glucose (FBG) and post prandial blood glucose (PBG) levels, glycated hemoglobin (HbA1c) were carried out.

Results: In study A, significant reduction seen in HbA1C from 7.7± 0.53 - 6.9 ± 0.6%, r = 0.67, P = 0.0057), FBG reduced from 151.53 ± 41.11 mg/dl to 117.3 ± 32.2 mg/dl, r = 0.76, P = 0.0009), PPG reduced from 210.73 ± 47.5 mg/dl to 159.66 ± 57.5 mg/dl, r = 0.86, P = 0.0001). In study B, HbA1C levels decreased from 8.2 ± 1.2 - 7.2 ± 0.8%, r = 0.85, P <0.0001. FBG decreased from 178.83 ± 68.21 to 122.58 ± 19.1 mg/dl, r = 0.59 P = 0.0021 and PBG decreased from 233.62 ± 114.9 to 143.04 ± 28.63 mg/dl, r = 0.65 P = 0.0005. No liver or kidney damage was seen in patients. Hypoglycemia was not seen in any of the patients.

Conclusion: Berberine is a potent, safe oral anti-diabetic for newly diagnosed and poor controlled type 2 diabetic patients.

RELATIONSHIP BETWEEN CARDIOVASCULAR DISEASE RISK AND INSULIN RESISTANCE IN A CAMEROONIAN POPULATION LIVING WITH HIV

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Background: HIV infection is still a worldwide concern despite the recent reduction in related mortality. Increase access to antiretroviral treatment has increased the life expectancy of HIV patients. However, the prevalence metabolic complications are increasing in this population. Given that insulin resistance precedes type 2 diabetes mellitus (known cardiovascular risk factor), we aimed to investigate the relationship between cardiovascular risk and insulin resistance in HIV patients.

Methods: We carried out a cross-sectional study in HIV patients aged 30 to 74 years and followed at the Yaoundé Central Hospital. Clinical examination was done and blood samples were collected to test for lipid profile, glycaemia and C-peptide. Cardiovascular risk was calculated using the Framingham and the DAD risk scores while the HOMA-IR index was used to assess insulin resistance (defined for each value ≥2.1).

Results: A total of 452 patients (80% of women) were included. Their mean age was 44.4 ± 9.8 years and most of them were on antiretroviral therapy. The mean 5-years cardiovascular risk was 1.7% and 1.1% according to Framingham and DAD equations respectively. 47.3% of participants were insulin resistant. When calculated with Framingham equation, the cardiovascular risk was significantly associated to insulin resistance both in univariate and multivariate analysis. However, with the DAD equation, we found no association.

Conclusion: The relationship between cardiovascular risk and insulin resistance in HIV patients depends on the cardiovascular risk score.

11B-HSD1 REGULATION IN HIGH-FAT-DIET INDUCED INSULIN RESISTANT RATS AND RATS TREATED WITH *SUTHERLANDIA FRUTESCENS*

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11βHSD-1 is an enzyme that converts inactive cortisone to cortisol within peripheral tissues and regulates tissue cortisol levels, thus influences glucose regulation. Literatures have implicated the activity of 11β-HSD1 involving glucocorticoid receptor (GR) and phosphoenolpyruvate carboxylkinase (PEPCK), as mediator of insulin resistance (IR) developed with consumption of high fat diet (HFD). At NMMU, a HFD on which rats developed IR within 56 days was established, while extract of *Sutherlandia frutescens*, a South African plant, prevented IR in rats fed HFD. We investigated the role of 11β-HSD1 in the development of observed IR and the effect of *S. frutescens* on the enzyme expression. Using quantitative RT-PCR, periodic (days 7, 14, 28, 56, 86) mRNA expressions of 11β-HSD1, GR and PEPCK were measured in rat liver tissues. Also, 11β-HSD1 protein expression was analysed using immunohistochemistry techniques. There was no significant change in 11β-HSD1 expression up till day 56, but increased mRNA and protein levels were observed at day 86 (i.e 30 days after IR had developed). Increased mRNA levels of PEPCK was observed prior to IR in rats fed HFD, indicating increased gluconeogenesis, but did not increase in rats fed HFD and *S. frutescens*. mRNA levels of GR showed no pattern of GR regulation. Increased 11β-HSD1 activity is possibly a consequence of IR rather than cause, but may play a role in the development of type 2 diabetes, by further enhancing IR. Increased gluconeogenesis was induced via other mechanisms, while *S. frutescens* prevented increased gluconeogenesis in rats fed HFD and *S. frutescens*.

TAURINE SUPPLEMENTATION ENHANCED THE DELETERIOUS EFFECTS CAUSED BY A HIGH-FAT-DIET ON GLUCOSE HOMEOSTASIS OF OVARIECTOMIZED MICE

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Background/Aims: Low levels of estrogens after menopause are associated with weight gain, insulin resistance and type II diabetes. Studies have shown that taurine (TAU) supplementation prevents obesity, glucose intolerance and insulin resistance. Due to the benefits of TAU on

glycemic control, we investigated the effects of TAU on glucose homeostasis of ovariectomized (OVX) mice.

***Experimental Design*:** Three-month-old female C57BL/6 mice underwent OVX. After one-week recovery, mice were divided into 4 groups: chow diet (OVXC), chow diet associated with 3% TAU (OVXCT), high-fat-diet (OVXH), and HFD associated with TAU (OVXHT) during 14 weeks.

Results: TAU supplementation enhanced the deleterious effects of HFD on body weight (OVXH=33.1 ± 0.9; OVXHT = 36.3 ± 0.8 g), retroperitoneal fat (1.18 ± 0.2; 1.83 ± 0.2% BW), plasma cholesterol (110.3 ± 13.2; 165.9 ± 16.5 mg/dl), fasting glycemia (126.5 ± 3.6; 140.9 ± 3.4 mg/dl), and fasting/fed insulinemia (0.73 ± 0.11/1.46 ± 0.20; 1.50 ± 0.23; 2.60 ± 0.52 ng/ml, respectively). OVXHT mice were more glucose intolerant and insulin resistant. Isolated pancreatic islets from OVXH mice challenged to a high glucose solution (2.18 ± 0.71) increased their insulin secretion compared to OVXC (0.58 ± 0.13), while islets from OVXHT mice presented similar secretion (0.78 ± 0.18 ng/islet.h). Akt was less phosphorylated in the muscle and liver from OVXHT, indicating impairment in their peripheral insulin signaling. Also, some genes involved in the oxidation of substrates such as PPARGC1A and PPARG were downregulated in peripheral tissues of OVXHT.

Conclusion: The association of TAU with a HFD in OVX mice increased adiposity and caused glucose homeostasis impairment, probably due to a peripheral insulin resistance in skeletal muscle and liver, and impaired peripheral transcription of genes related to substrate oxidation.

HYPOGLYCEMIC EFFECT OF METHANOLIC EXTRACT OF *ANACARDIUM OCCIDENTALE* LEAVES IN ALLOXAN-INDUCED DIABETIC RATS

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Background: *Anacardium occidentale* Leave (Anacardiaceae), a plant natively grown in wastelands in Africa is used as a folk remedy for diabetes mellitus.

Method: Previous studies, reported the hypoglycemic effect of the aqueous leaf extract of A. occidentale in diabetic rats and its prophylactic activity against the diabetogenic action of streptozotocin. This study evaluated the hypoglycemic effect of a methanolic extract of streptozotocin leaves and its fractions in Alloxan-induced diabetic rats in comparison to Tolbutamide, a reference drug. For moderately diabetic rat, A. occidentale caused a 79.2 % change over 4 hours and Tolbutamide caused a 63.1 % change over this same time period.

Result: When the rat were considered to be severely diabetic, the A. occidentale decreased the blood glucose levels by 20.8% change over four hours and the mean percent change over 4 hours for Tolbutamide was 47.63 %. These values were not considered significant ($p>0.05$).

Conclusion: So the same conclusion can be made about the efficacy of A. occidentale, when compared to the reference drug, Tolbutamide. These results that show that A. occidentale has a similar ability compared with Tolbutamide to lower blood glucose levels.

IS SHIFT WORK ASSOCIATED WITH INCREASED INSULIN RESISTANCE?

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Objective: Shift work is associated with higher risk of metabolic disturbances and cardiovascular diseases. There are contradictory reports on the effect of shift work on lipid parameters in the literature. No studies have investigated any possible association between shift work and serum triglyceride–to–HDL-C ratio (TG/HDL-C ratio). This ratio can be used as a predictor for insulin resistance. The main aim of the present cross-sectional study was to investigate the association between shift work and serum TG/HDL-C ratio, TG, and HDL-C.

Methods: One hundred and forty adult Jordanian employees were recruited. Demographic data, lifestyle habits, clinical parameters, and working patterns data were documented, through a well-structured questionnaire. Serum TG and HDL-C levels were measured, after at least 9 hours fasting, using enzymatic essay procedure.

Results: Compared to daytime workers, shift workers displayed higher TG/HDL-C ratio (p-value = 0.022), higher serum TG levels (p-value = 0.035), and lower HDL-C levels ($r = –0.200$, p-value = 0.016). Among shift workers, 30.5% were found to have a TG/HDL-C ratio >3.5 compared to 8.6% of daytime workers (p-value = 0.002).

Conclusion: In the present study, shift work was shown to be associated with higher TG/HDL-C ratio, higher TG and lower HDL-C levels. These findings might indicate that shift work is associated with increased insulin resistance and, consequently, higher risk of metabolic syndrome and cardiovascular diseases.

THE RELATION OF URINE PHTHALATE METABOLITES IS SPECIFIC FOR TYPE2 DIABETES BUT IS NOT MEDIATED BY OBESITY

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Background: Last year in this congress we have presented results of 170 patients with metabolic syndrome components where and we have found a significant relation of 4 urine phthalate levels to type 2 diabetes and no relation to dyslipidemia and hypertension. We have enlarged the sample to 300 patients and we have analyzed the relation to obesity. The 24 hours samples were sampled in phthalate free bottles. Bisphenol A (BPA) and 15 metabolites of phthalates were evaluated in relation to creatinine excretion. All were analysed with enzymatic cleavage of glucuronide using ultra-high-performance liquid chromatography--electrospray ionization tandem mass spectrometry in one laboratory with External Quality control.

Results: In the correlation analysis we have found only negative significant correlations of phthalate excretion to BMI and waist: In women we have found a signifiant negative correlation of BPA to BMI and waist. We have found 5 significant negative correlations of some pthalates metabolites to BMI in men and 3 in women. Using multiple linear regression with 3 variables- diabetes, hypertension and dyslipidemia only diabetes showed significant results $p<0.05$ in four phthalate metabolites: (mono (3-carboxypropyl) phthalate, mono OH-, OXO-, cx- (mono 2-ethyl--5-hydroxyhexyl) phthalate). In linear regression with two variables (diabetes, BMI) the influence of BMI was slightly negative but not significant in all 4 metabolites.

Conclusion: Urine levels of four phthalate metabolites are significantly related to type 2 diabetes. This influence is not mediated by high BMI, waist, hypertension and dyslipidaemia According to correlation analysiss BMI and waist can be even protective against high phthlate excression.

FARNESOID X RECEPTOR AGONIST OBETICHOLIC ACID RAISES LDL-CHOLESTEROL AND REDUCES HDL-CHOLESTEROL IN THE DIET-INDUCED NASH (DIN) HAMSTER, A NOVEL PRECLINICAL MODEL FOR EVALUATING EFFICACY AND SIDE EFFECTS OF DRUGS TARGETING NON-ALCOHOLIC LIVER DISEASES

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Background: Compared to humans, mice have a different lipid/lipoprotein metabolism and may respond differently to NASH therapies. The Golden Syrian hamster has a lipoprotein metabolism closed to humans and was used to develop a Diet-Induced NASH (DIN) hamster model and evaluate the effects of obeticholic acid (OCA).

Methods: Hamsters were fed for 20 weeks a control chow (CC) diet or a cafeteria (CF) diet, that consists of a choice between CC diet with normal drinking water or a high fat/high cholesterol diet with 10% fructose enriched drinking water. Hamsters under CF diet were then kept on the same diet without (control CF) or with OCA 15mg/kg/day (CF + OCA) for 5 weeks.

Results: Compared with CC, CF diet induced significantly higher body weight, HOMA-IR index, plasma total cholesterol, LDL-C, and ALT levels, by 10%, 46%, 85%, 117% and 27%, respectively. NAS scoring indicated advanced liver steatosis (mean score 2.7± 0.2 for grade 0-3), inflammation (1.3 ± 0.2; grade 0-3), hepatocyte ballooning (2 ± 0.3; grade 0-3) and fibrosis (2.7 ± 0.2; grade 0-4).

Compared to control CF, CF + OCA fed hamsters showed significant body weight loss, but significantly higher plasma cholesteryl ester transfer protein activity by 18%, higher LDL-C levels by 27%, and lower HDL-C levels by 20%. CF+OCA significantly reduced NAS score for inflammation, and tended to reduce total NAS score, but not significantly.

Conclusion: Compared to mouse models, the DIN hamster replicates benefits and side effects of OCA observed in humans and should be useful to evaluate novel drugs targeting NASH.

ROLES OF MICRORNA-21 IN THE PATHOGENESIS OF INSULIN RESISTANCE IN TYPE 2 DIABETES MELLITUS

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Background: The microRNA-21 (miR-21) is involved in numerous pathophysiological processes, including cancer, type 2 diabetes mellitus (T2DM), inflammation and cardiovascular diseases.

Methods: The aim of this study is to evaluate the relationship of miR-21 with insülin resistance (IR) in patients with DM and healthy controls. Serum samples from 80 patients

with T2DM and 20 controls were subjected to Taqman probe-based quantitative reverse transcription-polymerase chain reaction (RT-PCR). The data showed that the serum miR-21 expression level were significantly upregulated in diabetic patients, compared with the healthy controls ($p < 0.001$). Further miR-21 expression level was positively correlated with the IR and HbA1c.

Conclusion: Our study suggested that a higher expression of miR-21 was significantly associated with T2DM. miR-21 is also directly involved in the regulation of insulin secretion. MiRNA-21 may play an important role on IR in DM.

DAPAGLIFLOZIN IMPROVES GLYCEMIC CONTROL, HYPERTENSION AND IS NEUTRAL ON SEVERE RENAL IMPAIRMENT IN UNI-NEPHRECTOMIZED SDT FATTY RAT, A 10-WEEK MODEL OF ADVANCED RENAL COMPLICATIONS AND GLOMERULAR FILTRATION RATE DECLINE

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Background: SGLT2 inhibition (SGLT2i) may not be recommended in type 2 diabetic patients with severe renal impairment. To investigate the effects of SGLT2i, later in the course of diabetic nephropathy, dapagliflozin (DAPA) was evaluated in uni-nephrectomized Spontaneously Diabetic Torii (SDT) fatty rat. This novel hypertensive, obese, type 2 diabetic model, develops advanced renal complications and >50% glomerular filtration rate (GFR) decline within 10 weeks.

