Late Breaking Abstracts

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COMPLICATIONS—HYPOGLYCEMIA

1-LB

A Phase 2 Comparative Safety PK/PD Study of Stable Nonaqueous Glucagon (G-Pen) vs. Lilly Glucagon for Treatment of Severe Hypoglycemia

EUGENIO CERSOSIMO, MARTIN J. CUMMINS, JOHN H. KINZELL, JOEL MICHALEK, BRETT J. NEWSWANGER, STEVEN J. PRESTRELSKI, CURTIS TRIPLITT, RALPH A. DEFRONZO, *San Antonio, TX, Austin, TX*

Severe hypoglycemia remains a significant unmet medical need in patients with diabetes. Currently approved rescue products (Lilly Glucagon for Injection [rDNA origin]; Novo Nordisk GlucaGen® (glucagon [rDNA origin]) HypoKit®) are based on lyophilized formulations, which require reconstitution at time of use, complicating administration in emergency situations. Xeris is developing a ready-to-use, soluble liquid glucagon formulation in a pre-filled syringe, based on biocompatible, non-aqueous solvents that suppress the fibrillation of glucagon typically observed in aqueous solutions. The G-Pen™ (glucagon injection) formulation has demonstrated excellent chemical stability after storage as a liquid at room temperature. A Phase 2, double-blind, cross-over, comparative pharmacology study in fasted, healthy, non-diabetic volunteers (n = 30) demonstrated that subcutaneously (SC) injected G-Pen™ glucagon (1 mg) resulted in bioequivalent mean glucose AUC, Cmax, and Tmax as compared to 1 mg SC doses of Lilly Glucagon reference drug. The TOST procedure indicated significance ($p<0.05$) for all pairwise contrasts and all 95% pairwise confidence intervals for the ratio of means were contained in the interval 0.80 to 1.2, the FDA standard for bioequivalence. Injection of both 1 mg G-Pen™ [Cmax 148.0 (24.9) mg/dL] and Lilly Glucagon [Cmax 154.9.0 (28.0) mg/dL] showed rapid, marked elevation of blood glucose levels from baseline. Despite therapeutic equivalence, pharmacokinetic serum glucagon parameters (AUC, Cmax, Tmax) were significantly different between Xeris and Lilly preparations. There were no apparent safety or tolerability issues with any of the glucagon treatments; all AEs observed were those expected with rescue injections of glucagon. No serious adverse reactions were reported. Overall these data support the development of G-Pen™ as a commercial rescue treatment for severe hypoglycemia in a single-use auto-injector pen format.

Supported By: NIDDK (5R44DK085809-03)

2-LB

Different Clinical Predictors of Nonsevere and Severe Hypoglycemia during Treatment with Glargine or Standard Care in the ORIGIN Trial

MATTHEW C. RIDDLE, HERTZEL GERSTEIN, HYEJUNG JUNG, LARS E. RYDÉN, LINDA MELLBIN, JULIO ROSENSTOCK, JEFFREY PROBSTFIELD, *Portland, OR, Hamilton, ON, Canada, Stockholm, Sweden, Dallas, TX, Seattle, WA*

Hypoglycemia limits treatment of diabetes and is associated with increased risks. This large, long-term, randomized trial (NCT00069784) compared use of insulin glargine with standard care in people with dysglycemia (IGT, IFG, or T2DM) and high cardiovascular risk. We analyzed data from 12,537 participants to identify baseline and on-treatment factors associated with symptomatic hypoglycemia confirmed by glucose ≤3 mmol/L or (separately) severe hypoglycemia. Over median 6.2 yrs with median A1C ~ 6.5%, 28% of participants had ≥1 non-severe and 3.8% severe events. Independent predictors of events as time-varying covariates were assessed by Cox proportional hazard models including baseline characteristics, treatment allocation, and mean on-treatment A1C. Sulfonylurea use (Hazard Ratio [HR] 2.07 for non-severe, 1.35 for severe) and glargine treatment (HR 4.53 for non-severe, 3.57 for severe) were independently associated with higher risk in both categories. Risk of non-severe events was lower with older age (HR [95%CI] 0.98 [0.98-0.99]) and higher BMI (HR 0.97 [0.96-0.98]), and higher with presence of diabetes (HR 1.52 [1.21-1.92] and higher baseline A1C (HR 1.24 [1.14-1.35]). Risk of severe events was higher with older age (HR 1.04 [1.03-1.06]), hypertension (HR 1.51 [1.14-2.00]), higher serum creatinine (HR 1.01 [1.01-1.02]); lower with higher MMSE score (HR 0.96 [0.93-0.99]); and unrelated to baseline glycemic status. With glargine treatment, risk of both non-severe and severe events was higher at lower on-treatment A1C; with standard care risk of severe events increased at higher A1C. Conclusions: Overall incidences of hypoglycemia were low. Sulfonylurea and glargine are associated with both non-severe and severe events, but other independent predictors differ between categories. Non-severe and severe events affect different people and occur in different settings. Awareness of predictors may guide individualized therapy.

Supported By: Sanofi

3-LB

Warfarin Use and Hospitalization Events for Hypoglycemia among Elderly Patients on Glipizide

JOHN ROMLEY, DANA GOLDMAN, CYNTHIA GONG, ANNE L. PETERS, *Los Angeles, CA*

Oral hypoglycemic agents and warfarin account for nearly half of adverse drug events resulting in emergency hospitalization among elderly Americans. Clinical drug references note that warfarin may interact with glipizide, potentiating its hypoglycemic effects. These warnings, however, are based on pharmacokinetic data and case reports for older sulfonylureas which are rarely used. In this study, we investigated hospitalization events for hypoglycemia among elderly Americans with diabetes with concomitant glipizide and warfarin use. A 20% sample of Medicare claims (2006-2011) was used to identify individuals with diabetes who used glipizide (defined as at least one prescription fill in a Part D plan), and were continuously enrolled in Medicare Parts A and B (or died), during a calendar quarter. Concomitant warfarin use was determined, and whether individuals had a hospital admission or emergency department (ED) visit with a primary diagnosis of hypoglycemia, during the same quarter. Our analysis sample included 293,322 individuals and 2,639,392 person-quarters. Warfarin was filled in 9.4% of quarters, and a hypoglycemia admission or ED visit occurred in 569 quarters. Using logistic random effects analysis, the unadjusted odds ratio (OR) for hypoglycemia admission / ED visit was 1.54 ($p<0.001$) in quarters with warfarin use. When adjusted for age, sex, non-white race/ethnicity and comorbidities, the OR for warfarin use was 1.24 ($p=0.040$). Risk was elevated for hospitalization alone (OR of 1.53, $p=0.047$), and with initial warfarin use (OR of 3.61, $p<0.001$). Confounding was addressed with a fixed effects logistic analysis which accounted for unmeasured time-invariant person-level factors, and found an adjusted OR for hospitalization / ED visit with warfarin use of 1.57 ($p=0.023$). Hospitalization events for hypoglycemia are rare but serious, and clinicians should exercise caution when prescribing warfarin to elderly glipizide users, especially when initiating treatment.

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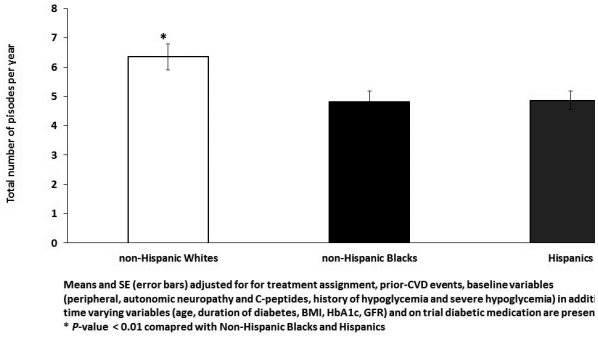
4-LB

Hypoglycemic Episodes among Race/Ethnicity Groups in the VA Diabetes Trial (VADT)

ARAMESH SAREMI, DERRICK KAUFMAN, DAWN C. SCHWENKE, PETER D. REAVEN, FOR THE VADT, *Phoenix, AZ, Hines, IL*

We have previously shown that the effect of intensive glycemic control on CVD outcomes differed across major race/ethnic groups in VADT. We now determined whether the frequency of hypoglycemic episodes in response to this therapy differed across major race/ethnic groups. The total numbers of interim hypoglycemia episodes with symptoms were reported at each visit. The current analysis included 1096 non-Hispanic Whites (NHW), 303 non-Hispanic Blacks (NHB) and 303 Hispanics (His). Total number of hypoglycemic episodes per year were more frequent in NHW compared with NHB and His [mean (95% CI): NHW, 10 (9-11); NHB, 6 (5-7) His, 7 (6-8), $P< 0.0$]. After adjustment for other predictors of hypoglycemia, including treatment assignment (Figure), NHW continued to have 32% and 31% ($P<0.01$) more frequent hypoglycemic episodes compared with NHB and His, respectively. Very similar patterns were seen for severe and nocturnal hypoglycemia. Although intensive treatment was a significant predictor of hypoglycemic events, there was no interaction between treatment effect and ethnicity. Together with our previous report, these data suggest that the risk/benefit ratio for intensive glycemic control differs between major race/ethnic groups in the VADT.



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For author disclosure information, see page LB91.

5-LB

Natural Language Processing of Clinical Notes in Electronic Health Records to Improve Capture of Hypoglycemia

ANTHONY P. NUNES, SHENGSHENG YU, KAREN M. KURTYKA, CYNTHIA SENERCHIA, JEFFREY M. HILL, KIMBERLY G. BRODOVICZ, LARRY RADICAN, SAMUEL S. ENGEL, SEAN R. CALVO, DAVID D. DORE, *Waltham, MA, Whitehouse Station, NJ, Boston, MA, North Wales, PA, Providence, RI*

Hypoglycemia is under ascertained in healthcare billing data, especially for mild or moderate events. Clinical notes in electronic health records (EHR) include details of medical encounters that may not be represented in structured data fields. We assessed whether natural language processing (NLP) of clinical notes increases capture of hypoglycemia events and hypoglycemia severity.

The Humedica statistically deidentified EHR database includes information on over 25 million patients from 195 hospitals throughout the United States. We identified all patients in Humedica with an International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code for diabetes mellitus between January 2007 and September 2013. Hypoglycemia was identified via NLP of clinical notes and ICD-9 codes within structured data fields. The hypoglycemia NLP algorithm was developed iteratively by specifying, reviewing, and updating term lists that originated from standard clinical nomenclature. Term analogs were included to account for differences in spacing, hyphenation, and spelling. A clinical nurse specialist manually identified additional terms from notes and the algorithm searched for expressions that were highly correlated with known hypoglycemia terms.

Of 1,914,324 patients with diabetes, 286,386 (15.0%) had ≥ 1 hypoglycemia event identified via NLP and 148,158 (7.7%) had ≥ 1 event identified via ICD-9. Only 49,544 patients had an event identified by both NLP and ICD-9. Information on severity was available for ≥ 1 event for 38,241 patients (13.4%) with NLP-identified hypoglycemia; 19,984 patients had ≥ 1 event described as mild to moderate and 23,237 had ≥ 1 event described as severe.

NLP of clinical notes broadened the capture of hypoglycemia events relative to ICD-9 diagnoses alone and identified a largely different set of events. Mild-moderate events were underrepresented and may not be reported to providers or may not include descriptions of severity when noted.

COMPLICATIONS—MACROVASCULAR—ATHEROSCLEROTIC CARDIOVASCULAR DISEASE AND HUMAN DIABETES

6-LB

Enhanced Prediction of Cardiovascular Events by Adding Novel Biomarkers to Clinical Risk Factors in the ORIGIN Trial

HERTZEL C. GERSTEIN, GUILLAUME PARE, MATTHEW J. MCQUEEN, SHUN FU LEE, HEINZ H. HAENEL, PETER S. JOHNSTON, SIBYLLE HESS, *Hamilton, ON, Canada, Frankfurt, Germany, Bridgewater, NJ*

The measurement of large numbers of biomarkers in stored blood, using new assay technologies, from carefully phenotyped and prospectively followed individuals may identify new biomarkers and physiologic pathways for cardiovascular (CV) events in people with dysglycemia and improve the ability of clinical risk factors to identify susceptible individuals. The concentration of 237 out of 284 biomarkers that were assayed in the stored baseline serum samples from 8401 ORIGIN trial participants using the Human Discovery Multi-Analyte Profile (DiscoveryMAP® 250+) platform (Myriad RBM, Inc., Austin, TX, USA) were detectable in >=99% of people. Participants were divided into a model building group (N=5630) and a model validation group (N=2771). The levels of these biomarkers were added to the following risk factors in the model building group (male sex, age [male>=55 or female >=65], prior CV event, albuminuria, smoking, established diabetes, LDL/HDL, established hypertension) in a Cox regression model if the P value for their inclusion was < 0.05/237 (i.e. 0.00021). The following biomarkers were identified as independently adding to the ability of clinical risk factors to predict the first occurrence of nonfatal MI, nonfatal stroke or CV death during a median follow-up period of 6.2 years: a) trefoil factor 3; b) angiopoietin-2; c) N Terminal pro BNP; d) glutathione S-transferase alpha; e) osteoprotegerin; f) alpha 2 macroglobulin; g) peroxiredoxin 4; and h) apolipoprotein B; the largest P value for inclusion of any biomarker was 0.000083. Inclusion of these biomarkers increased the area under the receiver operating characteristic curve from for predicting CV events from 0.62 (95%CI 0.60, 0.64) to 0.72 (95%CI 0.71, 0.74). If validated in the validation subset, we will have identified 8 novel biomarkers that together strongly increase the ability to predict CV events in people with dysglycemia.

Supported By: Sanofi

7-LB

WITHDRAWN

8-LB

Effect of Baseline Atherosclerosis on Long-term Consequences of Intensive Glycemic Control on Cardiovascular Outcomes: A Subset Analysis of Coronary Artery Calcification (CAC) in the Veterans Affairs Diabetes Trial (VADT)

PETER D. REAVEN, DAWN SCHWENKE, GIDEON BAHN, FOR VADT INVESTIGATORS, *Phoenix, AZ, Hines, IL*

We previously reported that intensive glucose lowering (INT) significantly reduced a composite cardiovascular outcome in those with low baseline CAC, but not in those with high CAC, over the median 5.6 years follow-up of the VADT. We now report the results of nearly 10 years of combined intervention and observational follow-up of this subset of VADT study subjects that were randomized to INT or standard (STD) therapy and received baseline measures of vascular calcification.

301 participants from 7 VA sites had baseline CT measures of CAC at the beginning of the VADT. Data were collected on these subjects during the VADT and during approximately 4 more years of observation utilizing the VA, CMS and NDI databases for procedures, hospitalizations and death. The pre-specified primary outcome was a composite of major cardiovascular events including non-fatal MI or stroke resulting in hospitalization, new CHF, amputation for ischemic diabetic gangrene, or cardiovascular-related death. All outcome assessments were fully blinded.

HbA1c separation between the INT and STD arms in the subset was 1.4% at the conclusion of the VADT (medians of 7.1% vs. 8.5%, respectively), declined to 0.9% one year after the trial ended (7.3% vs. 8.2%, respectively), and to 0.4% three years after the trial (7.7% vs. 8.1%, respectively). Blood pressure, lipid and lipoprotein concentrations were maintained at similar levels during and after the trial in the INT and STD arms. In individuals with low CAC (≤ 100 Agatston units) or high CAC (>100 units), INT was associated with a lower incidence of major cardiovascular outcomes ($p < 0.05$ for both groups).

After nearly 10 years of follow-up of this subset of VADT study subjects, the effects of INT on major cardiovascular events appeared favorable regardless of the degree of baseline atherosclerosis.

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9-LB

Accelerated but Compositional Unaltered Carotid Atherosclerosis Assessed by MRI in Newly Diagnosed Type 2 Diabetes

PERNILLE H. HØYEM, ESBEN LAUGESEN, ANDERS F.S. MIKKELSEN, BRITT CHRISTENSEN, ULLA KAMPMANN, PER L. POULSEN, MOGENS ERLANDSEN, BILL KERWIN, SAMUEL THRYSØE, ESBEN S. HANSEN, JENS S. CHRISTIANSEN, WON Y. KIM, TROELS K. HANSEN, *Aarhus, Denmark, Seattle, WA*

Type 2 diabetes is associated with macro-vascular complications such as cerebral infarctions, myocardial infarctions, and peripheral vascular disease. It is feasible that this may be caused by not only accelerated atherosclerosis, but also by altered composition of the arterial wall contents, as it is well-known that certain characteristics of the atherosclerotic plaque are associated with increased risk of a clinical event. We aimed to investigate whether there are differences in the morphology and composition of atherosclerosis in the carotid arteries assessed by MRI in newly diagnosed type 2 diabetic patients compared to non-diabetic control subjects.

One hundred type 2 diabetic patients diagnosed within the last 5 years and 100 age- and gender-matched non-diabetic control subjects underwent magnetic resonance imaging of carotid arteries bilaterally in a 1.5 Tesla Phillips Achieva MRI scanner with a dedicated carotid coil. Scans were performed with four different contrast weightings and subsequently analysed in a software tool to assess atherosclerosis morphology and composition.

In the diabetes group 142 carotid arteries and in the control group 172 carotid arteries were available for analysis. In diabetic patients the minimal lumen area was 20.8% smaller (P<0.001) and maximal normalized wall index was 3.7% higher (P=0.046) than in the control subjects. This remained significant after adjusting for LDL-cholesterol and smoking habits (minimal lumen area P<0.001 and maximal normalized wall index P=0.030). Relative maximal calcification was not significantly different between groups (P=0.497), as was the case for relative maximal necrotic core (P=0.066), relative maximal hemorrhage (P=0.172) and relative maximal loose matrix (P=0.876) (all volume percentages).

For author disclosure information, see page LB91.

Clear signs of accelerated carotid atherosclerosis assessed by MRI were found at a very early stage of type 2 diabetes, but no sign of altered arterial wall compositional contents was found.

10-LB

Ranolazine, Ethnicity, and the Metabolic Syndrome (REMS) Study: A Pilot Study Showing Differential Effects amongst Caucasians, African Americans, and Asians in Exercise Tolerance Time and Glycemic Control but Not Angina Scores

NARENDRA SINGH, PUJA DUBAL, HOLLY ADAMS, KATI TURNER, SANDEEP CHANDRA, DAVID SONG, LINDA YAN, DAVID SUH, *Cumming, GA*

Background: Ranolazine is a well proven and effective drug for the treatment of angina. It may also have some favorable antiarrhythmic and glucose metabolism properties. There is however limited data on the drug's safety and efficacy in non-Caucasian ethnic patient population.

Methods: Single center, prospective, randomized, 6 month open label trial of ranolazine (RAN) vs. standard of care (SOC) in stable CAD pts.

Results: Of the 122 pts randomized, there were 55 Caucasians, 50 African Americans and 17 Asians. Mean age 62+11yrs, 69% males. Hypertension (93%) was the most common metabolic syndrome component followed by abdominal obesity (61%), elevated glucose (46%) and low HDL (44%) or high triglycerides (28%).

Comparing RAN to SOC pts, more RAN pts improved their exercise treadmill (ETT) time (67% vs. 45%, p=0.03) while duration improved an average of 40 sec (p=0.13). Pts with angina improved ETT time more than those with angina equivalents (88 vs. 19 sec, p= 0.03). Lipid parameters (mean HDL 49, LDL 85 gm/dl) and anthropometric measurements (BMI=30, WHR=0.97) did not change. HgbA1c however was significantly less in the RAN group (6.2 vs. 7.1%, p=0.02) after 6 months.

Baseline characteristics between the 3 ethnic groups differed significantly (p<0.001). ETT duration improved in more Caucasians (64%) and Asians (56%) compared to African Americans (42%). Similarly glycemic control tended to improve in Caucasians and Asians while it worsen in African Americans. Adverse events trended higher in RAN group (25% vs. 13%, p=0.08) with Asians tolerating the drug best.

Conclusions: Our pilot study findings suggest that ranolazine improves exercise duration and glycemic control in CAD pts over 6 months. There may however be a differential effect on these parameters in pts with an African American or Asian ethnicity. These findings warrant further validation in larger sample sizes.

11-LB

Autoantibodies in Adult Type 2 Diabetes Having Atrial Fibrillation Cause Acute Intracellular Ca2+ Increase in HL-1 Adult Atrial Cardiomyocytes by IP3 Receptor-Mediated Mechanism

ZUI PAN, MARK B. ZIMERING, *Columbus, OH, East Orange, NJ*

Type 2 diabetes mellitus (T2DM) is associated with increased occurrence of atrial fibrillation (AF). Increased Ca2+ release from sarcoplasmic reticulum contributes to AF in animal models, however, the mechanism underlying the association between AF and T2DM is unknown. Since in our prior work, circulating T2DM autoantibodies (AA) caused elevated intracellular Ca2+ in endothelial cells, we hypothesize that T2DM AA perturb Ca2+ homeostasis in atrial cardiomyocytes contributing to AF. Protein A-purified IgG was obtained in a cohort of adult T2DM participants from the Veterans Affairs Diabetes Trial (mean: age 64 yrs, diabetes duration 11 yrs) and other subjects. To test the acute effects of AA on Ca2+ signaling, we used Ca2+ fluorescent dye fura-2 and cultured HL-1 adult mouse atrial cardiomyocyte cells that exhibit rhythmic Ca2+ oscillations. IgG (1 µg/mL) from 14/18 diabetic AF patients caused acute intracellular Ca2+ elevation in HL-1 cells compared to 1/22 diabetic and 1/9 non-diabetic subjects without AF, left ventricular hypertrophy or another arrhythmia ($P < 0.001$). The T2 DM, AF IgG- induced Ca2+ release in HL-1 cells was insensitive to verapamil (20 µm), mibefradil (25 µM) or BTP-2 (5 µM), indicating that the elevation of intracellular Ca2+ is not through voltage-gated Ca2+ channels or store-operated Ca2+ entry. On the other hand, Xestospongin C (10 µM) a membrane-permeable IP3 receptor antagonist, significantly decreased elevation of intracellular Ca2+ stimulated by the T2DM, AF IgG (60% reduction, $P < 0.01$, $n > 5$ experiments). 2-Aminoethoxydiphenyl borate (2-APB, 100 µM), another IP3R inhibitor, completely blocked IgG-induced Ca2+ elevation. These data suggest that AA cause IP3 receptor activation which may be involved in the mechanism for AF in some older type 2 DM subjects. AA preceded AF occurrence in some subjects suggesting they exert more than a bystander role in T2DM atrial fibrillation.