Methods: SDT fatty rats underwent unilateral nephrectomy (Unx; n=16) or sham operation (Sham; n=8). After a 1-week recovery, rats had free access to Purina 5008 chow diet and drinking water supplemented with 0.3% salt for 10 weeks. After 3 weeks of diet to enhance kidney complications, 8 Unx rats were treated with DAPA 1mg/kg/day for 7 weeks.

Results: After 10 weeks of diet and compared to Sham rats, albuminuria was 206% higher in Unx control rats, while plasma creatinine clearance and GFR (FITC-inulin injection) were substantially reduced by 46 and 60% (all $p<0.01$ vs. Sham). Histology analysis confirmed advanced glomerulosclerosis, inflammation and fibrosis (all scores $p<0.05$ vs. Sham). Compared to Unx control rats, DAPA treatment of Unx rats for 7 weeks did not change GFR decline, glomerulosclerosis, inflammation and fibrosis scores. Meanwhile, DAPA reduces HbA1c and blood pressure by 3.1% and 19% (both $p<0.01$ vs. control).

Conclusions: Our data suggest that SGLT2i with DAPA has no detrimental effect in uni-nephrectomized SDT fatty rat with advanced renal complications and >50% GFR decline. Whether treatment with DAPA at earlier time point would prevent renal impairment should be investigated.

GLUCOSE FLUCTUATION AND ENDOTHELIAL INJURY ARE CORRELATED WITH PANCREATIC B CELL DYSFUNCTION IN NON- TO PRE-DIABETIC PATIENTS WITH CAD

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Background: Glucose fluctuation (GF) is observed and causes vascular endothelial dysfunction (VED), which is the first step of coronary artery disease (CAD). However, which glucometabolic factor correlates with GF is still unknown. We evaluated the relevant GF causes VED and glucometabolic factor with lengthy oral glucose tolerance test (OGTT).

Methods: We performed a prospective cross-sectional study of 116 never diagnosed dysglycemia (HbA1c5.8±0.4%) patients with CAD as determined by coronary angiography and 4-h OGTT. Blood samples were collected prior to and 4-h after the glucose load to determine endothelial injury factor [von Willebrand factor (vWF) and the ratio of vWF/ a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13 (ADAMTS-13)]. GF was defined maximum glucose – minimum glucose during OGTT. We estimated relation between GF and glucometabolic factors.

Results: vWV ($R=0.255$, $P=0.035$) and vWF/ADAMTS-13 ratio ($R=0.322$, $P<0.001$) were significantly correlated with GF during 4 h OGTT. GF was significantly correlated with HOMA-IR ($R=0.262$, $P<0.001$), Matsuda index ($R=-0.405$, $P<0.001$), insulinogenic index ($R=-0.336$, $P<0.001$), HbA1c ($R=0.281$, $P<0.001$) and disposition index ($R=-0.672$, $P<0.001$). When divided GF [the average value: 122 mg/dL (6.7mmoL/L)] into two groups, impaired category group and preserved category group, multiple logistic analysis showed that, adjusted with age, sex, HbA1c, 1/ insulinogenic index and HOMA-IR, 1/disposition index was independent risk factor for impaired value of GF [Odd ratio (95% Confidence Interval): 69.51 (5.78-835.09), $P<0.001$].

Conclusion: Pancreatic β cell dysfunction is associated with GF-caused vascular endothelial dysfunction in CAD patients with early dysglycemia. Pancreas dysfunction may directly effects on vascular endothelial dysfunction.

THE STUDY OF COAGULATION PROFILE IN DIABETES

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Introduction: Diabetes Mellitus type 2 – formerly non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes – is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. Diabetes Mellitus is a heterogeneous disease affecting metabolism of various compounds including carbohydrates, lipids and proteins and also impairs biological processes such as coagulation homeostasis which cause vascular thrombotic problems. These problems are predominantly manifested as accelerated coagulation, vascular complications, and ultimately as serious problems such as cardiovascular disease and myocardial infarction.

Objectives: To investigate the hemostatic parameters and to assess their relationship with complications in type 2 diabetes mellitus.

Materials and Methods: Coagulation and fibrinolysis parameters were measured in 80 patients with type 2 diabetes, without diabetic microvascular complications and in 40 healthy subjects.

Results: The mean age of diabetic patients and healthy controls was 55.9 ± 8.45 and 48.5 ± 7.23 respectively (p = 0.05). The plasma levels of PAI-1, serum fibrinogen were increased and vWF activity was found to be increased in diabetics as compared to healthy controls. Also, plasma PAI-1 levels and vWF activity were significantly increased in diabetic patients with microvascular complications than those without microvascular complications. Diabetic retinopathy was associated with decreased vWF activity. Diabetic nephropathy was associated with increased PAI-1 levels and vWF activity. Diabetic neuropathy did not show any significant relationship with any of the haemostatic variables. We also compared the PT and APTT of the diabetics and the non-diabetics group. The PT and APTT values were found to be lower in the diabetic subjects as compared to the non-diabetics.

Conclusion: Hypercoagulable state in Diabetes mellitus is responsible for the development of microvascular complications. This procoagulant state not only contributes highly to major vessel diseases but also contributes to microvascular complications as studied in the present research.

ASSOCIATION BETWEEN METABOLIC SYNDROME AND HABITUAL COFFEE CONSUMPTION IN THE KOREAN POPULATION: A CROSS-SECTIONAL ANALYSIS OF THE KOREA NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEYS 2010–2011

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Background: We conducted this cross-sectional study to identify the association between coffee consumption and risk of metabolic syndrome (MetS) in the Korean population.

Methods: Subjects aged 30–79 years in the Fifth Korea National Health and Nutrition Examination Survey conducted in 2010 and 2011 were included (n = 8,246). The self-reported frequency of coffee consumption was classified as non-drinker, <1, 1, 2, and ≥3 cups/day. Among women, the level of coffee consumption was inversely associated with MetS and each component (P_{trend} = 0.002 for abdominal obesity and <0.001 for others). The dose-response inverse association remained significant between coffee consumption and MetS, high triglyceride, and low high-density lipoprotein cholesterol (P_{trend} = 0.001, 0.009, and <0.001, respectively; adjusted for age and body mass index). Compared with women who did not consume coffee, the adjusted odds ratio (OR) for MetS was 0.55 (95% CI, 0.37–0.83) for women who consumed ≥ 3 cups per day (P_{trend} = 0.001). Among women, excluding those receiving medical treatments for hypertension, diabetes, and dyslipidemia, a significantly lower OR for MetS (0.51 [95% CI, 0.29–0.88]) was observed with coffee consumption ≥ 3 cups, and the dose-response inverse association remained significant (P_{trend} = 0.005).

Conclusion: In men, there were no significant associations between coffee consumption and MetS. In conclusion coffee consumption is associated with a lower risk of MetS among Korean women. There was a dose-response inverse relationship between coffee consumption and the prevalence of MetS in Korean women.

REGULATION OF OBESITY AND INSULIN RESISTANCE BY *FOENICULUM VULGARE* AND *ANETHUM GRAVEOLENS* EXTRACT IN HIGH-FAT DIET-INDUCED OBESE RATS

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Introduction: Obesity is a risk factor for developing insulin insensitivity and cardiovascular disease. Adiponectin is a serum protein that is secreted primarily from adipose tissue, with concentrations that are inversely correlated to the body mass index (BMI). Leptin and proinflamatory interleukin-6 (IL-6) are directly proportional with obesity. Natural products *Foeniculum vulgare* and *Anethum graveolens* have been reported to have hypoglycemic and insulin-sensitizing activities.

Methods: In this paper, we explored the effects of combined extract of *Foeniculum vulgare* and *Anethum graveolens* on HFD – induced obesity in rats. We randomly divided Sprague-Dawley male rats into four groups: Control, high fat diet (HFD), HFD with the combined extract (0.045 g/kg/day) and HFD with the combined extract (0.45 g/kg/day) groups. Diabetic profile parameters (fasting blood glucose level, serum insulin, HOMA-IR), rat weight, total cholesterol, triglyceride, HDL-C, LDL-C, liver function, kidney function, adiponectin, leptin, IL-6, liver malondialdehyde, glutathione and glutathione peroxidase activity were measured in all groups. Feeding rats HFD for 8 weeks developed features of insulin resistance. These features presented in increased body weight, hyperglycemia, hyperinsulinemia, hypercholesterolemia (with increased LDL-Cholesterol and decreased HDL-Cholesterol) and hypertriglyceridemia and also decreased adiponectin levels and increased leptin and IL-6 levels and decreased glutathione and glutathione peroxidase activity. The combined extract (both doses) treatment decreased fasting glucose significantly, improved levels of diabetic profile parameters, lipid profile, liver and kidney function and elevated adiponectin, decreased leptin and IL-6 and decreased oxidative stress.

Conclusion: Our results suggested that the combined extract of *Foeniculum vulgare* and *Anethum graveolens* is a unique natural medicine against obesity.

THE EFFECTS OF ACUTE ENDURANCE TRAINING ON PLASMA VISFTAIN CONCENTRATION AND INSULIN LEVELS IN DIABETIC RATS

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Introduction: Recently, visfatin was identified as an adipokine, while is predominantly secreted from visceral adipose tissue both in humans and mice. Regular exercise by far induces anti- inflammatory effects, improves insulin sensivity and thus offers protection against these conditions. This study has been conducted to elucidate: 1- Effects of 8 weeks endurance training on visfatin concentration and its response to exercise. 2- to determine whether endurance exercise training could improve insulin resistance index in diabetic rats.

Methods: 60 male Wistar rats were fed a normal diets and randomly assigned to either a sedentary (n = 29) or endurance exercise trained group (n = 31). Exercise group underwent 8 weeks of treadmill exercise training (increasing from 10 – 25m/ mins day $^{-1}$) five times per week. Diabetes was induced by administrating STZ to rats.

Results: Results showed that the decrease in plasma visfatin as induced by exercise training most likely caused by body composition changes and weight loss. Plasma insulin concentration were elevated in exercise group when compared with control group and more importantly a significant decrease in insulin resistance were observed.

Conclusion: These results indicate that the endurance training affects body weight, and lipid profile. More importantly, it shows that significant decrease in plasma visfatin concentration has been induced by increased visfatin consumption in adipose tissue, muscle and liver in order to promote fatty asids mobilization, oxidation in peripheral tissues and gluconeogenesis.

METFORMIN AND ITS EFFECTS ON LEFT VENTRICULAR HYPERTROPHY IN INSULIN RESISTANT NON-DIABETIC PATIENTS WITH CORONARY ARTERY DISEASE (MET-REMODEL STUDY): RATIONALE, DESIGN, AND BASELINE CHARACTERISTICS OF MET-REMODEL STUDY

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Aim & Objective: Left Ventricular hypertrophy (LVH) is associated with an increase in mortality risk, often caused by high blood pressure (BP), but it occurs in patients with "normal" blood pressure too. Apart from BP, the other main risk factors linked to LVH are insulin resistance (IR) and central obesity. Metformin is an insulin sensitizer that reduces IR, causes weight loss and also stimulates the enzyme AMPK, all of which has been shown to regress LVH. We hypothesize that these pleotropic properties of Metformin may regress LVH.

Methods: The MET-REMODEL study is an ongoing, randomised control trial investigating the ability of Metformin in regressing LVH in 68 non-diabetic, normotensive CAD patients with left ventricular hypertrophy who are insulin resistant and/or prediabetic. Primary aim is to compare the effect of metformin therapy with that of placebo on changes in left ventricular mass indexed to height$^{1.7}$ (LVMI$^{1.7}$) as measured using state-of-the-art (MRI technology. Secondary end points include, changes in endothelial function, insulin resistance/prediabetes, central obesity as measured by MRI and changes in biomarkers such as NTproBNP, oxidised LDL, troponins and F2-Isoprostanes. A total of 187 patients were screened for this study and 36% (n = 68; 25% female, age 65 ± 8.2, fasting insulin resistance index 4.305 ± 4.803, $HbA_{1C\ 40.2}$ ± 2.61 mmol/mol, mean SBP/DBP 131/76, BMI 31.8±3.58 kg/m^2, LVMI$^{1.7}$ 101 ± 19.3 for men; 79.3±11.4 for women) met the study inclusion/exclusion criteria.

Conclusion: Recruitment was completed in August 2016. This trial may identify a novel way to regress LVH which often persists despite optimum medical therapy and may make a substantial contribution to the management of CAD with LVH by expanding our understanding of the disease mechanisms in LVH.

GENETIC ASSOCIATION OF CDH13 WITH LEFT VENTRICULAR MASS AND MODIFICATION BY SLEEP DURATION: THE BCMAS STUDY

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Objective: To assess the association of common variants from genome-wide association studies of adiponectin levels (CDH13 rs4783244, ADIPOQ rs10937273, rs1063538 and rs6773957, WDR11FGF rs3943077, CMIP rs889140, and PEPD rs889140) and left ventricular mass (LVM), and examine the potential effect modification by sleep duration in a young population with risk of metabolic syndrome.

Methods: Subjects aged 15-28 years were recruited from Beijing Child and Adolescent Metabolic Syndrome (BCAMS). All participants underwent a medical examination including color Doppler echocardiography, blood biomarkers analysis, lifestyle questionnaire, and genotype analysis.

Results: Among the seven loci, CDH13 rs4783244 SNPs was correlated with the level of Ln-adiponectin (β = -0.225 per T allele, P = 2.96×10-6). In multiple linear regression analysis, CDH13 rs4783244 was associated with increased LVM index (β = 1.522 per T allele, P = 0.009) after adjusted for age, sex, and BMI; and further adjusted for adiponectin (β = 1.541, P = 0.011), while there was no significant association between other selected loci and LVM or LVM index. In addition, we observed a statistically significant interaction effect between the CDH13 rs4783244 and sleep duration (P for interaction = 0.014) for LVM index. The association of CDH13 rs4783244 with LVM index were significantly attenuated by short sleep duration (β = -1.215, P = 0.378 for sleep time <7 h/day and β = 4.285, P = 0.001 for > 9h/day).

Conclusions: Our findings suggest that CDH13 rs4783244 is a novel susceptibility locus for cardiac structure, and this genetic association is modified by sleep duration.

BASAL HYPERINSULINEMIA BEYOND A THRESHOLD PREDICTS ADVERSE CARDIAC EVENTS AT ONE YEAR AFTER CORONARY ANGIOGRAM IN TYPE 2 DIABETES MELLITUS

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Objective: The aim of the present study was to evaluate factors associated with the cardiac outcome at one year after coronary angiogram in patients with type 2 diabetes mellitus and to compare the outcomes with nondiabetics.

Methods: A retrospective cohort study was carried out in subjects who underwent coronary angiogram for an evaluation of CAD, with follow-up data available for period of 12 months. The data consisted of 208 type 2 diabetic and 75 non-diabetic patients. Clinical, anthropometric and other biochemical risk factors of the study participants were recorded. Univariate and multivariate cox proportional hazard regression analyses were performed to evaluate the relation between the cardiovascular risk factors and major adverse cardiac events (MACE).

Results: At 1 year, MACE was observed in 50 (24.04%) type 2 diabetic subjects. The optimal cut-off for insulin was 20 IU/μl with sensitivity and specificity of 88% (95% CI: 0.71-0.96) and 74% (95% CI: 0.65-0.81) respectively. After adjustment for potential confounders hyperinsulinemia (>20 Symbol IU/ml) was significantly associated with MACE [adjusted hazard ratio (HR): 3.03, 95% CI:1.41-6.54, p = 0.005]. Interestingly, the MACE rate in individuals with insulin levels <20 μIU/ml (10.2%) and non-diabetics (12%) (p = 0.676) appears to be same.

Conclusions: In addition to severity of the CAD at the baseline, basal hyperinsulinemia beyond a threshold strongly predicts adverse cardiac events at one year in type 2 diabetes mellitus. Those below the threshold, appears to be having a risk equivalent to non-diabetics.

THE RELATIONSHIP BETWEEN MELATONIN, DEGREE OF LIVER FIBROSIS AND PREDICTORS OF CARDIOVASCULAR RISK IN PATIENTS WITH TYPE 2 DIABETES AND NAFLD

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Objective: The study was involved 23 patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease (NAFLD). 16 persons (72%) were diagnosed with slight degree fibrosis (F0-F1 on METAVIR), 4 people (18.2%) – with the stage of mild fibrosis (F2-F3 on METAVIR).

Methods: All patients were underwent determination of melatonin excretion of albumin and in daily urine, as well as the determination of homocysteine in the blood. The average level of melatonin excretion in urine was 89.50 ± 16.66 mg/day, the mean homocysteine was 11.19 ± 2.29 mmol/L. The level of urinary albumin excretion was 14.29 ± 7.10 g/mL.

Results: It was found a direct correlation between the fibrosis stage on METAVIR and melatonin levels in the urine (r = 0.24 ± 0.07, t = 3.52). A direct correlation between homocysteine and melatonin excretion (r = 0.43 ± 0.06, t = 6.67), and between the melatonin and urinary albumin excretion (r = 0.20 ± 0.07, t = 2.79) were revealed.

Conclusion: Thus, the level of excretion of melatonin in the daily urine can be not only a marker of liver fibrosis, but also a predictor of cardiovascular events in patients with type 2 diabetes mellitus and NAFLD.

EVALUATİON OF PERİPHERAL ARTERY DİSEASE İN ELDERLY PATİENTS WİTH TYPE 2 DİABETES MELLİTUS

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Introduction: Peripheral arterial disease (PAD) refers to the manifestation of atherosclerosis in the lower limb distal to the aortic bifurcation. PAD prevalence and incidence are both sharply age-related, rising >10% among patients in their 60s and 70s. The aims of the study were to determine the frequency of peripheral artery disease (PAD) by ankle

brachial index (ABI) in patients with type 2 diabetes mellitus (DM), and to compare the risk factors for PAD between patients with age ≥60 years and patients with age <60 years.

Subjects and Methods: The study population included 525 (patients with age≥60 years) (mean age; 68.0±6.6) and 284 (patients with age<60 years) (mean age; 51.8±5.8 years) patients with DM. Demographic and biochemical data were collected, retrospectively. PAD disease was evaluated by ABI. ABI was calculated and considered to be abnormal ABI if less than or equal to 0.9. However, if ABI was higher than 0.9 considered normal ABI.

Results: Abnormal ABI levels were detected in 157 (31.2%) of patients with age ≥60 years and 35 (15.4%) patients with age <60 years *(p=0.001)*. Patients with age ≥60 years, mean levels of ABI were found to be 0.69±0.2 in abnormal ABI group and 1.22 ± 0.8 in normal ABI group. However, mean levels of ABI were found to be 0.74 ± 0.5 in abnormal ABI and 1.35 ± 0.9 in normal ABI, in patients with age <60 years. History of cardiovascular disease, history of stroke, dyslipidemia, hypertension, neuropathy, retinopathy, nephropathy and smoking were statistically significantly associated with ABI in all diabetic patients ($p<0.05$).

Conclusions: The frequency of PAD was higher in patients with age ≥60 years than that of patients with age <60 years. Smoking, increased levels of duration of diabetes mellitus, fasting and postprandial glucose, HbA1c, triglyceride and chronic complications such as cardiovascular disease, stroke, dyslipidemia, hypertension, neuropathy, retinopathy and nephropathy were associated with risk of PAD in diabetic elderly patients.

APPLICATION OF THE MINIMAL MODEL IN SUBJECTS TREATED WITH SGLT2 INHIBITORS

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The minimal model (MM) has been widely used to assess insulin sensitivity (S_I) during intravenous and oral glucose tolerance tests. SGLT2 inhibitors (SGLT2i), a new treatment for type 2 diabetes mellitus (T2DM), increase urinary glucose excretion (UGE), thus providing an insulin-independent mechanism for glucose disposal that was not originally considered in the minimal model. Therefore, applying the classical MM to subjects treated with SGLT2i can overestimate S_I. To address this issue, an additional term is added to the MM, explicitly modeling UGE and thereby enabling an appropriate S_I estimate.

Methods: The classical oral glucose minimal model ($OGMM_c$) and updated model ($OGMM_{UGE}$) were applied to data from a 2-period crossover study in 20 healthy subjects receiving a single dose of canagliflozin 300 mg or placebo. Plasma glucose and insulin, and UGE were measured over 6h and glomerular filtration rate (GFR) was estimated using Modification of Diet in Renal Disease. Virtually no UGE was observed with placebo and mean estimated S_I was 5.2 10^{-4}/min/(μU/ml) using either model. With canagliflozin, estimated S_I was 5.5 versus 10.0 10^{-4}/min/(μU/ml), $p = 0.002$, with $OGMM_{UGE}$ and $OGMM_c$, respectively. As a single dose of SGLT2i is not expected to alter S_I in healthy subjects, the similar S_I values between placebo- and canagliflozin-treated subjects when using $OGMM_{UGE}$ ($p >0.05$) confirms that the updated model is appropriately accounting for UGE, whereas $OGMM_c$ overestimated S_I by 80%.

Conclusion: $OGMM_C$ should not be used in SGLT2i-treated subjects. These results suggest that $OGMM_{UGE}$ can be used, although further validation is required in subjects with T2DM.

THE APPLICATION OF TRIGLYCERIDE GLUCOSE INDEX IN IDENTIFYING ISOLATED POSTCHALLENGE HYPERGLYCEMIA IN POSTMENOPAUSAL WOMEN

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Objective: Isolated postchallenge hyperglycemia (IPH) (2-h plasma glucose >= 200 mg/dL and fasting plasma glucose <126 mg/dL), usually occurred in old age, is an early form of diabetes mellitus (DM). The purpose of this study is to investigate the relation of triglyceride glucose index (TyG) and other variables with IPH in postmenopausal women.

Research Design and Methods: We recruited 555 postmenopausal women without previous DM history in the study. Fasting blood samples were collected for measurement of biochemistry. All participants received 75 gram oral glucose tolerance test (OGTT) to identified subjects with IPH. Logistic regression was used to explore TyG index, a simple measure of insulin resistance, defined as ln (TG x glucose/2) and different variables including hemeostasis model assessment of insulin resistance (HOM-IR) and HbA1c in the association with IPH. Receiver-Operator curve (ROC) was performed to evaluate the performance of associated factor and constructed score.

Results: In univariate analysis, the best two predictors of IPH are HbA1c (Odds ratio [OR] 9.675, 95% confidence interval [CI] 4.32-21.68) and TyG (OR 3.931, 95% CI 2.59-5.96) while HOMA-IR had a OR of 1.364 (95% CI 1.20-1.55). The area under the ROC curve were 0.72 (95% CI 0.66-0.79) and 0.77 (95% CI 0.70-0.83) for HbA1c and score 1 (2.154 x HbA1c + 2.113xTyG).

Conclusions: HbA1c is the best single predictor of IPH in postmenopausal women. The score constructed using HbA1c and TyG are useful to identify subjects with undiagnosed IPH with better performance than HbA1c alone.

DNA ADVANCED GLYCATION END PRODUCTS (DNA-AGES) ARE ELEVATED IN URINE AND TISSUE IN AN ANIMAL MODEL OF METABOLIC SYNDROME

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Objective: More precise identification and treatment monitoring of prediabetic/diabetic individuals will require additional biomarkers to complement existing diagnostic tests.

Methods: Candidates include hyperglycemia-induced adducts such as advanced glycation end products (AGEs) of proteins, lipids, and DNA. The potential for DNA-AGEs as diabetic biomarkers was examined in a longitudinal study using the *Lepr*db/db animal model of metabolic syndrome. The DNA-AGE, *N2*-(1-carboxyethyl)-*2´*-deoxyguanosine (CEdG) was quantified by mass spectrometry using isotope dilution from urine and tissue of hyperglycemic and normoglycemic mice. Hyperglycemic mice displayed a higher median urinary CEdG value (238.4±112.8 pmol/24 h) than normoglycemic mice (16.1±11.8 pmol/24 h). Logistic regression analysis revealed urinary CEdG to be an independent predictor of hyperglycemia. Urinary CEdG was positively correlated with fasting plasma glucose for hyperglycemic animals and with HbA1c for all mice. Average tissue-derived CEdG was also higher in hyperglycemic mice (18.4 CEdG/106 dG) than normoglycemic mice (4.4 CEdG/106 dG). Urinary CEdG was significantly elevated in *Lepr*db/db mice relative to *Lepr*wt/wt, and tissue CEdG values increased in the order *Lepr*wt/wt <*Lepr*wt/db <*Lepr*db/db. Preliminary data from a clinical trial involving patients with type 2 diabetes will also be presented.
Conclusion: These data suggest that urinary CEdG measurement may provide a non-invasive quantitative index of glycemic status and augment existing biomarkers for the diagnosis and monitoring of diabetes.

THE RELATIONSHIP BETWEEN MAGNESIUM LEVEL AND INSULIN RESISTANCE IN PATIENTS WITH METABOLIC SYNDROME

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Objective: Magnesium, plays a major role in regulating insulin effect and insulin mediated glucose uptake. The aims of this study was to evaluate the relationship between magnesium level and insulin resistance using HOMA-IR (homeostasis model of insulin resistance) index.in patients with metabolic syndrome.

Patients and Methods: Fourty patients (20 males, 20 females) who met the criteria for metabolic syndrome defined as in ATP III enrolled in the study. Serum fastuing glucose, insulin and magnesium levels were evaluated, retrospectively. Insulin resistance (IR) was estimated using the homeostasis model assessment (HOMA).

Results: The mean age of the studied patients was 59.0 ± 11 years (age range of 40-66 years). Mean HOMA-IR and magnesium levels were measured 2.9 ± 0.5 and 2.0 ± 0.7 mgr/dl (normal range 1.5-2.6), respectively. And also, magnesium levels were negatively correlated with HOMA-IR levels (r - 0.750, p = 0.03).

Conclusion: Low serum magnesium levels may related to insulin resistance in patients with metabolic syndrome. Future stuudies are needed.

MANAGEMENT OF DIABETES IN PRIMARY CARE

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Purpose: We wanted to describe how primary care clinicians care for patients with type 2 diabetes.

Methods: We undertook a cross-sectional study of 95 primary care clinicians and 822 of their established patients

with type 2 diabetes from 4 practice-based. Clinicians were surveyed about their training and practice. Patients completed a self-administered questionnaire about their care, and medical records were reviewed for complications, treatment, and diabetes-control indicators.

Results: Participating clinicians (average age, 45.7 years) saw an average of 32.6 adult patients with diabetes per month. Patients (average age, 59.7 years) reported a mean duration of diabetes of 9.1 years, with 34.3% having had the disease more than 10 years. Nearly one half (47.5%) of the patients had at least 1 diabetes-related complication, and 60.8% reported a body mass index greater than 30. Mean glycosylated hemoglobin (HbA1c) level was 7.6% (SD 1.73), and 40.5% of patients had values <7%. Only 35.3% of patients had adequate blood pressure control (<130/85 mm Hg), and only 43.7% had low-density lipoprotein cholesterol (LDL-C) levels <100 mg/dL. Only 7.0% of patients met all 3 control targets. Multilevel models showed that patient ethnicity, practice type, involvement of midlevel clinicians, and treatment were associated with HbA1c level; patient age, education level, and practice type were associated with blood pressure control; and patient ethnicity was associated with LDL-C control.

Conclusions: Only modest numbers of patients achieve established targets of diabetes control. Reengineering primary care practice may be necessary to substantially improve care.

Introduction: In 2012, visits to primary care physicians accounted for 62.7% of all office visits in Kuwait, and diabetes mellitus ranked third, accounting for 3.1% of illness-related diagnoses.[1] Patients with type 2 diabetes often have acute or chronic comorbid health problems that force the clinician to prioritize and address the most pressing or symptomatic problems first.[2-6] The situation is further complicated by the lack of access to a complete multidisciplinary diabetes health care team or by the lack of systems within primary care practices to provide ongoing support for this chronic disease.[7] In this article we describe the care provided by primary care clinicians to their patients who have type 2 diabetes using data from 3 sources: reports from physicians on their training and the patient care strategies they use to treat diabetes; surveys of patients about their diabetes care; and medical record reviews to determine medications used for diabetes and cardiovascular risk factor control, indicators of glycemic control, and diabetes-related complications. Our purpose was to describe the processes and outcomes of care of type 2 diabetes achieved by clinicians and their patients in member practices from 4 practice-based research networks (PBRNs). In particular, we examined practice design strategies for diabetes care, the composition of the health care team, the complexity of the health problems experienced by patients with type 2 diabetes (including comorbid conditions), control of diabetes (including cardiovascular risk-factor control), and the spectrum of treatment provided by their clinicians.

ANTIHYPERGLYCEMIC EFFECT OF INDORENATE INDUCED BY A 5-HT2AGONIST ACTION

Enrique Hong; Abigail Silva-Arzave

Cinvestav, I.P.N.

The role of 5-hydroxytryptamine in the regulation of glycemia has been a controversial item for some time, there are recent findings suggesting that 5-HT1A increment the glycemia while 5-HT2 receptors do the opposite. Therefore, we decided to investigate the effect of indorenate, a central antihypertensive agent exerting this action by 5-HT1A central receptor stimulation, but also possessing a 5-HT2 peripheral receptor stimulation. Since less than 1 % of the oral administered dose penetrates into the CNS, most of the compound could stimulate the 5-HT2 peripheral receptors leading to an antihyperglycemic effect. The oral dose of glucose (2 g/kg) to fasted Wistar rats was followed by a hyperglycemia that was maximal one hr later, this effect was suppressed by the previous administration of an oral dose of 10 mg/kg of indorenate, however, metformin at an oral dose of 300 mg/kg only produce a slight, but significant decrease in hyperglycemia. Pelanserin, a 5-HT2 antagonist, blocked the effect of indorenate, but WAY 100635, a 5-HT1A agonist, did not. Indorenate also increase the glucose velocity needed to maintain blood glucose levels constant in an euglycemic insulin clamp in anesthetized Wistar rats. Indorenate (5mg/kg) also mantained its antihyperglycemic effect in a model of metabolic syndrome in wistar kyoto rats. The present data suggest that indorenate may have a potential therapeutic usefulness in both, metabolic syndrome and type 2 diabetes, particularly in those suffering from hypertension.