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12-LB

Rotating Night Shift: Risk of Type 2 Diabetes and Metabolic Disorders

NARSINGH VERMA, ANUJ MAHESHWARI, B. ANJUM, SANDEEP TIWARI, ABBAS ALI MAHDI, *Lucknow, India*

Compromised Quality and Quantity of sleep may be a novel risk factor for metabolic syndrome and type 2 diabetes mellitus due to interference with diet, circadian metabolic rhythms, and lifestyle. The long-term elevated cortisol leads to the high blood sugar level and decreased insulin associated with higher levels of cholesterol, triglycerides and BMI may contribute to the increased risk of metabolic syndrome and CVDs.

The aim of the present study was to investigate the risk of type 2 diabetes and metabolic disorders in rotating night shift workers.

In the present case-control study, we recruited 30 healthy nursing professionals, aged 20-40 year, performed day and night shift duties (continuous 9 days night shift with alternate day shifts) and were randomly selected from the Trauma Center, GM and Associated Hospitals, King George Medical University and 30 age sex matched controls were also recruited in this study. In the Present study, we have investigated the effect of rotating night shift on Fasting blood glucose level and Insulin resistance.

Data were analysed by unpaired t-test. BMI was higher in cases (23.69+1.96) as compared to controls (21.66+4.04) (p0.05) found in fasting blood sugar between night workers (78.38 +9.40) and controls (75.14+14.77). Fasting insulin level was increased in night workers (4.05+ 2.45) than controls (2.75+ 2.53) and was statistically significant ($p<0.05$). Insulin resistance was slightly increased among night workers (0.80+ 0.50) than controls (0.53+ 0.51) which was statistically significant ($p<0.05$).

Night shift work is associated with increased risk of insulin disturbance leading to insulin resistance making them more prone for metabolic syndrome and type 2 diabetes.

Supported By: India Council of Science & Technology

13-LB

Determinants of Metabolic Control in the Early Phase of Diabetes

KATHARINA S. WEBER, BETTINA NOWOTNY, KLAUS STRASSBURGER, ANETTE E. BUYKEN, MARSEL SCHEER, MARIE-CHRISTINE SIMON, CHRISTIAN HERDER, PETER NOWOTNY, GIOVANNI PACINI, JULIA SZENDRÖDI, KARSTEN MÜSSIG, MICHAEL RODEN, GDC STUDY GROUP, *Düsseldorf, Germany, Bonn, Germany, Padova, Italy*

Dietary habits and subclinical inflammation relate to insulin sensitivity and secretion. However, their impact on the early development of metabolic control of type 2 (T2D), but also type 1 diabetes (T1D) is largely unclear. We analyzed parameters possibly affecting metabolic control in diabetes patients during the first two years after diagnosis. Insulin secretion (ratio of C-peptide release (6 min/0 min) from the glucagon stimulation test) and glycemic control (A1c) were measured in 103 (31% T1D) diabetes patients. Insulin sensitivity (SI from the intravenous glucose tolerance test) was assessed in T2D (n=61). Multivariable regression models were used to assess the prospective associations of food consumption frequencies and cytokine concentrations at baseline with changes in glycemic control, insulin sensitivity and secretion after two years. Patients with T1D and T2D exhibited good glycemic control (A1c 7.1±1.6% and 6.4±1.0) at diagnosis. Within two years, insulin secretion did not change in T1D (1.7 ($Q_{25;75}$ 1.4; 2.0) vs. 1.6 ($Q_{25;75}$ 1.3; 2.1)). In T2D, insulin secretion increased (1.9 ($Q_{25;75}$ 1.6; 2.2) vs. 2.1 ($Q_{25;75}$ 1.8; 2.4), $p<0.001$) and insulin sensitivity (2.0 (1.3; 2.8) $*10^{-4}$ min^{-1} $[\mu U/ml]^{-1}$ vs. 1.8 (1.2; 3.0)) was unchanged during the first two years. In T1D, a more frequent baseline consumption of non-whole-grain foods related to lower insulin secretion (-15% (95% CI -26; -2), p=0.028) and increased A1c (0.81% (95% CI 0.20; 1.41), p=0.011) at follow-up, adjusted for age, sex, BMI, glucose-lowering medication. Also in T1D, higher baseline interleukin (IL)-6 predicted subsequently increased A1c (0.77% (95% CI 0.13; 1.42), p=0.021). In T2D, a more frequent consumption of meat/meat products related to lower insulin sensitivity (-8% (95% CI -15; -1), p=0.029) after two years. During the initial course of the disease, intake of non-whole-grain foods and subclinical inflammation negatively affect insulin secretion in T1D, whereas intake of meat/meat products impairs insulin sensitivity in T2D.

Supported By: German Center for Diabetes Research

14-LB

Beneficial Effect of Multifactorial Intervention on the Prognosis of Patients with Type 2 Diabetes Mellitus and Critical Limb Ischemia/ Peripheral Arterial Disease

CLEMENS HOEBAUS, GUNTRAM SCHERNTHANER, RENATE KOPPENSTEINER, GERIT SCHERNTHANER, *Wien, Austria, Vienna, Austria*

The combination of critical limb ischemia/peripheral artery disease (PAD) and diabetes mellitus type 2 (T2DM) is known for poor survival. The last major publication on successful management of such a patient population reported a

50% mortality and 25% amputation rate after six years of follow up. We have analyzed whether more recent treatment advances of T2DM and PAD in the last five years have ameliorated those detrimental effects.

In a prospective study we enrolled 366 patients (34% female) with PAD, 38% had T2DM, 33% impaired glucose tolerance (PRE) and 29% normal glucose tolerance (NGT). As expected the patient cohort had a high cardiovascular risk factor (CRF) burden: 92% hypertension, 97% hyperlipidemia, 74% active or former smoker; Coronary heart disease (CHD) was known in 32% and carotid artery disease (CAD) in 39% of the patients. Within 6 months the target values of CRF control - LDL-Cholesterol <100 mg/dl, blood pressure (<140/80 mm Hg, HbA1c in DM <7.0%) were reached in 58%, 69% and 69%. Patients followed a strict control visit program in the center for 5 years.

The overall survival of this cohort was 89.3% after 4.9 years. MACE (combination of death, non-fatal myocardial infarction or stroke) free survival was 84.3% and event free survival including interventional or surgical procedures due to critical limb ischemia/PAD was 68%. Patients with T2DM showed a survival of 87.8% compared to 89.3% PRE, and 95.2% NGT (p=0.161). MACE free survival was 81.3% for T2DM, 87.6% for PRE, and for 92.4% NGT (p=0.059). Additionally, event free survival was 65.5% for T2D, 71.9% for PRE, and 77.1% for NGT (p=0.155).

In summary, strict multifactorial management induced a dramatic reduction in the annual death rate (2.8 for patients with T2DM and PAD), MACE and amputation. Thus, management of such patients should be restricted to centralized centers to improve outcome for the patients.

15-LB

Impairment of Autophagy in Endothelial Cells Prevents Shear-Stress-induced Increases in Nitric Oxide Bioavailability

LEENA PANEERSEELAN-BHARATH, ROBERT MUELLER, YOU YOU LI, TING RUAN, DAVID KUNZ, REBEKAH GOODRICH, TYLER MILLS, LANCE DEETER, ASHOT SARGSYAN, PON VELAYUTHAM ANANDH BABU, TIMOTHY GRAHAM, J. DAVID SYMONS, *Salt Lake City, UT*

Autophagy is a lysosomal catabolic process by which cells degrade or recycle their contents to maintain cellular homeostasis, adapt to stress, and respond to disease. Impairment of autophagy in endothelial cells studied under static conditions results in oxidant stress and impaired nitric oxide (NO) bioavailability. We tested the hypothesis that vascular autophagy is also important for induction of NO production caused by exposure of endothelial cells to shear stress (i.e., 3 h x ≈ 20 dyn/cm^2). Atg3 is a requisite autophagy pathway mediator. Control cells treated with scrambled, non-specific siRNA to Atg3 (-Atg3 siRNA) showed increased autophagy, mitochondrial turnover, reactive oxygen species (ROS) production, endothelial NO synthase (eNOS) phosphorylation, and NO production upon exposure to shear stress ($p<0.05$ for all). In contrast, cells with > 85% knockdown of Atg3 protein expression (+Atg3 siRNA) exhibited less mitochondrial turnover, a profound impairment of eNOS phosphorylation, and were incapable of increasing NO in response to shear stress. Moreover, ROS accumulation and inflammatory cytokine production (MCP-1 and IL-8) were exaggerated (all $p<0.05$) in response to shear stress. These findings reveal that autophagy not only plays a critical role in maintaining NO bioavailability, but may also be a key regulator of oxidant / antioxidant balance and inflammatory / anti-inflammatory balance that ultimately regulate endothelial cell responses to shear stress.

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COMPLICATIONS—MACROVASCULAR—CELLULAR MECHANISMS OF ATHEROGENESIS IN DIABETES

16-LB

Endothelial Cells Respond to Hyperglycemia by Increasing the LPL Transporter GPIHBP1

AMY PEI-LING CHIU, BRIAN RODRIGUES, *Vancouver, BC, Canada*

In diabetes, when glucose uptake and oxidation are impaired, the heart is compelled to use fatty acid (FA) almost exclusively for ATP. The vascular content of lipoprotein lipase (LPL), the rate-limiting enzyme that determines circulating triglyceride clearance, is largely responsible for this FA delivery, and increases following diabetes. Glycosylphosphatidylinositol anchored high density lipoprotein binding protein (GPIHBP1) [a protein abundantly expressed in the heart in endothelial cells (EC)] collects LPL from the interstitial space and transfers it across ECs onto the luminal binding sites of these cells, where the enzyme is functional. We tested whether EC respond to hyperglycemia by increasing GPIHBP1. Streptozotocin diabetes increased cardiac LPL activity and GPIHBP1 gene and protein expression. The increased LPL and GPIHBP1 were located at the capillary lumen. *In vitro*, passaging EC caused a loss of GPIHBP1, which could be induced on exposure to high glucose. The high-glucose-induced GPIHBP1 increased LPL shuttling across EC monolayers. GPIHBP1 expression was linked to the EC content of heparanase. Moreover, active heparanase increased GPIHBP1 gene and protein expression. Both EC and myocyte heparan sulfate proteoglycan (HSPG) bound platelet-derived growth factor (PDGF) released by heparanase caused augmentation of GPIHBP1. Overall, our data suggest that this protein *"ensemble"* (heparanase-PDGF-GPIHBP1) cooperates in the diabetic heart to regulate FA delivery and utilization by the cardiomyocytes. Interrupting this axis may be a novel therapeutic strategy to restore metabolic equilibrium, curb lipotoxicity, and help prevent or delay heart dysfunction characteristic of diabetes.