ADIPOKINE PROFILES OFINSULIN SENSITIVE OBESITYAND INSULIN RESISTANCE OBESITY AMONG CHINESE CHILDREN: THE BCAMS STUDY

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Background: Obesity and insulin resistance coexist in most humans, however, a unique group of obese individuals, who exhibit better insulin sensitivity than expected for their adiposity. We aimed to analyze whether dysregulation of adipokines secretion could discriminate between insulin sensitive obesity(Obsens)versus insulin resistance obesity(Obres)phenotypes early in children.

Methods: This cross-sectional study included 1212 Chinese obese children (BMI ≥95th percentile, aged 6-18 years). Insulin resistance was determined by using homeostasis model assessment of insulin resistance index (HOMA-IR >3). Serum adipokines including leptin, High-molecular-weight(HMW)adiponectin, resist in, fibroblast growth factor 21 (FGF21), retinol binding protein 4 (RBP-4) and secreted protein acidic and rich in cysteine (SPARC) were determined by ELISA.

Results: After adjustment for potential confounders, Obsens had a more favorable adipokine profile than Obres: higher HMW adiponectin (P <0.001), and lower leptin (P <0.001), RBP-4 (P = 0.001),and SPARC (P = 0.015). Elevated levels of SPARC (OR = 1.15per SD, 95 CI = 1.027-1.29, P = 0.015), RBP-4 (OR =1.23, 95% CI = 1.07-1.41, P = 0.003), and leptin/HMW adiponectin(OR = 2.42, 95% CI = 2.0-2.92, P <0.001) were independent predictors of Obres. In addition, compared with those who had no abnormality of above-noted adipokines, children with 3 adipokine abnormalities had a dramatically lower odds of being Obsens (OR = 0.251, 95% CI = 0.12-0.45), and simultaneously a higher risk of having MS (OR = 2.92, 95% CI = 1.58-5.76).

Conclusions: Our findings suggest that healthy adipokine profile is associated with insulin sensitive obesity in children, and adipokine dysregulation may play an important role in obesity-associated insulin resistance and metabolic disorders early in childhood.

ASSOCIATIONS AMONG IMPAIRED FASTING GLUCOSE, HYPERTRIGLYCERIDEMIA, AND HYPERINSULINEMIA IN U.S ADULTS

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Evidence suggests deleterious relationships exist among impaired fasting glucose (IFG), hypertriglyceridemia, and hyperinsulinemia. However, few population studies have examined these associations.

Purpose: Examine race and gender stratified associations among combinations of glucose and triglyceride values and odds of hyperinsulinemia using a nationally representative sample of U.S. adults.

Methods: Sample included non-Hispanic white and black male (n=2106) and female (n=2323) adult (≥20 years of age) participants in the 2007-2012 National Health and Nutrition Examination Survey. Upper quartile of fasting insulin demarcated hyperinsulinemia. Logistic regression models were created for the analyses.

Results: Analyses in non-Hispanic white men [odds ratio (OR) 2.84] and non-Hispanic black men (OR 4.50) revealed significantly ($P \leq 0.001$ for both) greater odds of hyperinsulinemia in euglycemic men with hypertriglyceridemia. Analysis in non-Hispanic white women revealed significantly greater odds of hyperinsulinemia in euglycemic women with hypertriglyceridemia (OR 2.87, P = 0002) and in those with IFG and normal triglycerides (OR 10.11, P<0001). Analysis in non-Hispanic black women revealed significantly greater odds of hyperinsulinemia only in euglycemic women with hypertriglyceridemia (OR 4.25, P=0.003). Overall, the odds of hyperinsulinemia were found to be three to five times greater in men and five to seven times greater in women with both IFG and hypertriglyceridemia.

Conclusion: Approximately 1/3 of men studied had similar risk profiles predictive of hyperinsulinemia. Elevated glucose was predictive of hyperinsulinemia only in non-Hispanic white women. These data suggest that IFG alone is less predictive of hyperinsulinemia in three out of four groups.

TEN-YEAR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK ESTIMATION FOR POSTMENOPAUSAL WOMEN WITH ISOLATED POSTCHALLENGE HYPERGLYCEMIA

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Aim: Isolated postchallenge hyperglycemia (IPH), defined as fasting glucose <126 mg/dL and 2-h glucose ≥200 mg/dL, is an early form of diabetes mellitus (DM). The purpose of this study was to estimate the 10-year atherosclerotic cardiovascular disease (ASCVD) risk in postmenopausal women with IPH.

Methods: The study is a pooled analysis of individual data from subjects underwent oral glucose tolerance test (OGTT) at a teaching hospital. The 10-year risk for ASCVD was calculated by using the Pooled Cohort equations. Logistic regression models were used to explore the risk of having high 10-year ASCVD risk scores (≥5%) among women of different glucose tolerance status.

Results: The women with IPH had higher systolic blood pressure and worsened lipid profile than those without IPH. We calculated their 10-year risk scores under two different scenarios: (1) if their DM undiagnosed, (2) if their DM diagnosed. The median estimated 10-year risk increased significantly from 3.7% (scenario 1) to 7.1% (scenario 2). Eleven out of 53 IPH women (20.8%) with 10-year risk score <5% initially (scenario 1) were re-categorized to risk category of ≥7.5 % once the women were identified as early DM (scenario 2). The results of logistic regression showed that IPH was independently positively associated with 10-year ASCVD risk scores ≥5%.

Conclusion: Our results demonstrated that postmenopausal women with IPH were characterized by unfavorable cardiovascular risk profile and high estimated 10-year ASCVD risk. Knowing the women's hidden DM status would significantly alter their risk categorization.

Q192R AND L55M POLYMORPHISMS IN PAROXONASE 1 AND I/D POLYMORPHISM IN ANGIOTENSIN-CONVERTING ENZYME GENES ARE ASSOCIATED WITH CORONARY ARTERY DISEASE AND TYPE 2 DIABETES IN ASIAN INDIANS

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The incidence and prevalence of type 2 diabetes (T2D) and coronary artery disease (CAD) are increasing at alarming rates, worldwide. The purpose of present study was to investigate genetic variants in paroxonase 1 (PON 1) and angiotensin-converting enzyme (ACE) genes and risk of developing CAD in Asian Indian populations. A total of 1024 individuals (412 angiographically confirmed CAD patients; 152 with CAD+T2D, and 460 healthy controls) were included in this cross-sectional study. Anthropometric and clinical estimations including BMI, WHR, body fat, TG, TC, HDL, LDL, VLDL and glucose were done in all the subjects. We studied genetic polymorphisms in PON1 (Q192R and L55M) and ACE (I/D) genes using PCR-RFLP method. Results shows a pronounced abdominal obesity as represented by WHR in CAD and CAD+T2D subjects compared to healthy controls. Dyslipidemia was more predominant in all the CAD and CAD+T2D subjects, compared to controls ($p<0.005$). Insulin resistance was significantly higher in T2D+CAD subjects compared to CAD, and healthy controls. Logistic regression analysis of the data shows a significant association of Q192R polymorphism with CAD (OR; 2.23 (1.47-3.37) and CAD+T2D (OR; 3.41 (1.97-5.89), $p<0.001$]. Also, the risk of CAD was more pronounced in T2D subjects ($p<0.05$), compared to controls. Significantly low level of HDL-cholesterol was observed in CAD and CAD+T2D subjects carrying R-allele compared to Q-alleles of PON1 gene. However no significant association was observed in L55M gene polymorphism with CAD and CAD in T2D subjects. Furthermore, DD genotype of ACE (I/D) gene polymorphisms was associated with the risk of CAD [OR; 1.85 (1.31-2.60) $p<0.001$]. The frequencies of the R allele of PON1 gene and D allele of ACE gene were significantly higher in cases compared to control subjects ($p<0.005$). However, no significant differences were observed in the biochemical parameters in different genotypes of PON1 and ACE genes in CAD and T2D+CAD subjects. In conclusion, PON 1 (Q192R) and ACE (I/D) gene polymorphisms are associated with greater risk of CAD and severity of diabetes related complications in Asian Indians.

IMEGLIMIN PRESERVES BETA CELL FUNCTION AND MASS IN MALE ZUCKER DIABETIC FATTY RATS

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Aims: Progressive insulin resistance and loss of beta cell function and mass are primary defaults in type 2 diabetes mellitus. Imeglimin has been shown to decrease beta cell apoptosis against various acute stresses (high glucose; cytokines). The purpose of this study was to investigate Imeglimin effect on the delay in onset and subsequent control of diabetes progression in a Type 2 Diabetes model, the Zucker Diabetic Fatty rat (ZDF).

Methods: 7-week old ZDF rats were treated orally with Imeglimin 150mg/kg bid or vehicle for 5 weeks. Glucose tolerance, pancreatic insulin content, beta cell mass, apoptosis and proliferation were measured at the end of treatment.

Results: Imeglimin treatment induced a significant improvement of glucose tolerance (-33%, $p<0.05$), increased insulin levels both in the basal state and in response to glucose (+77%, NS) compared to controls. The insulinogenic index DI/DG (+165%, $p<0.05$) was increased demonstrating Imeglimin benefit on beta cell function. In parallel, Imeglimin increased pancreatic insulin content (+109%, NS). An irregular islet architecture was observed in ZDF control pancreases while Imeglimin treatment preserved islet architecture and increased significantly beta cell mass (+41%, $p<0.01$). In addition Imeglimin decreased significantly the proportion of apoptotic beta cells within islets (-52% vs ctrl, $p<0.05$) and increased significantly the proportion of proliferative beta cells (+111% vs ctrl, $p<0.001$).

Conclusion: Imeglimin improved beta cell function and slowed down the disease progression in ZDF rat, by preserving beta cell mass and islet architecture with a decrease in beta cell apoptosis and an increase in beta cell proliferation.

HYPERTENSION AND DIABETES MELLITUS IN CARDIOVASCULAR DISEASE

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Background: Cardiovascular diseases (CVDs) are the major causes of mortality in persons with diabetes, and many factors, including hypertension, contribute to this high prevalence of CVD. Hypertension is approximately twice as frequent in patients with diabetes compared with patients without the disease. Hypertension may induce multiple changes in lipoproteins and oxidation-peroxidation processes. Ox-LDL is an important risk factor in this respect.

Methods: The study was proposed to assess the LDL susceptibility to lipid peroxidation (LDL ox) in two study groups of elderly patients (aged 70 ± 18 years): a group of patients with cardiovascular disease (group I) and a group of patients with cardiovascular disease associated with type 2 diabetes mellitus (NIDDM) and hypertension (group II). The LDL susceptibility to *in vitro* induced lipid peroxidation was evaluated following its incubation with a prooxidant system.

Results: Our results showed the susceptibility of LDL to in vitro oxidation was increase in group II of patients compared with a group I (10.05 ± 4.91 v.s. 5.26 ± 2.34 mmoli MDA / dL serum) and constitute an evidence that the prevalence of cardiovascular disease is higher in individuals with diabetes and hypertension.

Conclusion: The results of this study indicate that oxidative processes increase in hypertension and cause increasing level of serum Ox-LDL. Diabetes mellitus and hypertension are interrelated diseases that strongly predispose an individual to atherosclerotic cardiovascular disease. The prevalence of coexisting hypertension and diabetes appears to be increasing in industrialized nations because populations are aging and both hypertension and NIDDM incidence increases with age.

PANCREATIC FAT ACCUMULATION IS DRIVEN BY ENVIRONMENTAL RATHER THAN GENETIC FACTORS: A CLASSICAL TWIN STUDY

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Several studies showed that intrapancreatic fat accumulation is associated with beta-cell dysfunction. Pancreatic fat can be quantitatively assessed by non-contrast-enhanced computed tomography (CT). The role of genetic and environmental factors in pancreatic lipid accumulation is unclear. Therefore, we sought to evaluate the contribution of

genetics and the environment on pancreatic lipid content within a cohort of healthy adult twin pairs.

We investigated 77 twin pairs (154 twin subjects; 98 women, 56 men) with a 256-slice CT-scanner, of whom 47 were monozygotic (MZ) and 30 were dizygotic (DZ) same gender pairs. Using non-enhanced CT images we measured the average value of pancreatic attenuation (Hounsfield [HU] unit) in three regions of interest (head, body and tail). Blood samples were collected before the CT scan. Intra-pair correlations were calculated and structural equation model was used for evaluating additive genetic (A), dominant genetic (D) and unique environmental (E) components.

Main clinical and laboratory findings of the twins were: age 56.1±9.4 years, BMI 27.7±5.3 kg/m^2, fasting glucose 97.5±25.7 mg/dL, HbA1c 5.5±1.0%, C-peptide 2.3±1.4 ng/mL, LDL-cholesterol 134±39 mg/dL, HDL-cholesterol 62±14 mg/dL, triglycerides 132±73 mg/dL (mean±SD). Average pancreatic attenuation was 47.2±11.3 HU in MZ and 47.6±11.8 HU in DZ twins. The intra-pair correlation between HU values were somewhat stronger in MZ as compared to DZ twins (rMZ=0.498, p<0.001; rDZ=0.080, p=0.674). Using the structural equation model, a predominant environmental influence (E: 59%) and a moderate additive genetic dependence (A: 41%) was found. Dominant genetic influence was not identified (D: 0%).

We found a moderate genetic and a much stronger environmental dependence of pancreatic lipid accumulation in our twin cohort indicating that environmental factors and lifestyle characteristics are predominantly involved in the development of fat accumulation in the pancreas.

INSULIN RESISTANCE IS ASSOCIATED WITH DECREASED BLOOD LEVEL OF HOMOARGININE

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Background: Recent studies indicate an association of low levels of homoarginine (hArg) in blood and high cardiovascular risk. Diabetes-related micro- and macrovascular complications are the major causes mortality in patients with diabetes. Thus hArg may be potentially useful for prediction of adverse cardiovascular events in patients with diabetes. The aim of this study was to compare the levels of plasma hArg in patients with or without insulin resistance which have cardiovascular disease.

Material and Methods: Blood samples from 45 patients aged from 30 to 77 years with pathology of heart left ventricular outflow tract were analyzed. Ten patients had insulin resistance state (impaired glucose tolerance or type 2 diabetes). Plasma samples from healthy regular blood donors aged from 30 to 61 years were compared as reference group. Plasma hArg levels were determined in deproteinized samples after ortho-phthalic aldehyde precolumn derivatization by means of reversed phase HPLC using Agilent 1100 chromatograph.

Results: The hArg levels in patients were significantly lower than in reference group (p<0.0001). Patients with insulin resistance had the lowest hArg levels compared to other patients (p=0.006). Level of hArg was inversely correlated with body mass index (r_s=-0.34; p=0.024).

Conclusion: HArg should be considered as new potential marker of cardiovascular complications in patients with insulin resistance.

NOVEL ORAL GLUCOSE LOWERING DRUGS COMPARED TO INSULIN ARE ASSOCIATED WITH LOWER RISK OF ALL-CAUSE MORTALITY, CARDIOVASCULAR EVENTS AND SEVERE HYPOGLYCEMIA IN TYPE 2 DIABETES PATIENTS

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To investigate if novel oral glucose lowering drugs (GLDs) compared with insulin were associated with risk of all-cause mortality, cardiovascular disease (CVD [fatal/non-fatal events]) and severe hypoglycaemia in a real world setting.

During 2013 to 2014 all type 2 diabetes patients identified as new users of novel GLDs, i.e. either dipeptidyl peptidase-4 inhibitors (DPP-4is) or sodium glucose co-transporter-2 inhibitors (SGLT-2is) or insulin treatment in the Swedish Prescribed Drug Register were included and followed in the National Patient- and Cause of Death Registers. Novel GLD and insulin groups were propensity score matched covering patient characteristics, co-morbid-

ities and drug treatment. Cox-regression models were used to estimate relative risks.

In all 37,603 patients initiated new therapy with novel GLDs and insulin, 33.4% and 66.6% respectively. After matching both groups consisted of 10,879 patients each and were similar at baseline. The novel group consisted of 19% and 81% new users of SGLT-2i and DPP-4i, respectively, whereof the former where 100% dapagliflozin. Median follow-up time (patient-years) was 1.51 (16,304) and 1.53 years (16,306) for novel and insulin groups, respectively. The novel group was associated with 44% (HR [95% CI] 0.56 [0.49-0.64]), 15% (0.85 [0.73-0.99]) and 74% (0.26 [0.12-0.57]) lower risk of all-cause mortality, CVD and hypoglycemia compared to insulin group respectively. Similar results were observed in both on-treatment and intention-to-treat analysis.

This observational study shows that novel glucose lowering drugs were associated with lower risk of all-cause mortality, CVD and severe hypoglycemia compared to insulin. New studies are encouraged to further elucidate these findings.

CARDIOVASCULAR AND ALL-CAUSE MORTALITY RISK ASSOCIATIONS WITH NEW USERS OF SGLT-2I OR DPP-4I VERSUS INSULIN IN THE TREATMENT OF TYPE 2 DIABETES

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To investigate the associated risk of all-cause mortality and cardiovascular disease (CVD) for sodium-glucose-cotransporter-2-inhibitors (SGLT-2is) or dipeptidyl peptidase-4 inhibitors (DPP-4i) separately compared to insulin. Type 2 diabetes patients identified as new users of either DPP-4i, SGLT-2i (100% dapagliflozin), or insulin during 2013 July 1st to 2014 December 31st in the national Swedish Prescribed Drug Register were included and followed in National Patient- and Cause of Death Registers. New users of dapagliflozin and DPP-4i were separately propensity score matched (1:2 and 1:1, respectively) with insulin patients. Cox-regression models were used to estimate relative risks. Patients treated with dapagliflozin (n = 2047) and DPP-4i (n = 10,279) were accordingly matched with insulin patients (n=4094 and n=10,279), respectively. Crude numbers (incidence per 1000 patient-years) for all-cause mortality and fatal/non-fatal CVD events for the dapagliflozin vs. DPP-4i analyses were 22 (9.8) and 106 (21.9) vs. 18 (16.8) and 79 (32.7), respectively. Compared to insulin, dapagliflozin was significantly associated with lower risk of all-cause mortality and CVD by 56% and 49% respectively, see table. Corresponding numbers for DPP-4i vs. insulin were 41% and 13% (non-significant), respectively. Similar results were observed in both on-treatment and intention-to-treat analysis. In conclusion, new use of dapagliflozin was associated with lower risk of both all-cause mortality and CVD compared to new use of insulin; while new use of DPP-4i was associated with lower all-cause mortality but no significant difference in CVD. Altogether, these results from clinical practice seem to be aligned with results reported from recent clinical CVD-outcome trials.

CUMULATIVE HEALTH CARE COSTS FOLLOWING INITIATION OF DAPAGLIFLOZIN OR INSULIN THERAPY: A 12-MONTHS COMPARATIVE PROPENSITY MATCHED STUDY

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New user T2DM patients of dapagliflozin or insulin were identified during 2013-2014 and followed in the mandatory Swedish Prescribed Drug Registry and the National Patient Register, respectively. Individual patient-level data were linked using unique personal identification numbers. Patients receiving dapagliflozin were propensity score matched (1:2) with insulin patients. Inpatient visits, outpatient visits, and drug dispenses were extracted from the National Patient and Prescribed Drug Registers. Medication costs were based on ATC codes, inpatient/outpatient care costs were estimated using Diagnosis Related Groups. Mean cost per patient was estimated for incremental 3-month intervals.

In total 2,047 dapagliflozin patients were matched with 4,094 insulin patients. Patients were followed for up to 12 months (427 dapagliflozin patients and 864 insulin pa-

tients). At baseline, 3 to 6 months prior to treatment initiation, mean 3 month per patient health care cost was $546 for dapagliflozin and $549 for insulin patients. Costs increased in both groups following treatment initiation, yet, the increase was 38% higher in insulin compared to dapagliflozin patients ($941 and $1300 at 3 months, respectively). Over the observation period, cumulative per patient healthcare costs for insulin patients remained higher (approx. 36%) than for dapagliflozin. The cost difference was mainly driven by higher costs for inpatient care for insulin patients.

Over 12 months, cumulative per patient healthcare costs were consistently higher for patients newly initiated on insulin than dapagliflozin. New studies are encouraged to further elucidate these findings.

THE ROLE OF THE COMPLEMENT SYSTEM ACTIVATION AMONG PATIENTS WITH ABDOMINAL OBESITY

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Background: The abdominal obesity is associated with a low-grade chronic inflammatory status, to which the complement system is an important contributor. However, the studies of C3-convertase functional activity haven't been taken yet.

Aim: To evaluate a potential association between hsCRP level and C3-convertase stabilization of the classical pathway of complement system activation in middle-aged individuals with abdominal obesity at low cardiovascular risk. Patients and methods: A pilot study, including 45 patients without evidence of atherosclerosis at low CVD risk in the next 10 years according to SCORE, was designed. Abdominal obesity was detected according to the IDF criteria (2009). The C3-convertase functional activity (%) - a key enzyme complex of the classical pathway complement activation, were assessed by using original techniques.

Results: Analysis included 45 participants (mean age: 41(9) years; body mass index: 27(5) kg/m^2; and 47% male). Mean lipid values were as follows: total cholesterol: 5.4 (1) mmol/l; LDL-C: 3.8 (1) mmol/l; HDL-C: 0.98 (0.3) mmol/l; triglycerides 2.5 (1.5 – 2.1) mmol/l. 27 (60%) participants of the sample had signs of abdominal obesity. There were found significant differences in the hsCRP level of patients with abdominal obesity and without it ($p<0,01$). The median of hsCRP level of patients with abdominal obesity was 6.5 mg/l (3.3 – 8.2) and 2 mg/l (0.8 – 1.6) in patients without abdominal obesity. The activity of stabilized C3-convertase was high (mean 18.5 (7.6)%) in the majority of patients (82%), independently of BMI, WC, blood pressure, levels of TG, LDL-C, HDL-C and hsCRP.

Conclusion: The observed fact of stabilization of C3 convertase, apparently, can serve as a predictor of the autoimmune nature of abdominal obesity. The association between obesity and innate immune system need to be studied in larger samples.

THE IMPACT OF OBESITY ON THE THROMBOSIS RISK AMONG LOW CARDIOVASCULAR RISK INDIVIDUALS

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Aim: To evaluate the mannose binding lectin associated serine protease (MASP) activity of the lectin pathway of the complement system activation among in middle-aged individuals at low cardiovascular risk.

Patients and Methods: A pilot study was designed that includes 30 patients without evidence of atherosclerosis, with low CVD risk in the next 10 years according to SCORE. Abdominal obesity was detected according to the IDF criteria (2012). The MASP activity and the cholesterol of modified LDL level were assessed using original techniques.

Results: Analysis included 30 patients (mean age: 41(9) years; body mass index: 27(6) kg/m^2; and 53% male). Among them 23 % (7) with overweight, 27 % (8) with obesity. 18 (63%) participants of the sample had signs of abdominal obesity (9 male and 9 female). Mean lipid values were as follows: total cholesterol: 5.4 (1) mmol/l; LDL-C: 3.7 (1) mmol/l; mLDL -C: 1.04 (0.4) mmol/l; HDL-C: 0.97 (0.2) mmol/l; triglycerides 1.85 (1.2 – 2.5) mmol/l. Median of the fasting glucose – 5.4 (4.9 – 5.5) mmol/l. 7 patients with obesity demonstrated the high MASP activity (over 10%).The MASP activity was associated with mLDL-C (Spearman up to 0.3, $p<0.05$), independently of LDL-C and other variables. Significant differences in the MASP activity among patients with abdominal obesity and without it ($p< 0,05$) were found. The median of the MASP activity among patients with abdominal obesity was 8.5% (5 – 13), while the median of the MASP activity level among patients without abdominal obesity was 4% (0 – 9).

Conclusion: The discovered information about high MASP activity among patients with general obesity at low risk of cardiovascular disease can serve as a predictor of the risk

of thrombosis. Determination of the functional MASP activity analysis opens a qualitatively new approach to risk assessment of thrombosis and possible therapeutic intervention.

DYSLIPIDEMIA IN PREGNANT WOMEN AND THE AGE-RAGE AXIS IN MOTHERS AND THEIR NEONATES

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Objective: The receptor for advanced glycation end-products (RAGE) has been implicated as one factor that may affect insulin signaling and perpetuate insulin resistance (IR) and inflammation. Its soluble form, sRAGE, may act as a signaling decoy by binding AGEs, thereby dampening RAGE signaling. Lower levels of sRAGE have been found to correlate with higher Coronary Vascular Disease (CVD) risk. Pregnancy is well known as a physiological status of insulin resistance and studies have shown elevated serum AGEs in women with gestational diabetes. Our study measures lipid panels, sRAGE and AGE status in healthy pregnant women at term and their newborns. LMW-AGEs reflect AGE catabolism and renal excretion, therefore studying them coupled with sRAGE explores the AGE-RAGE axis.

Methods: We studied 64 healthy, non-diabetic pregnant women at term aged 34.1 ± 4.2, their newborns and 30 non pregnant women as controls. Total cholesterol, triglycerides, LDL-C, HDL-C were measured by standard autoanalyzer methods. Total and low molecular weight AGEs were measured by fluorescence. Serum sRAGE was measured by an enzyme-linked immunosorbent assay (R&D Systems Inc., Minneapolis, MN, USA).

Results: Eighty seven percent of pregnant women displayed hypertriglyceridemia (HTG); 67% showed TG >150 mg/dl; 16% TG >300 mg/dl and 4.5% TG> 400 mg/dl. TG was 267.3 ± 60.0*; HDL-C 71.4 ± 14.7; LDL-C 101.9 ± 38.9*; TG 230.6 ± 85.5* mg/dl respectively and TG/HDL 3.31 ± 1.43* (*p <0.01 vs controls). AGEs did not differ and sRAGEs were significantly lower between pregnant women: 0.97 ± 0.58 mg/ml and controls: 1.52 ±0.46 mg/ml ($p<0.01$). Of note, newborns had markedly higher levels of sRAGE and a higher ratio of LMW/total AGEs compared to their mothers and controls; sRAGE = 2.31 ±1.02 mg/ml in babies and 0.97 ± 0.58 mg/ml in mothers ($p<0.01$). LMW/total AGE = $2.94 \pm 1.19 \times 10^{-2}$ in babies and $1.19 \pm 0.61 \times 10^{-2}$ in mothers ($p<0.01$).

Conclusions: Our data reveals the magnitude of insulin resistance in late pregnancy as evidenced by almost 90% prevalence of HTG and high TG/HDLC ratio in this population. We confirm previous reports showing lower sRAGE in this condition, strengthening the hypothesis for a role of RAGE in IR and dyslipidemia. This data, combined with the unexpected finding of higher LMW-AGEs, coupled with much higher sRAGE in neonates suggest new avenues for the study of the AGE-RAGE axis in development and insulin resistance states.

EFFECT OF FIBROBLAST GROWTH FACTOR 21-SECRETING HUMAN ADIPOSE-DERIVED MESENCHYMAL STEM CELLS ON THIOACETAMIDE-INDUCED HEPATIC FIBROSIS IN MICE

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Liver fibrosis refers to the scarring process that occurs after liver damages. It was recently reported that mesenchymal stem cells (MSCs) has anti-fibrotic and anti-inflammatory effects and fibroblast growth factor 21 (FGF21) has effects to regulate lipid accumulations. Here, we investigated the effect of fibroblast growth factor 21(FGF21) secreting adipose tissue-derived mesenchymal stem cells (ADSCs) on liver fibrosis in an animal model and elucidated the underlying mechanism. Liver fibrosis was induced by intraperitoneal injection of 200 mg/kg body weight thioacetamide (TAA) thrice a week for 8 weeks. ADSCs were transfected with a plasmid expressing FGF21 under CMV promoter and confirmed the secretion of FGF21 in media. ADSCs or FGF21 secreting ADSCs (FGF21-ADSC) ($1x10^6$ cells/mouse) were then injected into TAA-induced hepatic fibrosis mice through tail vein. Liver tissue was harvested for analysis of histological changes and serum samples were obtained for analysis of biochemical parameters. Hematoxylin & eosin staining and Masson's Trichrome staining of liver tissue sections showed that fibrotic area was decreased in ADSC- or FGF21-ADSC-treated mice compared with saline-treated mice. In addition, Oil-red-O staining showed a decrease of lipid accumulation in ADSC-treated mice and further decrease in FGF21-ADSC-treated mice. ADSC transplantation decreased serum ALT and AST levels and FGF21-ADSC further decreased these levels. Based on these results, we suggest that transplantation of FGF21 secreting ADSCs might have better therapeutic effects than ADSCs only against liver fibrosis.

INSULIN RESISTANCE AND CARDIOVASCULAR RISKS IN ADOLESCENT OBESE GIRLS

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During puberty a mild insulin resistance (InRES) is observed; however, InRES, if persists, could have an impact for cardiovascular disease during adulthood. Identifying the subset of adolescent girls with obesity and insulin excess could provide valid information in assessing cardiovascular risk in young women. The aim of this study was to investigate insulinogenic response to glucose stimulation, and differences in adiponectin and leptin concentrations and correlate them with clinical features in obese and normal weight adolescent girls.

Material and Methods: We studied 144 girls (age 13-18 yrs) after body mass index was calculated, we selected two groups: 64 normal weight (NOR, BMI 22+0.3) and 80 obese (OBS, BMI 30+0.5). In all girls we took a medical history, anthropometric measurements, physical examination, and serum levels of metabolic and hormonal profiles were investigated. InRES was estimated based on the indices driven from the results of a standard 75-g OGTT.

Results: All tested girls had normal fasting plasma glucose concentration, irrespective of their BMI. Results are in the table (mean + SE).

Conclusion: Adolescent OBS girls have significant insulin resistance, severe hyperinsulinemia after glucose stimulation and they have 3-fold higher frequency of prediabetes. OBS girls have marked cardiovascular biomarkers: increased blood pressure, decreased adiponectin and increased leptin. These results may forecast significant cardiovascular comorbidities in the adulthood.

INVESTIGATING THE MECHANISM BY WHICH HUMANIN IS INVOLVED IN GLUCOSE-STIMULATED INSULIN SECRETION AND B-CELL SURVIVAL

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Objective: Humanin (HN) is a 24 amino acid polypeptide transcribed from an open reading frame within a region of mtDNA.