Supported By: CDA

17-LB

Protein Kinase C Theta Is Involved in Angiotensin II-stimulated PAI-1 Expression in Vascular Smooth Cells

HONG-CHI CHEN, YI-CHUN LIAO, YUNG-CHIEH LIN, *Hualien City, Taiwan*

Protein kinase C (PKC), a diverse family of serine/threonine kinase, is involved in many important physiological events in various cells, including development, memory, differentiation, proliferation, apoptosis, survival, migration and carcinogenesis. Increased expression/activity of PKC isoforms in vascular smooth muscle cells (VSMC) have been shown to cause vasoconstriction, leading to hypertension. Furthermore, the activation of PKC resulted from high concentrations of glucose and nonesterified fatty acids has been shown in vascular cells of diabetic and insulin resistant patients, and of animal models, suggesting that it has significant roles in microvascular complication, cardiac hypertrophy, and in promoting atherosclerosis. PKC-theta, a member of noble PKC, is expressed in mouse skeletal muscle, human B lymphocytes, thymocytes, T cell lines, megakaryoblastic cells and platelets. Studies on T cell activation recognize PKC-theta as a master inducer of T cell proliferation and IL-2 production, ascertaining its essential role for the activation and survival of T cells. However, current understanding of PKC-theta's role in VSMC is very limited. Our studies revealed that Angiotensin II (Ang II) stimulated PKC-theta phosphorylation in rat VSMC and that both Ang II-stimulated mRNA and protein expressions of plasminogen activator inhibitor-1 (PAI-1), the major regulator of both tissue and urokinase plasminogen activators, were inhibited by a myristoylated PKC-theta pseudosubstrate, suggesting a functional role of PKC-theta in VSMC. In addition, the expression of a constitutively active PCK-theta induced PAI-1 promoter activity, and the PKC-theta inhibition reduced Ang II-induced nuclear factor-κB (NF-κB) activation. In summary, our data strongly suggest that PKC-theta-NF-κB signaling plays an important role in mediating Ang II-stimulated PAI-1 transcriptional activation in VSMC.

18-LB

Protein Phosphatase 2A Activation Contributes to Cardiovascular Complications that Occur in Mice with Diet-induced Obesity

LEENA PANNEERSEELAN-BHARATH, TING RUAN, YOU YOU LI, LANCE DEETER, DAVID KUNZ, QUAN-JIANG ZHANG, E. DALE ABEL, J. DAVID SYMONS, *Salt Lake City, UT, Iowa City, IA*

Cardiovascular complications exist in individuals with diet-induced obesity (DIO) and type 2 diabetes (T2DM). Our results from endothelial cells treated with palmitate, lipid-infused mice, and obese mice indicate that protein phosphatase 2A (PP2A) binds directly with eNOS and disrupts interactions among Akt-Hsp90-eNOS. When this occurs, eNOS enzyme function and NO bioavailability are impaired, and endothelial dysfunction and hypertension exist. In each model system indices of NO bioavailability are restored by pharmacological and genetic approaches that limit production of the FFA metabolite ceramide. Further, indices of NO bioavailability are preserved in endothelial cells and lipid-infused mice when PP2A activation is suppressed. We hypothesized that arterial dysfunction and hypertension that occur in obese vs. lean mice is prevented by PP2A inhibition. First we verified the ability of Lixte Biotechnology 100 (LB1; Setauket, NY) to suppress ($p<0.05$) arterial PP2A activity in mice after 3 and 14 days. Next, 7 week-old mice consumed standard (CON, n=20) or high-fat (HF, n=20) chow for 12-weeks. Subgroups (n=10) of CON and HF mice received IP injections of vehicle (V) or LB1 (1 mg/kg/day) for the last 14-days. HF mice had greater body mass, gonadal fat pad mass, and area under the curve during a glucose tolerance test vs. CON mice (all $p<0.05$) regardless of LB1 treatment. Hypertension existed in HF-V mice vs. all groups ($p<0.05$). p-eNOS to total eNOS was impaired ($p<0.05$) in homogenates of aorta, iliac, femoral arteries from HF-V mice vs. all groups. In the same admixture, Akt and Hsp90 co-immunoprecipitation with eNOS was less ($p<0.05$) in samples from HF-V mice vs. all groups. Endothelium-dependent vasorelaxation was attenuated ($p<0.05$) in femoral arteries from HF-V vs. all groups. Suppression of PP2A activity *in vivo* preserves indices of arterial function in obese mice.

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COMPLICATIONS—NEPHROPATHY—BASIC AND EXPERIMENTAL SCIENCE

19-LB

Disruption of Mitochondrial Quality Control by Myo-Inositol Oxygenase (MIOX) in Diabetic Kidney Disease

MING ZHAN, TATSUYA TOMINAGA, YASHPAL KANWAR, *Chicago, IL*

Diabetic kidney disease (DKD) is believed to be associated with oxidative stress and mitochondrial injury. MIOX, a specific tubular enzyme, modulates redox imbalance and apoptosis in tubular cells in diabetes, but the mechanisms remain unclear. We investigated the role of MIOX in perturbation of mitochondrial quality control machinery including mitochondrial dynamics and selective autophagy (mitophagy) under high glucose (HG) ambience both in vitro and in vivo. In HK-2/LLC-PK1 cells with HG treatment or cells stably transfected with MIOX, upregulation of MIOX was accompanied with mitochondrial fragmentation and depolarization, inhibited autophagy and mitophagy, and altered expressions of mitochondrial dynamic and mitophagic proteins. As a result, dysfunctional mitochondria without autophagic removal generate excessive ROS and initiate apoptotic pathway, as indicated by increased MitoSox intensity, Bax activation, cytochrome C release and apoptosis. MIOX siRNA or D-glucarate, an inhibitor of MIOX could partially reverse these perturbations. The mechanism by which MIOX disrupt mitochondrial integrity may be via its modulation on ROS production and Pink1-dependent Mfn2-Parkin interaction. In proximal tubules of STZ-induced diabetic mice, an increased MIOX expression and mitochondrial fragmentation but defective autophagy was observed. Dietary supplementation of D-glucarate to diabetic mice decreased MIOX expression, which also attenuated tubular damage and improved renal functions. Importantly, the tubular cells with drug treatment showed partial restoration of mitochondrial quality control, together with decreased oxidative stress and apoptosis. These results suggest a novel mechanism linking MIOX to mitochondrial dysfunctions in the pathogenesis of DKD, and D-Glucarate may be a potential therapeutic agent for the treatment of this disease.

Supported By: NIDDK

20-LB

Nucleobindin-2 Regulates Insulin-stimulated Glut4 Translocation in Podocyte

SHUICHI OKADA, TSUGUMICHI SAITO, EIJIRO YAMADA, KIHACHI OHSHIMA, KOSHI HASHIMOTO, TETSUROU SATOH, MASATOMO MORI, MASANOBU YAMADA, *Maebashi, Japan, Bunkyo-ku, Japan, Midori, Japan*

Insulin resistance and diabetes are strongly associated with kidney complications leading to impaired podocyte function and microalbuminuria. Although normal and pathophysiology of insulin signaling is well studied in classical insulin target tissues, the molecular pathways in podocytes remains poorly described. Previous studies have identified Septin 7 as a negative regulator of insulin simulated Glut4 translocation and glucose uptake in podocytes. We have found that Nucleobindin 2 is a constitutive binding partner for Septin 7, although Nucleobindin 2 over expression or knockdown had no significant effect on 2-deoxyglucose uptake or Glut4 translocation. However fenofibrate treatment had a dramatic effect on podocyte morphology associated with a 10% reduction in Septin 7 mRNA and increases in Nucleobindin 2 mRNA (10%), Nephrin mRNA (20%), Syntaxin4 mRNA (50%), and Clic5 mRNA (50%). In the presence of fenofibrate, Nucleobindin 2 knock down significantly inhibited Glut4 translocation. We hypothesize that Nucleobindin 2 can function as scaffolding protein that suppresses Septin 7 negative function to promote insulin signaling lead to glucose uptake in podocytes.

21-LB

WITHDRAWN

COMPLICATIONS—NEPHROPATHY—CLINICAL AND TRANSLATIONAL RESEARCH

22-LB

The Intraglomerular Hemodynamic Profile of Hyperfiltration Before and After SGLT2 Inhibition in Patients with Type 1 Diabetes

MARKO SKRTIC, GARY YANG, BRUCE A. PERKINS, NIMA SOLEYMANLOU, MAXIMILIAN EYNATTEN, HANS J. WOERLE, ODD ERIK JOHANSEN, ULI C. BROEDL, THOMAS HACH, MELVIN SILVERMAN, DAVID Z. CHERNEY, *Toronto, ON, Canada, Burlington, ON, Canada, Ingelheim, Germany*

Renal hyperfiltration in type 1 diabetes mellitus (T1D) occurs through several mechanisms, including altered tubuloglomerular feedback (TGFB), leading to afferent vasodilatation. Our aim was therefore to determine if TGFB activation with sodium-glucose co-transporter 2 (SGLT2) inhibition increases afferent arteriolar resistance.

Glomerular hemodynamic parameters were evaluated in 40 normotensive and normoalbuminuric T1D patients, 27 with baseline hyperfiltration (T1D-H, GFR≥135 ml/min/1.73m^2) and 13 with normofiltration (T1D-N, GFR 90-134 ml/min/1.73m^2) at baseline and after 8 weeks of SGLT2 inhibition with empagliflozin (EMPA, 25 mg daily).

Gomez's equations were used to derive efferent (R_E) and afferent (R_A) arteriolar resistances, glomerular hydrostatic pressure (P_{GLO}) and glomerular oncotic pressure (ϖ_G) from inulin (glomerular filtration rate) and paraaminohippurate (renal plasma flow) clearances, plasma protein and estimated ultrafiltration coefficients (K_{FG}). Measurements were obtained during clamped euglycemia (4-6 mmol/L) and hyperglycemia (9-11 mmol/L). At baseline during euglycemia, T1D-H had lower R_A (785±442 vs. 2097±616 dyne·sec·cm^{-5}, p<0.001) and higher P_{GLO} (67±5 vs. 56±4 mmHg, p<0.001) vs. T1D-N, whereas R_E was similar. After EMPA treatment, R_A in T1D-H increased from 785±442 to 1307±615 dyne·sec·cm^{-5} (p<0.0001) and P_{GLO} decreased from 67±5 to 61±5 mmHg (p<0.001) during euglycemia, while parameters remained unchanged in T1D-N. Similar findings were observed during clamped hyperglycemia.

The renal hemodynamic effect of EMPA on hyperfiltration is facilitated by increasing R_A without altering R_E, thereby leading to a partial correction of abnormally high baseline P_{GLO} in T1D-H. Our findings suggest that the effect of SGLT2 inhibition on increased distal tubular sodium delivery leads to altered TGFB. Based on these results, renal protection studies with SGLT2 inhibition are warranted in patients with T1D.