Methods: It has been shown to have cytoprotective properties against Alzheimer's disease-, myocardial infarction-, and diabetes-associated cellular insults. We have previously reported that HN improves survival of β-cells in response to cytokine-induced cell death and delays onset of diabetes in the NOD mouse. We also demonstrated that HN directly associates with insulin molecules and that glycemia regulates HN expression in rodent insulin-producing cells. Therefore, we hypothesize that endogenous HN is important for glucose-stimulated insulin secretion.

In order to examine the role of endogenous HN in insulin-producing cells, we sought to knockdown (KD) HN. Mouse HN (mHN) expression was effectively KD with siRNA targeted to the nuclear sequence in MIN6 cells. We then used siRNA KD to assess the role of mHN in insulin secretion. Upon mHN KD, glucose-stimulated insulin secretion was completely abolished in MIN6 cells when compared to transfection with a control scrambled siRNA. We then investigated the potential mechanism by which this is mediated. Our preliminary data suggests that HN KD leads to reduced ATP production in MIN6 cells, and this may contribute to impaired glucose-stimulated insulin secretion.

Conclusion: In summary, our preliminary data demonstrate that HN is a novel binding partner for insulin and is essential for glucose-stimulated insulin secretion. This is the first description for a physiologic role for HN in a biologic process and presents additional avenues for discovery in β-cell pathophysiology.

EXENDIN-4 ATTENUATES DEXAMETHASONE-INDUCED MUSCLE ATROPHY THROUGH REGULATING ATROPHY-RELATED GENES EXPRESSION

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Muscle atrophy is defined as decreased muscle weight and loss of muscle function caused by the reduction of muscle structural proteins. Glucagon-like peptide-1 (GLP-1) and GLP-1 receptor (GLP-1R) agonists has been widely used as anti-diabetic drugs. In this current study, we investigated whether exendin-4 (Ex-4), GLP-1R agonist, has any effects on dexamethasone (Dex)-induced muscle atrophy both in *vivo* and in *vitro* models. In mice, administration of Dex (10-weeks-old male C57BL/6J mice, 20 mg/kg/i.p./daily for 8 days) induced severe muscle atrophy, which re-

sulted in the impairment of muscle function. In contrast, Ex-4 treatment (100 ng/mouse/i.p./daily for 12 days) recovered muscle function as shown by the increased myofiber size and myogenic factor expression (e.g. Myogenin and MyoD), as well as the decreased expression of muscle atrophy-related genes compared with Dex-administrated mice. In line with in *vivo* data, Ex-4 treatment (20 nM for 6 hours) significantly decreased the expression of muscle atrophy-related genes including Atrogin-1 and MuRF-1 in differentiated C2C12 cells compared with Dex-treated cells. Ex-4 also inhibited glucocorticoid receptor (GR) expression and its cellular translocation from cytosol into nucleus, which may potentially affect expression of genes related to muscle atrophy. Collectively, our data suggests that Ex-4 may prevent muscle atrophy through the regulation of muscle atrophy-related genes and muscle regeneration factors.

OVERWEIGHT AND OBESITY AMONG ELEMENTARY PUPILS IN THE CENTRAL SCHOOLS OF THE DIVISION OF OLONGAPO CITY, PHILIPPINES: INCIDENCE AND CAUSATIVE FACTORS

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Objectives: To determine the incidence of overweight and obesity among elementary school children and to determine the possible associated causative factor(s) that led to promotion of overweight and obesity.

Subjects: Subjects were 71 boys and 46 girls ages 11 and 12 who are overweight or obese based on the BMI for Children and Adolescents calculator, in the four Central Schools of the Division of Olongapo City, Philippines.

Methods: A descriptive study in which subjects in the registry completed demographic and weight history. Body Mass Index (BMI) measurement was used to determine and categorize subjects as overweight or obese. Questionnaire on parental and subject's weight profile, dietary intake, physical and non-physical activity (sedentary behavior) and community characteristics were used as part of the evaluation and assessment.

Results: The overall incidence of overweight and obesity is 10.67%. The incidence rate of overweight is 5.01% and obesity is 5.65%. Mean BMI of overweight boys is 21.45 and girls is 22.25, while the mean BMI of obese boys is 25 and girls 27.5. The girls have greater rate of overweight/obese mothers while the boys have greater rate of overweight/obese fathers. There is a higher incidence of overweight/obesity among the low socio-economic group (monthly family income less Php 20,000). Despite having higher rate of the boys' parents reaching college, there are more overweight and obese boys than girls. Majority of subjects eat breakfast (92%boys; 93%girls) and yet are overweight/obese. A greater consumption of processed food, canned food, fastfood, artificially-flavored sweetened drinks, and iced tea is noted among overweight and obese subjects. A greater number of overweight and obese subjects are involved into either competitive and/or leisure sports as compared with their parents. More boys than girls are involved. For non-physical activity or sedentary behavior both subjects were noted to spend time to either watching TV, playing computer games or spending time in the internet. Considering community characteristics, neighborhood was deemed safe by boys' (70%) and girls' (69%) parents. More girls (71%) have no access to recreational facilities than boys (65%) but both subjects have easy access to fast food chains and restaurants.

Conclusion/Application: The causative factors that lead to overweight and obesity are multifactorial. Approach (es) to reverse or prevent the process need to be addressed carefully and individually depending on where the problem is attributed.

COMPOSITE ENDPOINT ANALYSIS OF DAPAGLIFLOZIN VERSUS SAXAGLIPTIN AS ADD-ON THERAPY IN PATIENTS WITH TYPE 2 DIABETES INADEQUATELY CONTROLLED WITH METFORMIN

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Options to advance oral therapy in patients with uncontrolled type 2 diabetes (T2DM) on metformin include sulfonylureas, dipeptidyl peptidase-4 inhibitors (DPP-4i) or sodium–glucose cotransporter-2 inhibitors (SGLT2i). Unlike sulfonylureas (often prescribed because of low cost), DPP-4i and SGLT2i have a low risk of hypoglycemia due to glucose-mediated insulin secretion (DPP-4i) or insulin-independent effects (SGLT2i; are not directly affected by beta-cell dysfunction or insulin resistance). This *post-hoc* analysis from a double-blind, randomized, 24-week clinical trial (NCT01606007) in poorly controlled (8% ≤ HbA1c <12%), metformin-treated (≥1500mg/day) patients with T2DM, compared dapagliflozin 10mg (n = 179) with saxagliptin 5mg (n = 176). Endpoints included HbA1c, fasting plasma glucose (FPG), 2-hour postpran-

dial glucose (2h-PPG) and body weight, as well as composite outcomes comprising combinations of HbA1c, body weight, systolic blood pressure and no documented hypoglycemia. Both dapagliflozin and saxagliptin demonstrated efficacy (mean change from baseline [standard error]), however, dapagliflozin significantly reduced HbA1c (–1.20 [0.08] vs –0.88 [0.08]%; p=0.004), FPG (–32 [3] vs –14 [3]mg/dL; p<0.0001) and 2h-PPG (–70 [6] vs –36 [4]mg/dL; p<0.0001) to a greater extent than saxagliptin. More dapagliflozin than saxagliptin patients achieved the composite endpoint of HbA1c reduction ≥0.5% and weight loss ≥2kg (38% vs 12%; p<0.0001). There were no major events of hypoglycemia in either treatment group, however, 6% of dapagliflozin- versus 0.6% of saxagliptin-treated patients experienced genital infections. In conclusion, dapagliflozin demonstrated greater glycemic efficacy than saxagliptin with an additional beneficial effect on body weight. The safety profiles of both treatments were consistent with previous observations from their respective clinical trial programs.

HBA1C AND BMI CHANGES OVER 2 YEARS IN PATIENTS WITH TYPE 2 DIABETES (T2DM) INITIATING SECOND-LINE ORAL THERAPY: RESULTS FROM THE UNITED KINGDOM CLINICAL PRACTICE RESEARCH DATALINK (UK CPRD)

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The aim of this study was to determine use of second-line therapies and their associations with HbA1c and weight change in people with T2DM. The analyses included patients aged 18–75 years initiating second-line oral treatment (add-on or switch) between 1-August-2013 and 30-April-2015 (n = 10,817) in the UK CPRD; only patients remaining on the same therapy throughout were considered.

At the time of second-line treatment initiation, 59.1% were male, mean age was 57.4 years, HbA1c 9.1%, time since diagnosis 5.1 years and time since first-line therapy initiation 2.7 years, with 84.0% of patients having received first-line metformin. The most common second-line therapies were sulfonylureas (SU; 45.4%) and dipeptidyl peptidase-4 inhibitors (DPP4i; 30.3%). HbA1c decreased at 6- and 24-months with every second-line therapy except "any-other-monotherapy" at 24-months; overall, 47.8% of patients achieved HbA1c<7.5% (24-months). Patients on metformin+sodium glucose cotransporter-2 inhibitors (SGLT-2i), or metformin+DPP4i or DPP4i-monotherapy, experienced weight reductions (24-months: –5.5, –2.2 and –0.3kg, respectively); weight increases were observed for all other second-line therapies.

In conclusion, UK patients with T2DM are initiated on second-line therapy after a long time (~3 years) and at high HbA1c levels. Most patients are initiated on metformin (first-line), with SU the most frequently selected second-line treatment. Clinically significant reductions are observed in HbA1c at 6-months following second-line therapy, but this is less pronounced at later timepoints. Weight loss is only observed with SGLT-2i and DPP4i therapies. Overall, glycemic targets are not being achieved by more than half of patients, suggesting an urgent need to overcome therapeutic inertia.

REFERENCE VALUES OF EIGHT NOVEL PROPOSED INSULIN RESISTANCE BIOMARKERS IN A COLOMBIAN POPULATION

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Background: The gold standard for insulin resistance (IR) diagnosis is the hyperinsulinemic-euglycemic clamp, a complicated procedure. Novel IR biomarkers have been proposed, but little is known about their population distribution.

Objective: To describe the distribution of plasma levels of 8 novel proposed IR biomarkers: Brain-derived neurotrophic factor (BDNF), follistatin, fibroblastic growth factor-21 (FGF21), myonectin, myostatin, pigmented epithelium-derived factor (PEDF), YKL-40, and retinol binding protein-4 (RBP4) in Colombian adults with different degrees of IR.

Methods: We collected fasting plasma samples from 81 apparently non-diabetic subjects aged 30-69 years and measured by commercial immunometric techniques the concentration of biomarkers, plus other relevant clinical and laboratory indicators of IR. The study was approved by the Universidad de los Andes IRB.

Results: Mean participant characteristics were: Age 55, body-mass index 26.4 Kg/m2, HbA1c 5.5%, fasting plasma

insulin 18.9 microUI/mL. Fourty-four percent were males. Mean plasma concentrations +/- SD of the eight biomarkers were: BDNF: 107+/-37 ng/mL, follistatin: 2517+/-830 pg/mL, myonectin: 170+/-68 ng/mL, FGF-21: 185+/-129 pg/mL, PEDF: 11.2+/-2.4 ng/mL, YKL-40: 742+/-563 pg/mL, myostatin 2963+/-1890 pg/mL, RBP-4 76.4+/-44.9 microg/mL. Males had significantly higher plasma FGF-21, myostatin, PEDF and RBP4. RBP4 showed the largest sex difference (median 89.1 microg/m in males, 67.2 in females, p=0.005). Age was positively correlated with PEDF (Spearman's r=0.27, p=0.022) and YKL-40 (r=0.28, p=0.015), while HbA1c correlated positively with myostatin (r=0.32, p=0.007) and YKL-40 (r=0.44, p<0.001).

Conclusion: Potential IR biomarkers vary widely and may be influenced by age and gender. Some of them would require the development of age and sex-specific reference values. RBP4 (microg/mL) Myostatin (pg/mL) PEDF (ng/mL) FGF21 (pg/mL) Frequency BDNF (ng/mL)YKL40 (pg/mL) Follistatin (pg/mL) Frequency Myonectin(ng/mL)

EFFECT OF INSULIN GLARGINE 300 U/ML AND GLARGINE 100 U/ML ON CLINICAL OUTCOMES AMONG INSULIN NAÏVE PATIENTS WITH TYPE 2 DIABETES: A MEDICAL CHART REVIEW STUDY IN THE US

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Background: Insulin glargine 300 units/mL (Gla-300) became available in the US in 2015. This real-world study examined changes in clinical measures before and after initiation of insulin glargine 100 units/mL (Gla-100) and Gla-300 among insulin-naïve patients with type 2 diabetes (T2D).

Methods: Data were obtained from patient charts in clinical practice. Each physician completed case report forms for one Gla-100 and four Gla-300 initiators. Insulin-naïve patients were on Gla-100/Gla-300 for ≥30 days. Generalized linear mixed-effect models examined whether glycated hemoglobin A1c (A1C), daily basal insulin dose, and hypoglycemic episodes differed among groups before and after treatment, controlling for demographics, comorbidities, diabetes complications, and medication history.

Results: The included 298 Gla-300 and 92 Gla-100 initiators had comparable mean age (53.8 years), percentage of males (54.4%) and mean follow-up time (4 months). Patients who experienced a hypoglycemic event during the 6-month pre-treatment period were more likely to initiate Gla-300 than Gla-100 (12.9% vs 8.5%, $P = 0.29$). After treatment initiation, both groups experienced reductions in A1C (least squares mean: 1.21% for Gla-300, 1.12% for Gla-100; $P < 0.001$ for both groups) with no between-group difference ($P = 0.62$). Compared to Gla-100, Gla-300 was associated with lower hypoglycemic risk (relative risk ratio: 0.31, 95% CI: 0.12-0.81; $P = 0.018$) at similar daily insulin doses.

Conclusion: This study revealed that both Gla-300 and Gla-100 were effective in reducing A1C among insulin naive patients with T2D. Risk of hypoglycemia was lower for Gla-300 with comparable daily insulin doses.

Disclosure: Gupta, Liebert, Lee: employees of Kantar Health, which received funding from Sanofi US, Inc. to conduct this study. Tong: was an employee of Pro-Unlimited, under contract with Sanofi US, Inc. during time of the study. Wang and Preblick: employees of Sanofi US, Inc. Stella, Cali: employees of Sanofi Global.

LOWER SOLUBLE RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS IN ADOLESCENTS WITH OBESITY FROM GUANAJUATO: ASSOCIATIONS WITH INSULIN RESISTANCE DYSLIPOPROTEINEMIA

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Background: The worldwide prevalence of obesity in adolescents is about 35% while in Guanajuato, Mexico it is 42%. Obesity in this age group may be accompanied by insulin resistance and its consequent increased cardiovascular risk (CVR), however, not all the mechanisms by which this occurs are yet known. The receptor for advanced glycation endproducts (RAGE) has been implicated as one factor that may affect insulin signaling and perpetuate insulin resistance and inflammation. Its soluble form (sRAGE) may act as a decoy from excessive ligand signaling, including AGEs. Lower levels of sRAGE have been found to correlate with higher CVD risk. In adults, advanced glycation end products (AGEs) and its receptors are associated with cardiovascular complications, diabetes and chronic renal insufficiency, but there are scant data in obese adolescents. For this reason we set out to investigate the status of sRAGE and its association with cardiovascular risk markers in adolescents with and without obesity.