23-LB

Optimal Blood Pressure Targets for Favorable Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-analysis

NAM HOON KIM, SUN HWA KIM, HYE SUK KIM, KYEONG JIN KIM, JAE HEE AHN, JI HEE YU, JEE HYUN AN, HYE JIN YOO, HEE YOUNG KIM, JI A. SEO, SIN GO KIM, KYUNG MOOK CHOI, SEI HYUN BAIK, DONG SEOP CHOI, NAN HEE KIM, *Seoul, Republic of Korea, Anyang, Republic of Korea*

Most large clinical trials and epidemiologic analyses have proven that lowering blood pressure (BP) improved cardiovascular outcomes. Most guidelines generally recommend a systolic BP goal < 140mmHg, and a diastolic BP goal < 90 or 80 mmHg. However, there is uncertainty about optimal BP targets improving renal outcomes in patients with type 2 diabetes.

We searched PUBMED, EMBASE, and Cochrane Library for randomized controlled trials between 1965 and October 2013, and performed a systematic review and meta-analysis. We identified 13 randomized clinical trials enrolling 28703 type 2 diabetic patients and comparing prespecified BP targets. Outcome measures were development of microalbuminuira, macroalbuminuria, doubling of serum creatinine, and end-stage renal disease (ESRD)/ dialysis.

Overall, intensive BP control was associated with a significant decrease in the risk for composite renal outcome (odds ratio (OR), 0.74, 95% CI, 0.61-0.90), and this effect was largely dependent of reducing development of micro- and macroalbuminuria (OR, 0.66, 95% CI 0.53-0.82). In the analyses according to the prespecified BP targets, systolic BP targets < 140 mmHg was associated with significant reduction of composite renal outcome (OR, 0.77, 95% CI, 0.72-0.83), and albuminuria (OR, 0.76, 95% CI, 0.70-0.83), but not doubling of serum creatinine and ESRD/dialysis. Similar results were shown with systolic BP < 135 mmHg. However, there was no significant benefit with lowering BP < 130 mmHg for any renal outcome measures.

In patients with type 2 diabetes, lowering systolic BP < 140 mmHg, or < 135 mmHg may be beneficial in terms of renal outcomes, especially reduction of development of albuminuria. However, more intensive systolic BP lowering < 130 mmHg did not reduce adverse renal outcomes.

24-LB

Improved Urinary Inflammatory Profile in GFD-Adherent Adolescents with Type 1 Diabetes and Celiac Disease

EMILIA N. DEMELO, LIVIA DEDA, RONNIE HAR, HEATHER N. REICH, JAMES W. SCHOLEY, DENIS DANEMAN, DAVID B. DUNGER, RAHIM MOINEDDIN, LAURA MOTRAN, YESMINO ELIA, DAVID CHERNEY, ETIENNE B. SOCHETT, FARID H. MAHMUD, *Toronto, ON, Canada, Cambridge, United Kingdom*

Recent data implicate Celiac Disease (CD) as a risk factor for microvascular complications in Type 1 diabetes (T1D), including diabetic nephropathy (DN). Urinary inflammatory cytokine/chemokines have been implicated as early markers of DN. We characterized the urinary cytokine/chemokine excretion in adolescents with T1D and CD following a Gluten Free Diet (GFD) and evaluated if adherent CD and T1D patients (T1D-CD) represent a distinct group with altered urinary inflammatory markers compared to T1D without CD (T1D) and healthy controls (HC). T1D-CD and T1D patients aged 10-16y, with duration of T1D ≥ 1 year and no vascular complications were included. Eighteen T1D-CD biopsy-positive patients were matched 2:1 for age, sex, T1D duration and HbA1C to 36 T1D subjects and 36 HC. T1D-CD patients were adherent with a GFD; confirmed by levels of anti-tissue transglutaminase. Urine and serum levels of cytokines/chemokines as well as baseline clinical and laboratory variables were assessed. T1D alone had higher systolic blood pressure and Albumin Creatinine Ratio (ACR) than HC. Other baseline clinical characteristics were similar between the groups. T1D-CD patients exhibited lower levels of urinary TNF-α, IL-1a, IL-4, IL-5, IL-1B and G-CSF compared with T1D ($p<0.05$). Urinary biomarker levels between T1D-CD and HC were similar. In contrast, urinary FGF-2, GM-CSF, IL-12P70, IL-2, MCP-3, MDC, MIP-1β, sCD40L excretion was higher in T1D vs. HC ($p<0.05$). Therefore, "Dual Diagnosis" T1D-CD patients, who were adherent to a GFD, demonstrate decreased urinary excretion of inflammatory cytokine/chemokines which was similar to HC, suggesting a modulatory role of Celiac Disease and a GFD on urinary biomarkers.

25-LB

Gait Speed as an Indicator of Microvascular Disease and Inflammation in Older Adults with Type 2 Diabetes

DANIELA A. PIMENTEL, AZIZAH J. JORDAN, CHENCHIH CHUNG, BRAD MANOR, JERRY D. CAVALLERANO, VERA NOVAK, *Boston, MA*

Type 2 diabetes mellitus (DM) is associated with slower walking, chronic inflammation and endothelial dysfunction negatively affecting the brain, kidney and eye. In DM patients, slower walking is linked to impaired cerebral vasoreactivity (CVR). However, the link between walking with central and peripheral microvascular disease remains unclear. We investigated the association between gait speed, serum soluble vascular and intercellular adhesion molecules (s-VCAM and s-ICAM), CVR, diabetic retinopathy (DR) and UACR (urine albumin/creatinine ratio) in older adults with DM. 143 participants, 72 DM, age 65.1±8.4 years, 74 F, DM duration 13.1±10.3 years. Global CVR was calculated as the slope of the regression between perfusion measured at baseline and in response to hyper- and hypocapnia conditions using perfusion MRI. Slower gait speed correlated with increased s-ICAM levels (r^2_{adj}=0.1, p= 0.004) and with higher DR scores (r^2_{adj}= 0.1, p=0.03). In DM patients, slower gait speed was associated with reduced global CVR (r^2_{adj}= 0.09, p=0.04), with higher levels of s-ICAM (r^2_{adj}= 0.05, p=0.01), s-VCAM (r^2_{adj}= 0.03, p=0.04) and UACR (r^2_{adj}= 0.04, p=0.03) independent of BMI, DM duration and HbA1c. Higher s-VCAM levels in the DM group were associated with higher UACR (r^2_{adj}= 0.1, p= 0.04), independent of DM and HT duration and HbA1c. Slower gait speed may indicate chronic inflammation, microvascular disease and decreased vascular reserve in diabetic patients. UACR, along with s-VCAM, could reflect the detrimental microvascular changes affecting different vascular beds in the DM population.

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COMPLICATIONS—NEUROPATHY

26-LB

mTOR/p70S6K Pathway-mediated Hyperphosphorylation of Tau Is Involved in Cognitive Dysfunction of STZ-induced Diabetic Mice

JING WU, SHAN WANG, SHAN-LEI ZHOU, FANG-YUAN MIN, JIN-JU MA, XIA-JIE SHI, *Changsha, China*

Abnormal levels of mammalian target of rapamycin (mTOR) signaling have been recently implicated in the pathophysiology of neurodegenerative diseases, such as Alzheimer's disease (AD). The implication of mTOR in diabetes mellitus (DM)-related cognitive dysfunction still remains unknown. In the present study we detected alterations of mTOR/p70S6K signaling and increased phosphorylation of tau in the hippocampus of streptozotocin (STZ)-induced diabtetic mice. The expression of phosphorylated mTOR (p-mTOR), phosphorylated p70S6K (p-p70S6K) and phosphorylated tau (p-tau) in the hippocampus of diabetic mice significantly increased when compared with control mice. A low dose of rapamycin was used to elucidate the role of mTOR signaling in DM-related cognitive deficit. Rapamycin restored abnormal mTOR/p70S6K signaling and attenuated the phosphorylation of tau protein in the hippocampus of diabetic mice. Furthermore, the spatial learning and memory function of diabetic mice significantly impaired compared with control mice, was also reversed by rapamycin. These findings indicate that mTOR/p70S6K signaling pathway is hyperactive in the hippocampus of STZ-induced diabetic mice and inhibiting mTOR signaling with rapamycin prevents the DM-related cognitive deficits partly through attenuating the hyperphosphorylation of tau protein.

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27-LB

The Role of Proxynitrite in Peripheral Diabetic Neuropathy

JOSHUA F. EDWARDS, IRINA G. OBROSOVA, CAROLINA M. CASELLINI, HENRI PARSON, MARK A. YOREK, AARON I. VINIK, *Norfolk, VA, Baton Rouge, LA, Iowa City, IA*

Accumulation of nitrotyrosine (NT) has been associated with sympathetic nerve and endothelial dysfunction. NT can be measured in the peripheral circulation as a marker of peroxynitrate action. The objective of this study was to determine NT levels in healthy controls (HC), diabetic patients without diabetic peripheral neuropathy (DM-Non-DPN) and diabetic patients with DPN (DM-DPN). We hypothesized that a correlation would exist between NT levels and severity of neuropathy.

This was a cross-sectional study of 49 patients (15 HC, 12 DM Non-DPN, 11 possible/probable (PP) DM-DPN, and 11 Definite DM-DPN). Neuropathy diagnosis was stratified according to the Toronto Consensus guidelines. Severity of neuropathy was classified according to Total Neuropathy Scores (TNS) which assess neuropathy symptoms as well as motor and sensory function.

Mean NT levels (pmol/mg protein) in serum were 3.14±0.31 for HC, 4.32±0.44 for DM Non-DPN, 4.47±0.46 for PP DM-DPN, and 4.81±0.46 for Definite DM-DPN. Mean levels in all diabetic subgroups were significantly higher than controls. NT levels correlated significantly with TNS (r =0.374, p<0.0001), total symptom score (TSS) (r =0.353, p =0.013), motor score (MS) (r =0.485, p =0.0004), and sensory score (r =0.318, p =0.026) for the whole group, and with TSS (r=0.673, p =0.026) and MS (r=0.798, p =0.0032) for the PP DM-DPN group. Linear regression analysis revealed a significant correlation between TNS and NT levels for all subjects (p =0.0032) and PP neuropaths (p=0.023). There were no significant correlations found between NT and weight, BMI, BP, HbA1c or lipoprotein levels.

Our findings suggest that peroxynitrate production may have a pathogenic role in DM independent of glycemic and metabolic control. The significantly steeper slope of the PP DM-DPN group compared to the whole group further suggests that circulating levels of NT are increased in patients with and without DPN. In conclusion, NT could serve as a biomarker for the presence and severity of neuropathy.

28-LB

Effects of Plasma Kallikrein on the Neuroretina in Diabetic Rats

GONGXIONG WU, EDWARD FEENER, *Boston, MA*

Diabetic retinopathy is often associated with manifestations such as microcirculatory abnormalities and impairment of neuroretinal structure and function primarily due to reduced thickness of retinal layer, particularly the ganglion cell layer leading to visual impairment. However, the mechanisms underlying neuro-retinal injury and dysfunction in diabetes and DME are not fully understood. Here, we report that the Plasma Kallikrein (PK) engages in regulation of retinal ganglion cell death through a cleavage-dependent activation of NDMA receptor in the neurons. In the STZ-induced type 1 diabetes model in rats, intravitreal (IVT) injection of activated PK in diabetic rats triggers retinal neuron degeneration. Consistently, selective knockdown of PK by PK antisense (PK ASO) decelerates this retinal neuron degeneration. In vitro, PK-induced cortical neuronal cell death requires the presence of NMDA receptors (NR). Interestingly, we found that the PK directly cleaves NR1 at Arg323 residue located in the extracellular N terminal domain in vitro. The truncated NR1 enhances the function of NMDA receptor and subsequent activation of the downstream calcium mediated signal transduction. Furthermore, PK inhibitor protected against retinal neuron degeneration in diabetic condition. Together, these results indicate that PK plays a critical role in retinal neuro-degeneration in diabetes and suggest that PK may serve as a potential therapeutic target for clinical intervention and treatment of diabetic retinal neuro-degeneration.

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29-LB

The Role of Neurospecific Proteins in the Diagnosis of Cognitive Dysfunction in Patients with Diabetes Mellitus Type 1

MARIIA NOVOSELOVA, JULIA SAMOYLOVA, *Tomsk, Russian Federation*

One of the targets of diabetes mellitus type 1 (DM1T) is the central nervous system with the further formation of cognitive dysfunction. In the case of timely diagnosis and treatment of cognitive impairment associated with metabolic changes that can partially or completely regress.

The aim of this study was to identify neurospecific proteins as biomarkers of the brain damage in patients with DM1T.

We examined 58 patients at the age of 22,45 ± 4,627 years, disease duration 6,6 ± 3,951 years, the control group was consisted of 29 healthy people at the same ex and age. To assess mental status used Montreal Assessment Scale cognitive dysfunction (MoCa test). Statistical processing was carried out using an application software package R-system. It was found that DM1T may manifest cognitive impairment of the central nervous system according MoCa test. Analysis of the results showed that patients with DM1T had cognitive impairment (total score of 25 points) to 72.2 % while in the control group cognitive functions were normal in 100% (total score of 30 points) . When evaluating MoCa test recorded a statistically significant reduction of parameters that assess short-term memory and attention in patients with DM1T compared with the control group.The study found a significant increase in all neurospecific proteins: S100, myelin basic protein and glial fibrillary acidic protein in patients with DM1T compared with the control group, which were correlated with Hba1c (p<0,001). The most important finding was the reduction in memory functions while increasing neurospecific proteins. The final total score reflecting the total value of cognitive function had negative correlation with all the studied biomarkers.

As a consequence, it is recommended indication of neurospecific proteins in patients with DM1T who have not achieved the target values of carbohydrate metabolism, there is a decrease of compliance, as well as cognitive impairment.

COMPLICATIONS—OCULAR

30-LB

A New Mechanism in Regulation of RPE Tight Junctions in Diabetic Retinopathy

SARAH X. ZHANG, JACEY H. MA, JOSH J. WANG, *Buffalo, NY*

The retinal pigment epithelium (RPE) is a monolayer of pigmented epithelial cells located adjacent to photoreceptors cells and plays an essential role in supporting the structural and functional integrity of the neural retina. One of the major functions of the RPE is to form the outer blood-retinal barrier (BRB). Damage of the RPE barrier leading to increased permeability is believed to contribute in part to retinal edema in diabetic retinopathy. Herein, we investigate the role of ER stress and X-box binding 1 (XBP1), a central coordinator of cellular response to ER stress, in regulation of RPE tight junctions. Exposure of differentiated human RPE cells to pharmacological ER stress inducers thapsigargin and tunicamycin results in increased ER stress, evident by elevated levels of GRP78, P58IPK, CHOP, and splicing of XBP1 mRNA. Pharmacological inhibition of XBP1 splicing prevented the upregulation of GRP78 and P58IPK, but did not affect CHOP expression. Sub-lethal dose of thapsigargin, but not tunicamycin, reduced ZO-1 expression and impaired tight junction formation. Interestingly, pretreatment with XBP1 inhibitor sensitizes the cells to tight junction damage in the presence or absence of tunicamycin. In contrast, forced expression of active XBP1 gene largely reversed the tight junction damage caused by pharmacological XBP1 inhibition. In line with the results from in vitro study, conditional knockout of XBP1 in RPE cells leads to defective tight junction formation, which was exacerbated in diabetic condition. Taken together, our results have revealed that tunicamycin and thapsigargin differentially regulate ER stress and tight junction formation, suggesting that other mechanisms independent of ER stress are involved in RPE barrier regulation. Furthermore, out study suggests that activation of XBP1 by ER stress may play a protective role in the RPE barrier function and in diabetic retinopathy.

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31-LB

Comparing Technical Failure Rates in Diabetic Retinopathy Screening between RETeval, a 30 Hz Flicker Electroretinogram Device, and Mydriatic, 7-Field, Stereo Fundus Photography

APRIL MAA, ENSA PILLOW, WILLIAM FEUER, TARA BROWN, RACHEL CAYWOOD, QUENTIN DAVIS, JOEOL CHASAN, STEPHEN FRANSEN, *Decatur, GA, Oklahoma City, OK, Miami, FL, Gaithersburg, MD*

Diabetic retinopathy (DR) is a cause of preventable blindness and screening reduces vision loss. There are limitations to current screening methods. ERG implicit time correlates with extent of DR but using ERG for DR screening is impractical because of difficulty performing and interpreting ERG results. This study measured the performance of RETeval, a handheld ERG device. 500 diabetic patients were selectively recruited to obtain 80 patients in each category: 1) no DR; ETDRS level 10. 2) Mild DR without CSME; ETDRS levels 14-35. 3) Moderate DR without CSME; ETDRS levels 43-47. 4) Mild/moderate DR with CSME; ETDRS levels 10-47. 5) Severe DR or PDR; ETDRS levels 53 and higher. The RETeval test was performed. Patients were dilated and ETDRS-compliant 7 field fundus photographs were taken. These photographs were double-read in a masked fashion in a reading center. Photographic results differing by more than 1 ETDRS step were sent to adjudication where 2 readers and a retinal specialist determined the final ETDRS level. The photography results served as the gold standard to which the RETeval findings were compared. 392 patients completed the study. There were 340 male and 52 female. The RETeval device had a technical failure rate (no results generated) of 0.5% (2/392 patients) whereas ETDRS fundus photography (ungradeable images) had a significantly higher (p<0.001, exact McNemar test) technical failure rate of 15% (57/392 patients). The RETeval device is a new handheld ERG device. Compared to fundus photography, the RETeval device had a low technical failure rate that was statistically significant. This study shows that the RETeval device has promise as a new screening tool for DR because its easy to use and has low failure rates.

Supported By: NIH

32-LB

Compliance with Recommended Follow-up for Diabetic Retinopathy in a County Hospital Population

ANH-DANH T. PHAN, ERIC D. DOERR, JUN XIE, MARK M. KAEHR, CHI-WAH (RUDY) YUNG, ALLISON A. PERNIC, *Indianapolis, IN, West Lafayette, IN*

The purpose of this study is to assess the association between insufficient follow-up and demographic, clinical, and social parameters among diabetic patients at an inner-city county health system. This is an IRB-approved, case series of the Wishard-Eskenazi Teleretinal Diabetic Retinopathy Screening Program using retinal cameras conducted at four primary care clinics from June 2009 through February 2013. Patients identified with diabetic retinopathy (DR) were referred for eye clinic examination based on the American Academy of Ophthalmology's Guidelines. Compliance was determined by adherence to recommended eye clinic follow-up interval through medical records review. Analysis applied Pearson's chi-squared test or Fisher's exact test for categorical variables and Student's t test for continuous variables. Multivariate logistic regression model was employed to obtain adjusted odds ratios (ORs) for compliance with the significant variables. Of 258 patients referred, 93 were compliant and 165 were noncompliant. We observed significant association between compliance with DR severity alone (p=0.033) and when combined with diabetic macular edema (p=0.025), as well as with White and Asian vs. Black and Hispanic patients (p=0.043). In the final multivariate logistic regression model, the effects of DR severity and its interaction with age were found to be significant: Odds of compliance of those with severe or proliferative DR were much greater than those with mild or moderate DR (OR=8.4); Odds of compliance for elder (older than 50 years) is slightly greater than for younger patients (OR=1.2). History of "no-show" to medical appointments (0-1 vs. 2 or more) trended toward significance (p=0.094). We conclude that patients with poor follow-up adherence were significantly more likely to have less severe DR and younger age. Targeted education campaign at the primary care level in this vulnerable population to prevent future vision loss would be beneficial.

DIABETIC DYSLIPIDEMIA

33-LB

Identification of a Putative Glucocorticoid Receptor Element in Human Cholesteryl Ester Transfer Protein Gene

YONG B. PARK, MI AE KANG, OH-SHIN KWON, *Daegu, Republic of Korea*

Transcriptional regulation of human cholesteryl ester transfer protein (CETP) by glucocorticoid was investigated using a transient reporting system. A series of deleted vectors generated from 5'-upstream region (3434 bp) of the CETP gene linked to the chloramphenicol acetyl transferase (CAT) reporter gene was individually transfected to HepG2 cells. Promoter analyses revealed an essential regulatory machinery in the -138/-101 region of the upstream sequence of the human CETP gene. When the cells, transfected with the reporter vectors with the -138/-101 region deleted, were treated with dexamethasone (Dexa), the CAT activity was increased, suggesting that there may be a glucocorticoid receptor element (nGRE) in the region. Competition analyses on the gel mobility shift assay, using the consensus GRE and a purified glucocorticoid receptor as competitors, confirmed the -138/-101 region as a GRE. Footprinting analyses showed that the DNA segment at the -133/-108 is protected by the nuclear extract from HepG2. The identified GRE sequence did not show homology with the consensus GRE sequences. It may be a unique negative GRE existing in the CETP gene.

34-LB

Serum Triglyceride Levels are Correlated with Markers of Inflammation in Isolated Hyperlipidemia Patients

MUHARREM AKHAN, HAKAN SARLAK, MUSTAFA CAKAR, OMER KURT, SEVKET BALTA, EROL ARSLAN, KENAN SAGLAM, *Ankara, Turkey*

Hyperlipidemia is characterized by elevation of serum cholesterol, triglyceride and LDL cholesterol and decreased level of HDL cholesterol. Hyperlipidemia leads to atherosclerosis and cardiovascular diseases. Studies have shown that there was a correlation between hematological parameters and atherosclerotic cardiovascular diseases. We aimed to investigate some markers of inflammation (Red Cell Distribution Width and Nutrophil to Lymphocyte Ratio) in newly diagnosed and isolated hyperlipidemia patients.