Hypothesis: sRAGE are different in adolescents with obesity as compared to controls, in association with higher cardiovascular risk markers.

Methods: Cross-sectional study of 30 obese adolescents (with body mass index (BMI) higher than the equivalent of 30 kg /m^2 for an adult, as corrected for gender and age) and 30 controls (with normal BIM), Total cholesterol, triglycerides (TG), LDL-C, HDL-C and HbA1c were measured by standard auto-analyzer methods. Serum sRAGE was measured by an enzyme-linked immunosorbent assay (R&D Systems Inc., Minneapolis, MN, USA).

Results: The obesity group showed significantly higher levels of: % body fat 37.5 ± 7.7**vs 23.9 ± 6.7; systolic blood pressure 116 ± 7.3** vs 105.4 ± 18.8 mmHg and diastolic 72.7 ± 6.7* vs 67.8 ± 6.2 mmHg; waist 98.5 ±9.4** vs 72.3 ± 5.3 cm and hip circumferences 112.6 ± 7.9** vs 92.5 ± 6.4 cm; insulin 15.6 (12.6-19.6) ** vs 7.7 (6.7-8.9) μIU/mL; HOMA 3.4 (2.7-4.9)** vs 1.7 (1.4-2); HbA1c 5.04 ±0.5* vs 4.7 ± 0.6; TG 132 (108-146)** vs 75.5 (56-84) mg/dl and TG/HDL ratio 2.2 (1.8-2.8)** vs 1.2 (0.8-1.3). More than a third (36%) showed TG >150 mg/dl. sRAGE were 30% lower in the adolescents with obesity 1306.1±505.7** vs 1805.7 ± 589.3pg/ml as compared to controls. (*p<0.05 vs controls) (**p<0.01 vs controls).

Conclusions: Apparently healthy, obese adolescents from Guanajuato display metabolic signs of insulin resistance (higher HbA1c, HOMA and insulin) together with higher TG and TG/HDL ratio. Soluble RAGEs were significantly lower in this population. Lower sRAGE have been associated with increased CVD risk in multiple studies in adults. Our data suggest that metabolic alterations found in adults are already present in obese adolescents without the metabolic syndrome and support the need for early intervention as well as a role for the AGE-RAGE axis in this process.

INSULIN THERAPY FOR DIABETES DOES NOT MODIFY THE EFFECT OF PATIROMER ON SERUM POTASSIUM IN HYPERKALEMIC PATIENTS WITH TYPE 2 DIABETES ON RAAS INHIBITORS

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Background and Aims: Hyperkalemia (HK) is common in type 2 diabetes (DM2) due to CKD, hyporeninemic hypoaldosteronism and RAAS inhibitors. Insulin plays an important role in potassium (K) homeostasis by increasing skeletal muscle K uptake, an effect that is preserved in insulin resistant states. The effect of daily insulin on sK in DM2 and HK is unknown. In patients with HK and CKD, with and without DM2, we previously showed no difference in sK reductions with patiromer, a sodium-free non-absorbed K-binder. Here we explore whether daily insulin modifies patiromer's sK-lowering effects.

Materials and Methods: Post-hoc pooled analysis of DM2 patients on patiromer (N=443) in two studies of HK treatment in CKD (AMETHYST-DN, NCT01371747; OPAL-HK; NCT01810939). Entry sK was >5.0 to <6.0 mEq/L and 5.1 to <6.5 mEq/L, respectively; patiromer starting doses were 8.4–33.6 g/d and 8.4–16.8 g/d, respectively. Change in sK from baseline through 4 weeks and proportion with sK 3.8–5.0 mEq/L at 4 weeks were assessed in patients using (DM2+ins) and not using insulin (DM2-ins).

Results: 177 (40%) patients used insulin, mostly (87.6%) short- or rapid-acting. Compared with DM2-ins, DM2+ins had higher baseline mean sK. sK change at Week 4 was similar in DM2+ins and DM2-ins. sK values <3.5 mEq/L occurred in 1.1% (DM2+ins) and 2.6% (DM2-ins). Patiromer was generally well tolerated; ≥1 AE occurred in 30.5% (DM2+ins) and 27.1% (DM2-ins). Constipation (none severe) occurred in 7.3% (DM2+ins) and 5.3% (DM2-ins).

Conclusion: Patiromer reduces sK in hyperkalemic patients with CKD and DM2 irrespective of daily insulin use.

INTRA- AND INTER-SUBJECT VARIABILITY FOR INCREASES IN PLASMA KETONE BODIES IN PATIENTS WITH TYPE 2 DIABETES TREATED WITH THE SGLT2 INHIBITOR CANAGLIFLOZIN

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Overnight-fasted plasma ketone body concentrations are typically ~50-200 μM. Dramatic increases occurring during prolonged fasting or diabetic ketoacidosis have been well characterized, but the effects of modest changes in ketones occurring under different conditions are less understood. Recent findings indicate that failing hearts increasingly rely on ketones for energy, and that sodium glucose co-transporter 2 inhibitors (SGLT2i) modestly increase plasma ketones in most patients. These observations have stimulated a hypothesis that increases in ketones may contribute to SGLT2i-associated reductions in adverse cardiovascular and renal outcomes.

Data from SGLT2i trials indicate that mean plasma ketone concentrations approximately double, with high between-subject variability. Here, we analyze data from Phase 3 studies with the SGLT2i canagliflozin. Overnight-fasted ketone concentrations were measured every 4 weeks for 52 weeks in 1,278 Japanese subjects treated with canagliflozin 100 or 200 mg. Median (interquartile range) percent change from baseline was 62% (180) for acetoacetate and 78% (234) for β-hydroxybutyrate. Approximately 2/3 of the variability in each measure was attributed to within-subject variability. Within-subject variability for plasma ketones is higher than that for other metabolites, and accounted for only 9%-17% of total variability for plasma glucose and HbA1c. Subjects in the lowest-response tertile exhibited no mean increase in ketones at any visit. Those in the highest-response tertile tended to be male and have the largest decrease in fasting glucose. Moreover, changes in plasma ketones were not fully explained by changes in plasma fatty acids, suggesting downstream effects of SGLT1i on hepatic metabolism that favor ketogenesis.

CHARACTERISTICS OF PATIENTS INITIATING SODIUM GLUCOSE COTRANSPORTER-2 INHIBITORS (SGLT-2I) COMPARED TO PATIENTS INITIATING OTHER GLUCOSE LOWERING DRUGS (GLD) – A STUDY ACROSS FOUR COUNTRIES WITH MORE THAN 1.4 MILLION PATIENTS

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SGLT-2i are a novel class of GLDs approved in Europe and the US for the management of people with type 2 diabetes (T2D). A recent clinical trial reported a reduction in cardiovascular death and heart failure for an SGLT-2i in T2D patients with established cardiovascular disease (CVD). The use of SGLT-2i in real-world practice is not well described. Our aim was to evaluate characteristics of patients initiating SGLT-2i compared with initiators of other GLD in four countries: UK, US, Germany and Sweden.

New users of SGLT-2i (n = 143,801) and other GLD (n = 1,306,217) in T2D ≥18 years old were included from the following datasets: UK: THIN/CPRD 11/2012–09/2015 (THIN) and 01/2016 (CPRD); US: Truven Health-MarketScan 3/2013–6/2015; Humedica 03/2013–03/ 2014; Sweden: National Prescribed Drug Register 11/2012–2014; Germany: Diabetes Patientenverlaufsdokumentation (DPV) register 11/2012–07/2016. Baseline characteristics were retrieved via practice records (UK, Germany), claims/EHR (US), health registers (Sweden) and hospital records (Germany).

Patients initiating SGLT-2i were younger, had lower frequencies of CVD and chronic kidney disease/eGFR<60ml/min/1.73m^2, more microvascular disease, and in the UK and Germany higher HbA1c and more obesity versus other GLD initiators (Table). SGLT-2i initiators were more likely to have other glucose-lowering drugs the year prior[§]. These differences generally remained in multivariable analyses (data not shown).

In conclusion, SGLT-2i initiation in this cohort appears to be associated with factors such as HbA1c and weight, rather than established CVD. Based on recent evidence of cardio-protective benefits in patients with CVD, the profile of patients treated with SGLT-2i may change in the future.

LARGER ADIPOCYTES FROM VISCERAL ADIPOSE TISSUE ARE ASSOCIATED WITH HIGHER CARDIOVASCULAR RISK IN OBESE PATIENTS

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Introduction: Larger-size adipocytes produce adipokines that promote subclinical inflammation and cardiovascular risk (CVR) in obese patients.

Methods: Cross-sectional design. Obese patients submitted to bariatric surgery. Omental depot and peripheral blood were sampled. Evaluations: adipocyte size (morphometry); plasma adiponectin (ELISA); insulin, glucose, total cholesterol, HDL-c, LDL-c (nephelometry); and insulin resistance (HOMA-IR). Flow Mediated Dilation (FMD)

reflected endothelial function. Subgroups divided by adipocyte size median value were compared. Multiple correlation and prevalence of Metabolic Syndrome (MS) analysis (Pearson and Fisher, respectively) were performed.

Results: Twelve patients (4 male, 8 female, 5 MS), aged 44.2 ± 7.2 y-o. Mean adipocyte size = 2045.1 ± 300.4 μm^2, waist circumference (WC) = 131.1 ± 10.1cm, total cholesterol = 177.1 ± 36.9 mg/dL, HDL-c = 50.5 ± 15 mg/dL, HOMA-IR = 5.9 ± 3.2 and adiponectin = 118.6 ± 70.7 pg/mL. The patients with adipocytes size over the median (larger adipocytes; mean value = 2228.5 ± 219.5 μm^2) showed WC = 125.8 ± 7.8 cm, HDL-c = 42.0 ± 9.0mg/dL and adiponectin = 92.0 ± 72.5pg/mL, compared with the group of smaller adipocytes (mean value = 1815.7 ± 223.9 μm^2) WC = 140.5 ± 8.4cm (p = 0.03), HDL-c = 61.5 ± 13.8mg/dL (p = 0.03) and adiponectin = 138.6 ± 72.6pg/mL (p >0.05). Significant inverse correlation was observed between adipocyte size and adiponectin (Rho = –0.8[95% CI = –0.29, –0.96]; p = 0.009), being more significant in patients with MS. Greater prevalence of MS (100% *vs* 22%, p = 0.04) and lower FMD values (1.57 ± 3.9% *vs* 11.7 ± 2%, p = 0.03) were observed in patients with larger adipocytes.

Discussion: Adipocytes size did not relate with classical anthropometric measures like WC. However, larger size adipocytes were associated with increased CVR (lower HDL-c and inverse correlation with adiponectin). Endothelial dysfunction, reflected by lower FMD, was associated with larger adipocytes, closely related with MS. These results suggest the usefulness of adipocyte size for CVR stratification in obese/MS patients.

Conclusion: Larger size adipocytes associated with lower values of HDL-c, adiponectin and FMD, reflecting increased CVR, particularly associated with MS.

RELATIVITY IN THE UNIVERSE OF INSULIN RESISTANCE: MULTIPLE ENDOCRINOPATHIES CONTRIBUTE SIMILARLY TO HEPATIC DYSFUNCTION IN INSULIN RESISTANT PATIENTS

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Background: We earlier reported liver function measures, fractal slopes +Sb, and –Sw; here we report a sensitive new parameter, Fn.

Methods: Liver-spleen SPECT used Tc-99m-sulfur colloid. Best and worst liver function related to Sb and Sw from log plots of isocontour (Is) thresholds and their average (Av) counts. F = Sb –Sw was normalized (to Fn) for liver and spleen size, BMI, BSA and ECF.

Results: In 5 near normal patients, plots of Ln (Is) vs. Ln(Av) were nearly linear with Fn 2.42 +–0.10 and Sb 0.554 +–0.044, distinct (p <0.0002) from Sw -0.891+–0.107. In IR or type 2 DM alone, Fn depended on liver disease stage: 4.09+-0.47 for NAFL; 7.17+-0.77 for NASH and 10.71+–1.93 for fibrosis. Other diseases coexisting with IR usually further increase Fn: thyroid disease to 5.0+–1.1 in near normal, to 6.95+-1.8 in NAFL, to 9.91+–1.2 in NASH and to 14.2+-1.3 in fibrosis; adrenal disease and IR to Fn 3.22+-0.76 in near normal, 6.08+–1.23 in NAFL, 9.29+–1.81 in NASH and 13.7+–4.2 in fibrosis; alcohol use with IR increased Fn to 4.73+–0.47 in near normal, to 6.57+–0.92 in NAFL, 8.24+–0.49 in NASH and 10.63+–1.64 in fibrosis (p <0.05 for comparisons to IR alone except for alcoholic or adrenal fibrosis). Hypogonadism had similar trends.

Conclusion: Liver disease stage correlates strongly with a new fractal parameter, Fn, which also detects liver abnormalities due to subclinical thyroid disease, adrenal disease, or alcohol use. Moreover, Fn quantitatively integrates hepatic effects of IR and multiple other endocrinopathies.

STUDY OF NEUTROPHIL- LYMPHOCYTE RATIO (NLR) AS A MARKER OF INFLAMMATION IN TYPE 2 DIABETES MELLITUS: CAN IT BE MODIFIED BY METICULOUS GLYCEMIC CONTROL?

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Objective: The prevalence of Type 2 Diabetes mellitus (T2DM) is assuming epidemic proportions worldwide. It is projected to rise to 7.7% ie 439 million adults by 2030. The major brunt of this increase is predicted to be in developing countries like India. The rise in prevalence of T2DM is parallel with rise in obesity, insulin resistance and metabolic syndrome and is associated with chronic low grade inflammation. Neutrophil to lymphocyte (NLR) ratio in peripheral blood is a simple, cheap, reliable marker of systemic inflammation.

Aim: To study whether inflammation as reflected by NLR was greater in patients' as compared to controls and whether it could be modified by the degree of glycemic control.

***Material and Methods*:** 60 patients of T2DM and 69 healthy controls were included. NLR, body mass index (BMI), waist circumference, waist / hip ratio, lipid profile, C-reactive protein (CRP), fasting blood sugar and HbA1c was estimated in both groups. Patients of T2DM were divided in 2 groups based on HbA1c values <7% and >7%.

Results: The NLR,CRP, triglyceride, VLDL, TG/HDL FBS, and HbA1c levels were significantly higher and values of HbA1c were lower in patients as compared to controls ($p < 0.05$). There was no significant difference in BMI, waist circumference, W/H ratio, total cholesterol levels in both groups. (p NS). NLR was not higher in patients' with poor glycemic control.

Conclusion: Dyslipidemia and systemic inflammation were significantly higher in patients with T2DM. The inflammation was not modified by meticulous diabetic control.

ONE YEAR POST-MARKETING SURVEILLANCE STUDY OF SAROGLITAZAR IN PATIENTS WITH DIABETIC DYSLIPIDEMIA AND HISTORY OF CORONARY HEART DISEASE

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Introduction: Saroglitazar is a novel dual PPAR α/γ agonist, approved in India for the treatment of diabetic dyslipidemia.