The study recruited 82 patients (46 females, 56.1%) with a newly diagnosed and isolated hyperlipidemia applied in our outpatient clinics. The patients had no other documented atherosclerotic cardiovascular disease, hypertension, diabetes or renal failure. The mean ages of the male and female groups were 41.36 and 53.87 years, respectively. Mean serum triglyceride (Trig), low density lipoprotein, and high density lipoprotein levels of the whole group were 277.2±290, 186.3±45.1, 50.6±13.3 mg/dL, respectively. As markers of inflammation, mean red cell distribution width (RDW) and neutrophil to lymphocyte ratio (NLR) of the study patients were 14.35±1.31 % and 1.69±0.58, respectively. In correlation analysis, serum Trig levels were found correlated with RDW and NLR values (Pearson, r and p values, -0.402 and -0.257; <0.001 and 0.020, respectively). In the regression analysis, 1 unit increase in RDW and NLR were associated with 124 and 170 mg/dL increases in serum Trig levels.

Dyslipidemic patients have higher levels of atherosclerosis and further future cardivovascular risks. Our study emphasizes the idea that these patients have higher levels of endothelial inflammation finally leading to damage, atherosclerosis and cardiovascular problems.

FOOT CARE—LOWER EXTREMITIES

35-LB

Comprehensive Assessment of Sensitivity in the Feet of People with Type 2 Diabetes Mellitus

VALENTINA RIVAS-ACUÑA, YADIRA MATEO-CRISOSTOMO, HERMINIA GARCIA-BARJAU, AMALIA MARTINEZ-SERRANO, MARGARITA MAGAÑA-CASTILLO, RODOLFO GERONIMO-CARRILLO, *Villahermosa, Mexico*

The purpose of the study was to evaluate in a comprehensive way the sensation in the feet of people with type 2 diabetes mellitus at a Highly Specialized Hospital and an Urban Health Center in Villahermosa, Tabasco. Methods: The study design was correlational descriptive, sampling was 198 people with diabetes. To evaluate the feet sensitivity we was used the Michigan Neuropathy Screening Test designed to detect the presence of diabetic neuropathy, it identify the sensitivity and risk factors for developing foot ulcers. Data was performed in SPSS version 20.0. Results: 70.2% female and 29.8% male, average age was 56.44 years old (SD = 10.1) and the average years with disease was 12.3. 46% with neuropathic symptoms moderate, 26.3% severe neuropathic symptoms , 65.7% had risk of positive neuropathy, 40.9% of them were women and 24.8% men, 41.1% had a moderate level of sensitivity as only 29.3% had normal sensitivity. In regard to glycemic control 74.7% had poor control. Discussion: The results obtained at the level of sensitivity, differ from the Camacho study (2011), who reported that the 44.9% of the study subjects have normal sensitivity, 24.1% mild and 12.2% moderate sensitivity. Risk factors that were detected with higher prevalence in our study was helomas and hyperkeratosis 83%, deformities 62.1% of patients, this results differs from the study of Gonzalez et al., (2010) who reported 33.1% helomas and hyperkeratosis. In our study, women had more risk of neuropathy in age 50-69 years old. There is a significant correlation between the sensitivity over the years with disease (r =. 159), capillary glycemia (r =. 189), symptoms of neuropathy (r =. 420) and with the risk of neuropathy (r =. 290) p = .01.

Conclusion: The study showed that people who have more years with type 2 diabetes mellitus have greater loss of sensitivity, more symptoms of neuropathy and uncontrolled glycemic, in women predominantly.

36-LB

Ertapenem for Diabetic Foot Infections in China: A Multicentre, Randomised, Double-Blinded, Active-Controlled Study

Z.R. XU, X.W. RAN, YANG XIAN, X.D. YAN, G.Y. YUAN, S.M. MU, J.F. SHEN, B.S. ZHANG, W.J. GAN, JUE WANG, DFI STUDY GROUP, *Beijing, China, Chengdu, China, Nanning, China, Zhenjiang, China, Shanghai, China*

Diabetic foot infections (DFIs) are common and serious complications affecting worldwide diabetes population. Few randomised studies have assessed antibiotic regimens in Asian populations. Our objective was to assess the efficacy and safety of ertapenem versus piperacillin/tazobactam (TZP) for DFIs in Chinese population.

Diabetic adults (n=565) with moderate-to-severe DFIs requiring intravenous (IV) antibiotics were randomly assigned either ertapenem (1g daily) or TZP (4.5g every 8h) for a minimum of 5 days. Oral amoxicillin/clavulanate (625mg every 12h) could be given for 23 days at maximum after IV therapy. Vancomycin may be allowed for bacterial species known resistant (i.e. *Enterococcus spp*) to study therapy. The primary outcome was the proportion of patients with a favourable clinical response on the day that IV antibiotic was discontinued (DCIV). An evaluable-patient population was identified for primary analysis. Safety was assessed across the study.

At DCIV, 443 patients were assessed clinically evaluable and 533 MITT qualified. Baseline characteristics between groups were comparable. Findings on primary outcome were summarised in table.

Safety was similar by ertapenem versus TZP based on drug-related AE (13.5% vs. 16.0%) and AE leading to discontinuation (4.0% vs. 5.8%).

Ertapenem is non-inferior to piperacillin/tazobactam and may be an option for DFIs in China.

Results of DFI study primary outcome in Clinical Evaluable/Modified LOCF and MITT/Modified LOCF Populations

	Treatment Group							
	Ertapenem (A)			Piperacillin/Tazobactam (B)				
		Estimated‡ Response			Estimated‡ Response		Estimated† Difference (A-B)	
Analysis Population	n/N	%	(95% CI)	n/N	%	(95% CI)	%	(95% CI)
DCIV – Clinical Evaluable	205/219	93.6	(89.5, 96.5)	218/224	97.3	(94.3, 99.0)	-3.8	(-8.3, 0.0)
DCIV - MITT	237/267	88.8	(84.3, 92.3)	241/266	90.6	(86.4, 93.8)	-1.9	(-7.3, 3.3)

† Based on Miettinen & Nurminen method stratified by strata. ‡ Based on Exact method without adjusting strata.

n = Number of patients with favourable response (Cure or Improvement); N = Number of patients in analysis population.

LOCF = Last observation carried forward; Modified LOCF: Only clinical failure was carried forward.

Non-inferiority margin for primary outcome (ertapenem - piperacillin/tazobactam) was prespecified at -15%.

Supported By: MSD

DIABETES EDUCATION

37-LB

MICROCLINIC Social Network Interventions for Obesity and Diabetes in Jordan: A Three-Armed Cluster Randomized Controlled Trial

ANDREA B. FEIGL, DANIEL E. ZOUGHBIE, KATHLEEN T. WATSON, NANCY BUI, LEILA MAKARECHI, YAZEED M. IBRAHIM, ERIC L. DING, *Boston, MA, San Francisco, CA*

Background: Diabetes and obesity are suggested to propagate within social networks, with diabetes a concern in the Middle East. Leveraging pre-existing social networks to propagate healthy behaviors, we conducted the first ever social-network randomized trial to improve obesity and diabetes in a developing country.

Methods: Based in community health clinics in Amman, Jordan, we tested the effects of various Microclinic Social Network (MSN) behavioral interventions in collaboration with the Jordanian Ministry of Health and Royal Health Awareness Society. A 3-armed 28-week cluster randomized trial was designed: Arm A) enhanced MSN social network program in weekly interactive

For author disclosure information, see page LB91.

sessions led by health-educators; Arm B) basic MSN social network program but without extensive class interactions; Arm C) controls with standard care. Weight, waist circumference, HbA1c, and blood pressure were collected. Longitudinal multilevel mixed models levels of community, classrooms, and microclinic social clusters were used.

Results: The trial enrolled 911 participants, comprised of 9 community-cohorts, 45 classroom clusters, and 523 social clusters. Participants were 66% women, mean age 55.1 years (10.2), mean BMI 33.6 (3.2). After 12 weeks, Arm B reduced weight vs. C (-0.99 kg, 95% CI: -1.93 to -.06; P=0.037), while A yielded borderline weight change vs. C (-0.59 kg, P=0.096). However, by end of 28-weeks of intervention, Arm A showed the strongest sustained weight reduction versus control (-1.11 kg, -1.87 to -0.35; P=0.004), while B did not (-0.64, -1.69 to 0.41, P=0.23), with overall P for program*time interaction=0.019. HbA1c showed borderline significant drop at 28 weeks for A vs. control (-0.20, P=0.08), but not B vs. control (-0.15, P=0.27). Waist circumference and blood pressure were not significant.

Conclusions: Results demonstrate the effectiveness of MSN health interventions in a resource-limited, high chronic disease burdened, developing-country setting.

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38-LB

Improved Diabetes Control Using SMBG Pattern Management in High-Risk Minorities (HRM)

JAMES R. GAVIN III, LENORE T. COLEMAN, IKENNA MEYERS, *College Park, GA*

SMBG in a diabetes education program improves T2D outcomes. This study was done to evaluate if use of SMBG data taught by clinical pharmacists or educators improved A1C compared to diabetes classes or medication review in HRM. A pretest-posttest format was used. Subjects (n=807) were referred by providers from 5 federally qualified health centers and a practice group. HEDIS measures collected included: A1C, BP, FPG, BMI, total cholesterol (TC), LDL-C, HDL-C, and TGs. Subjects received a validated knowledge test initially, 3 months after taking a diabetes class and at study end. A psychosocial inventory was collected initially and at study end. This multi-component model was a four-arm study comparing Diabetes Classes (DC), Pharmacist Medication Management (MTM), Pattern Management (PM) using a glucose meter data management system, and control subjects who did not participate (Ctl). Subjects had at least two interventions prior to assignment to PM. 258 subjects attended the diabetes classes, 71 in the MTM arm, 44 in the PM arm, and 138 Ctls. 296 were lost due to incomplete and/or lost data. Demographics revealed 77% in the 20-64 y.o. range, 21% in the >65 age group, and 16% in the <20 age group, with 65% female subjects. The mix was 86% non-Hispanic black and 13% non-Hispanic white. 60% of subjects were on Medicare/Medicaid, 30% employer-insured, and 16% uninsured. Mean A1C levels in the DC group decreased from 7.93 to 7.60, 8.06 to 7.32 in the MTM group, 7.70 to 7.28 in the PM group, while Ctls increased from 7.00 to 7.36. The PM group had the greatest mean changes in multiple measures including BMI, BP, FP, TC, and TG. The MTM group had the greatest improvement in A1C. Conclusions: The PM group had the largest changes in overall measures of T2D control. There was increased diabetes knowledge and reduced ER visits. Thus, in HRM using PM from SMBG, the improvements suggested better monitoring of multiple metrics of relevance in T2D control.

39-LB

Can Promotoras Reconnect Individuals to the Healthcare System?