Objective: To evaluate 1-year safety and efficacy of saroglitazar in Indian diabetic dyslipidemia patients with history of coronary heart disease (CHD).

Methodology: It is a phase IV, multicenter, single arm, and prospective, post-marketing surveillance study. Subjects with type 2 diabetes and dyslipidemia (diabetic dyslipidemia) having history of CHD were included. Eligible patients were prescribed saroglitazar 4mg once daily at discretion of treating physicians as per the prescribing information of saroglitazar. Total duration of follow-up was 1 year. Statistical analysis was done using SAS system for Windows (release 9.3; SAS Institute). Significant differences in the means from baseline to post baseline were assessed by paired t-tests. $P<0.05$ was considered significant.

Results: Total 67 patients with diabetic dyslipidemia and history of CHD were included in this analysis. The baseline patient demographics were: mean age 58 years; mean BMI 27.2 kg/m^2; average duration of diabetes 7.09 years; 67.2% male participants. At baseline, 88% and 68.7% patients were reported to be on antidiabetic and statin therapy respectively. One year treatment with saroglitazar resulted in significant improvement in glycemic and lipid parameters (results are shown in Table). There were no serious adverse events reported. Saroglitazar was found to be safe, well tolerated and was not associated with edema or weight gain.

Conclusion: One year treatment with saroglitazar in patients with diabetic dyslipidemia and history of CHD is safe and effective for controlling lipids and blood glucose levels.

CAPSAICINOIDS SUPPLEMENTATION DECREASES PERCENT BODY FAT AND FAT MASS *ADJUSTMENT* USING *COVARIATES* IN A POST HOC ANALYSIS OF A DOUBLE BLIND RANDOMIZED CLINICAL TRIAL

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Objective: The main objective of the study was to evaluate the effects of Capsaicinoids on percent body fat and fat mass while considering interaction with body habitus, diet and metabolic propensity.

Subjects and Methods: This study was a parallel group, randomized, double-blind, placebo controlled study. Seventy-five (N = 75) volunteer (male and female, age: 18 and 56 years) healthy subjects were recruited. Subjects were randomly assigned to receive either placebo dosing (2 capsules), 2 mg CAPs dosing (1 active and 1 placebo capsule) or 4 mg CAPs dosing (2 active capsules) for 12 weeks. After initial screening, subjects were evaluated with respect to fat mass and percent body fat at baseline and immediately following a 12-week treatment period. The current study evaluates two measures of fat loss while considering six baseline variables related to fat loss. Baseline measurement of importance in this paper are those used to evaluate body habitus, diet, and metabolic propensity. Lean mass and fat mass (body habitus); protein intake, fat intake and carbohydrate intake (diet); and total serum cholesterol level (metabolic propensity) were assessed. Percent body fat and fat mass were respectively re-expressed as percent change in percent body fat and percent change in fat mass by application of the formula: outcome = ((12-week value – baseline value) / baseline value) x 100. Thus, percent

change in percent body fat and percent change in fat mass served as dependent variables in the evaluation of CAPs. Inferential statistical tests were derived from the model to compare low dose CAPs to placebo and high dose CAPs to placebo.

Results: High dose CAPs 4 mg subjects evidence a loss of percent body fat (–0.70 percent less body fat) while the placebo groups exhibit a 2.7 percent gain in percent body fat. A substantial difference between CAPs 4 mg and placebo for percent change in fat mass is observed after adjustment for baseline factors and the high dose CAPs 4 mg vs. placebo contrast is statistically significant (difference = –6.68, p = 0.0487).

Conclusion: These results suggest potential benefits of Capsaicinoids (CAPs) if used as long-term, natural weight-loss aids. Further studies are required to explore pharmacological, physiological, and metabolic benefits of both chronic and acute Capsaicinoids consumption.

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Conclusion: These results suggest potential benefits of Capsaicinoids (CAPs) if used as long-term, natural weight-loss aids. Further studies are required to explore pharmacological, physiological, and metabolic benefits of both chronic and acute Capsaicinoids consumption.

CT ANGIOGRAPHY-IMAGED CORONARY ARTERY STENOSIS PROVIDES BETTER RISK PREDICTION THAN TRADITIONAL RISK FACTORS IN ASYMPTOMATIC DIABETIC INDIVIDUALS: A LONG-TERM STUDY OF CLINICAL OUTCOMES

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Objectives: We investigated the efficacy of coronary computed tomography angiography (CCTA) on the long-term risk prediction in asymptomatic type 2 diabetic patients in addition to traditional risk factors.

Research Design and Methods: We analyzed 933 asymptomatic type 2 diabetic patients who underwent CCTA. Stenosis was scored using CCTA as obstructive (≥50%) in each coronary artery segment. The extent and severity scores of coronary artery disease (CAD) were evaluated.

The primary end-point was major adverse cardiovascular events (MACE), including all causes of mortality, non-fatal myocardial infarction, and late coronary revascularization during a mean follow-up of 5.5 ± 2.1 years.

Results: A total of 94 patients with MACE were found to have more obstructive CAD and higher extent and severity scores of CAD (p<0.001 for all). After adjusting for confounding risk factors, obstructive CAD remained an independent predictor of MACE [hazard ratio 3.11, 95% confidence interval 2.00-4.86, p<0.001]. Adding a finding of obstructive CAD on CCTA to traditional risk factors, including age, male, hypertension, hyperlipidemia, smoking, eGFR and HbA1C, significantly improved the performance of a risk prediction model that was based on C-statistics (C-index 0.788 [0.747-0.829]; p=0.0349). Both integrated discrimination improvement (IDI) and net reclassification improvement (NRI) analyses further supported this finding (IDI 0.046 [0.020-0.072]; p<0.001, and NRI 0.55 [0.343-0.757]; p<0.001). In contrast, coronary artery calcium score failed to improve its risk predicting power (C-index 0.740, p=0.547).

Conclusion: Our data suggest that adding obstructive CAD to models that include traditional risk factors improves predictions of MACE in asymptomatic type 2 diabetic patients.

CONTRIBUTION OF THE TCF7L2 RS7903146 (C/T) GENE POLYMORPHISM TO THE SUSCEPTIBILITY TO TYPE 2 DIABETES MELLITUS IN CAMEROON

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Background: Data on the genetic variants for type 2 diabetes mellitus (T2DM) in sub-Saharan African populations are very scarce. This study aimed to investigate the association of transcription factor 7-like (TCF7L2) with T2DM in a Cameroonian population and explore possible genotype-phenotype correlation.

Methods: This is a case–control study involving 37 T2DM patients and 37 non-diabetic volunteers of Cameroonian ethnicity aged 40 years old and above. We collected clinical and biological data to determine phenotypic traits. TCF7L2 was analyzed by genotyping for rs7903146 (C/T) using PCR-RFLP. Biochemical analyses were performed using a spectrophotometer with Chronolab kits. Statistical analyses were carried out using IBM SPSS, PS and Quanto.

Results: TCF7L2 was associated with T2DM in this Cameroonian population (p = 0.013 for alleles, and p = 0.013 for genotypes). The risk allele was C (9.5% patients vs. 0% healthy controls, OR = 16.56) and the protective allele was T (90.5% patients vs. 100.0% healthy controls, OR = 0.06). The risk genotype was C/T (18.9% patients vs. 0% healthy controls, OR = 18.44), while the protective genotype was T/T (81.1% patients vs. 100.0% healthy controls, OR = 0.054). The statistical power was 99.99%. TCF7L2 was not preferentially associated with a specific disease phenotype.

Conclusion: TCF7L2 is associated with T2DM in this Cameroonian population. The association is not dependent on a specific T2DM phenotype. Clinical genetic testing for TCF7L2 can help to predict the occurrence of T2DM in Cameroon.

THE INCIDENCE OF AMPUTATION IN THE DAPAGLIFLOZIN CLINICAL TRIAL PROGRAM

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Approximately 60% of non-traumatic lower-limb amputations (in ≥20 year olds) occur in people with diabetes, often due to concomitant neuropathy or peripheral artery disease; major drivers for the development of diabetic foot syndrome. An increase in lower-limb amputations (mostly affecting toes) was observed in a cardiovascular trial of the sodium glucose cotransporter-2 inhibitor (SGLT-2i), canagliflozin. Here, the occurrence of amputation with the SGLT-2i dapagliflozin was assessed. A total of 30 completed Phase II/III trials (≥12 weeks) across a diverse range of patient populations receiving dapagliflozin as monotherapy or in combination with other glucose-lowering drugs were included in the analysis. In total, 9195 and 4629 patients received dapagliflozin and placebo/active comparator, respectively (8059 and 4177 patient-years exposure, respectively). As surgical procedures were not specifically collected as adverse events during the clinical trial program, a manual free-text search was used to determine the occurrence of 'amputation', including both major and minor amputations. Overall, events of lower limb amputation were identified in 15 patients, 8 (0.087%) of whom

received dapagliflozin and 7 (0.151%) of whom received placebo or active comparator. The incidence rate of lower limb amputation was, therefore, 0.99 and 1.68 per 1000 patient-years exposure with dapagliflozin and placebo/active comparator, respectively.In conclusion, the occurrence of amputation (both major and minor) was very low across the global dapagliflozin clinical trial program, with no imbalance observed between active and comparator arms.

SAFETY AND TOLERABILITY OF DAPAGLIFLOZIN: UPDATE ON BONE FRACTURES, RENAL SAFETY AND DIABETIC KETOACIDOSIS

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Adverse events (AEs) of fractures, renal function and diabetic ketoacidosis (DKA) are of special interest when treating with sodium glucose cotransporter-2 (SGLT2) inhibitors. We assessed the frequency of these events with the SGLT2 inhibitor dapagliflozin, versus control, in patients with Type 2 diabetes (T2D) in a large clinical trial program of this drug.

Fracture data were derived from a pool of 14 short-term Phase IIb/III studies (≤24 weeks). Renal data were derived from a pool of 12 short-term Phase IIb/III studies (≤24 weeks), five of which had long-term extensions (≤102 weeks). DKA (and renal events) data were derived from a pool of 21 Phase IIb/III studies (≤208 weeks).

Proportions of patients reporting fractures, renal AEs or DKA in the dapagliflozin and control groups are listed in the Table. Total events of fracture, including lower limb fractures, were similar for dapagliflozin versus placebo. Furthermore, in a dedicated bone mineral study of patients with T2D inadequately controlled on metformin, dapagliflozin (N = 91) had no effect on the dynamics of bone formation/resorption markers, or bone mineral density. In dapagliflozin-treated patients, there was a transient decrease in estimated glomerular filtration rate (week 1: –4.2 mL/min/1.73m^2), and a subsequent gradual return to baseline, remaining stable up to 102 weeks (overall change: 0.02 mL/min/1.73m^2). No imbalance in DKA was observed for dapagliflozin versus control.

In conclusion absolute numbers of fractures, renal AEs and DKA were low and similar in the dapagliflozin and control groups in these pooled analyses across the dapagliflozin clinical trial program.

DISSOCIATION BETWEEN HEPATIC INSULIN CLEARANCE AND HEPATIC INSULIN ACTION SUPPORTS INDIRECT CONTROL OF LIVER GLUCOSE PRODUCTION

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Background: Obesity is highly associated with hepatic insulin resistance, where insulin(ins) fails to completely inhibit hepatic glucose production (HGP). After secretion, ins binds to it receptors on the liver where it is internalized and ~55% of the ins mass is degraded. It has long been assumed that ins acts directly on the liver after receptor binding to inhibit HGP, but studies have found that ins acts indirectly to modulate HGP. If ins acts indirectly, it is possible that clearance of the hormone and its liver degradation will not be highly correlated. Therefore, in this current study, we sought to examine the relationship between hepatic ins clearance (HE) and ins action at the liver and periphery.

Methods: HE was directly assessed in the dog model (n = 9) using a paired portal/peripheral insulin infusion protocol (PPII). Ins is infused at 3 rates (dose-response) on 2 separate days: into either the portal or peripheral vein. HE is accurately calculated as ($1-m_{po}/m_{pe}$) where m is the ratio of the slopes of ins infusion vs concentration for the 2 delivery routes. Euglycemic hyperinsulinemic clamps using radioactive tracer were also performed for assessment of hepatic and peripheral ins sensitivity (S_I) and action.

Results: The animals had a broad range of HE (25.4 - 71.8%) and whole body S_I (2.5 -26.2 x 10^{-4}dl/min/pM). We observed weak and nonsignificant correlations between HE vs. *hepatic* ins action ($r = 0.37$, $p = 0.32$), as well as between HE and *hepatic* S_I ($r = 0.44$, $p = 0.24$). In sharp contrast, HE had a strong and highly significant correlation with *both peripheral ins action and peripheral* S_I ($r = 0.88$, $p = 0.002$ and $r = 0.76$, $p = 0.017$; respectively).

Conclusion: HE is not associated with ins action at the liver, and demonstrates a stronger relationship with peripheral ins action. This indicates that liver ins action and its clearance may be differentially regulated which is consistent with a peripheral effect of ins (on adipose, CNS, kidney) which secondarily controls liver glucose output.

INSULIN GLARGINE 300 U/ML (GLA-300) PROVIDES MORE STABLE AND MORE EVENLY DISTRIBUTED STEADY-STATE PHARMACODYNAMIC/PHARMACOKINETIC PROFILES COMPARED WITH INSULIN DEGLUDEC IN TYPE 1 DIABETES (T1DM)

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Background and Aims: To compare steady-state pharmacodynamic (PD) and pharmacokinetic (PK) profiles of insulin glargine 300 U/mL (Gla-300) with insulin degludec 100 U/mL (Deg-100) in two parallel cohorts with fixed once-daily dose regimens in T1DM, in a multiple-dosing, crossover, euglycemic glucose clamp study.

Methods: For both insulins participants received 0.4 U/kg/day (Cohort 1; n = 24) or 0.6 U/kg/day (Cohort 2; n = 24), before breakfast, for 8 days. Metabolic activity was measured by glucose infusion rate (GIR) over 30 hours. Main endpoint: within-day variability (fluctuation) of smoothed GIR over the dosing interval (GIR-smFL$_{0–24}$; treatment ratios were obtained using a linear mixed-effects model). Insulin concentrations were measured using validated radioimmunoassays.

Results: GIR-smFL$_{0–24}$ was significantly lower with Gla-300 than Deg-100 at 0.4 U/kg/day (p=0.047; treatment ratio 0.7978 [90% CI: 0.6637 to 0.9591]; Figure) (LOESS smoothing 0.15), but was comparable for Gla-300 and Deg-100 at 0.6 U/kg/day. Both doses of Gla-300 provided plateau-like insulin exposure from 2 to 16 hours post-injection, with a slight decline afterwards, whereas Deg-100 concentrations (total insulin) after both doses increased from ~1 hour to a T_{max} at ~10 hours after dosing, followed by a steady decline with no plateauing. Both insulins provided exposure and activity until 30 hours and were generally well tolerated.

Conclusions: This PK/PD analysis supports a superior glucodynamic profile of Gla-300 versus Deg-100 at a dose clinically relevant for T1DM (0.4 U/kg/day), in terms of within-day variability. An overall more stable and more evenly distributed insulin exposure over the dosing interval was observed at both dose levels under Gla-300.