LOURDES M. OLIVAS, CAROL TURNER, RICHARD A. JACKSON, MATTHEW BERGER, JULIE GOLDMAN, *Las Cruces, NM, Boston, MA*

Pathways to Better Health through Workforce and Community Engagement (Pathways) in New Mexico is part of a large CMS Health Care Innovation Project (HCIP) testing the scalability, reproducibility and clinical impact of a program using local community health advocates to deliver well-established health information classes. The overall HCIP program has enrolled 1,111 participants in the first year, with over 70% completing the 3-month follow-up and data collection. The program has produced significant improvements in BP (75.8% < 140/90 follow-up vs. 62.9% baseline, p 8.0% (p < .001). Of 156 people with pre-diabetes (A1C 5.7%-6.4%) at baseline, 26.3% moved to the non-pre-diabetes range (A1C < 5.7%) at follow-up, p < .001. In the past the Pathways program had used dietitians and New Mexico State University Extension agents for delivery of this program, but has now switched to a promotoras model to extend the reach of the program, and to reduce costs. Changes in BP, A1C, and pre-diabetes are similar when the program is delivered by promotoras, and, when compared to non-promotoras, there is an improvement in participants' re-engagement with the healthcare system. Re-engagement is measured by looking at those participants who had not seen a healthcare provider (HCP) in more than six months. Of these "healthcare-disconnected" participants, 33% said at follow-up that they had made an appointment with a HCP, while 33% said that they had shown their A1C and BP results to a HCP. In the prior incarnation of the program, not delivered by promotoras, only 16% of "disconnected" participants had shown these values to an HCP, p < .001. Thus, promotoras can effectively and efficiently reconnect individuals to the healthcare system.

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40-LB

Impact of Ramadan Fasting on People with Diabetes

MAHMOUD IBRAHIM, LAURA N. MCEWEN, ALY A. MISHA'L, FIRAS A. ANNABI, EBTESAM M. BA-ESSA, M. TEMEL YILMAZ, HYAM TANTAWI, WILLIAM H. HERMAN, *Atlanta, GA, Ann Arbor, MI, Amman, Jordan, Dhahran, Saudi Arabia, Istanbul, Turkey, Cairo, Egypt*

Muslims who fast during Ramadan abstain from eating and drinking from predawn to after sunset. The ADA has recommended that people with diabetes who fast during Ramadan receive education to achieve a safer fast. Our objectives were to describe the characteristics and behaviors of people with diabetes in Egypt, Jordan, Saudi Arabia, and Turkey who intended to fast during Ramadan 2013. Pre-Ramadan surveys were administered to 186 people, 171 (92%) of whom also completed post-Ramadan surveys. 40% reported usually receiving advice about fasting from a physician, 10% from a religious authority, and 45% from both. Mean age was 49 ± 16 years, BMI was 26 ± 11 kg/m2 and HbA1c was 8.4 ± 1.9%. 92% had type 2 diabetes. 48% were treated with insulin, 32% were treated with sulfonylureas, and 19% were treated with non-sulfonylurea oral medications or diet alone. 81% reported receiving care from endocrinologists. Patients who saw endocrinologists were more likely to report receiving education about fasting during Ramadan than patients who saw only primary care physicians (55% vs. 33%, p=0.0280). 25% reported never monitoring their blood glucose while fasting. 41% reported that nothing prompted them to break their fast. 85% reported that they actually fasted for a mean of 23 ± 10 days. After Ramadan, 94% reported receiving education before and 88% reported receiving education during Ramadan. 96% reported monitoring their glucose while fasting. 48% reported that they experienced hypoglycemia with an average blood glucose of 58 mg/dl. Five people reported hospitalizations including one for hypoglycemica and one for hyperglycemia. For people with before and after Ramadan measurements, the change in HbA1c was -0.5 ± 1.4%. Despite guidelines for managing diabetes during Ramadan, glycemic management is not optimal. Individualized education programs that address each person's treatment and monitoring during Ramadan are needed. An enhanced education program addressing the limitations observed in this study is being tested this year in 6 countries.

41-LB

Cognitive Function and Self-Efficacy in Type 2 Diabetes with Poor Glycemic Control

JOAN MONTSERRAT, XAVIER DEBUSSCHE, CYRIL FERDYNUS, SONIA MICHALON, MICHÈLE KOLECK, JEAN-PIERRE SERVEAUX, *Ivry-sur-Seine, France, Saint-Denis, Réunion, Bordeaux, France*

Self-management plays a central role in type 2 diabetes (T2D) for the prevention of complications. Cognitive impairment is frequent and occurs earlier in T2D, and executive dysfunction has been shown to hamper self-care. The relationship between self-efficacy and cognitive function have not been studied so far. This cross-sectional study aimed to assess the prevalence of cognitive impairment and its relation to self-efficacy in patients with poorly controlled T2D. Face-to-face interviews have been administered in a population of people with T2D followed in secondary care settings with following tests and questionnaires: self-efficacy and outcome expectancies, MMSE, MOCA, FAB, five words (5WT), Mac Nair, I-ADL, B-ADL. A group of 84 consecutive patients were studied (54% M, 46% F; 41-90 yrs; diabetes duration 12.7±9.3 yrs; HbA1c 9.2±2.7%; educational achievement ≤8 yrs 60.7%; coronaropathy 34.5%; nephropathy 35.7%). Low MMSE, MoCA, 5WT and FAB scores were present in 27.4% [95% CI:17,5-36,5], 76.2% [66.9-85.1], 20.2% [11.4-28.6], and 52.4% [41.3-62.7] of patients, respectively. Significant impacts on instrumental daily life activities (21.6%) and physical activity (46.0%) were present, related to 5WT and FAB. Cognitive complaints (McNair) were present in 31 patients (36.9%; 95% CI: 26.6-47.2%), related to MMSE and 5WT. Self-efficacy was low, with high outcome expectancies, and related to McNair, but not to other tests. In conclusion, in this population of T2D patients with low education level and poor glycemic control, low self-efficacy was related to memory complaints but not to impaired executive function. In contrast, there was evidence of good understanding of outcome expectancies of health actions. Self-management programs should take into account several domains of cognitive impairment: executive function, for self-care activities; and memory impairments which could hamper self-confidence in one's ability to manage the complex health actions in the long term.

For author disclosure information, see page LB91.

42-LB

A Comparison of Two Methods of Foot Care Education: The Fremantle Diabetes Study

MENDEL BABA, JENNY DUFF, LAURIE FOLEY, WENDY A. DAVIS, TIMOTHY M.E. DAVIS, *Perth, Australia*

The purpose of this study was to compare the effectiveness of two methods of diabetic foot care education on foot health, behaviours and attitudes in a community-based cohort of patients with type 2 diabetes. Community-based patients enrolled in Phase II of the Fremantle Diabetes Study were randomly allocated to receive either written foot care education (Group A) or an interactive 90-minute foot care education program presented by a credentialed diabetes educator (Group B). A quantitative foot score (maximum 90 points score based on graded severity of pathology ranging from skin abnormalities to ulcers/gangrene in both feet), the Nottingham Assessment of Functional Foot Care (NAFFC) survey score (maximum 30 points based on foot care behaviours) and a 6-question survey of attitudes to diabetes-related foot complications were recorded at baseline and 3 months. 154 patients (mean±SD age 68±10 years, 59.7% males, median [interquartile range] diabetes duration 11.5 [5.6-18.9] years) were recruited. There was a significantly greater change (Δ) in foot score in Group A vs. Group B at 3 months (8.3±3.6 at baseline, Δ-1.8 (95% CI -2.4 to -1.2) vs. 6.8±2.6, Δ-0.1 (-0.7 to 0.4); P<0.001) that persisted after adjustment for baseline values, but no change in NAFFC survey score (P=0.13). In the attitudes survey, Group B felt they better understood how to prevent foot complications than Group A (P=0.031). Written information was more effective at improving foot health, while interactive education improved participants' confidence in undertaking preventive measures. These data suggest that the most effective foot care education should include both written information and interaction with a qualified diabetes health care professional.

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43-LB

Nonvisual Foot Examination for People with Visual Impairment

ANN S. WILLIAMS, BRYAN D. CALDWELL, JILL S. KAWALEC, *Cleveland, OH, Independence, OH*

People with diabetes and visual impairment have high risk of foot problems. In diabetes self-management education (DSME), usual care is to teach them to seek sighted assistance for regular home foot exams, yet many report not doing this. A simple nonvisual technique for inspecting feet, using touch and smell, may help people detect foot problems in early, treatable stages, ultimately decreasing ulcers and amputations.

The purpose of this pilot study was to compare the efficacy, acceptability, and feasibility of nonvisual foot examination with usual care (requesting sighted assistance for examination of feet).

Fifty-seven visually impaired adults with diabetes were recruited, consented, and assigned to experimental or comparison groups. both groups received comprehensive DSME, with emphasis on foot care. The experimental group was taught nonvisual foot examination, the comparison group to ask for sighted assistance for regular foot checks. All had a baseline podiatric evaluation, with visits at 3 months and 6 months. Focus groups were conducted for all at the end of the study.

Analysis included total frequency of home foot checks and frequency of home foot checks according to instructions given each group; number of symptoms reported per podiatrist visit; number of foot problems documented by podiatrists per visit; and qualitative acceptability analysis from focus groups.

Total number of foot checks was similar between the two groups. There was a large difference in frequency of home checks by the instructions given each group ($p < .001$). The experimental group did more nonvisual examinations, while many in the comparison group had others check their feet rarely or never and checked their own feet "as best they could." The podiatrists discovered slightly fewer problems in the experimental group. In the experimental group, overall response was positive to nonvisual foot examination. In the comparison group, many were reluctant or unable to ask for sighted assistance.

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44-LB

Understanding the Effect of Cooking on Glucose Availability: Glycemic Index Analysis of Korean High-Carbohydrate Food with Different Cooking Method

HYUNJUNG LIM, HANSONGYI LEE, DO YEON KIM, HYERANG KIM, RYOWON CHOUE, *Kyunggi-do, Republic of Korea, Seoul, Republic of Korea*

Although glycemic response to carbohydrates in different foods has been quantified, the changes in glycemic index after cooking is not well-understood. This study aimed to investigate the effects of cooking by different methods on the glycemic index of Korean food. The most popular carbohydrate foods, including white rice (62.9g), glutinous rice (61.1g), barley (64.4g), brown rice (65.0g), corn (170.0g), potato (359.7g) and sweet potato (160.3g), from Korean National Health and Nutrition Examination Survey nutrient database were cooked using various conventional domestic methods. Sixty young healthy adults were recruited to participate in the feeding trial and consumed each test food on 6 separate days. Blood glucose and insulin levels were subsequently measured at times 0, 15, 30, 60, 90, and 120 minutes after consuming glucose and each test food containing 50g of carbohydrates. Glycemic indices calculated from different cooking methods for boiled, steamed, baked and puffed food and incremental areas under the curve were calculated by weighing geometrically. Depending on cooking methods, steamed rice cake (50.6 ± 7.2), boiled glutinous rice (75.7 ± 10.6), boiled barley (35.4 ± 9.2), puffed corn (69.9 ± 11.4), grinded and pan-fried potato (28.0 ± 5.1), fried sweet potato (57.7 ± 10.9) may be considered the low and medium glycemic index foods, which may prove beneficial for diabetic or insulin-resistant consumers. Further investigation for glycemic index and glycemic load analysis in different food group, especially fruit, is required to identify the beneficial food items and cooking methods for dietary therapy for diabetes management.

Supported By: Republic of Korea Rural Development Administration

45-LB

Population Focused Peer Support to Reach Those Not Receiving Recommended Diabetes Services

DIANA M. URLAUB, HUMBERTO PARADA, JUANA BALLESTEROS, YUDY GALVAN, MANUELA MCDONOUGH, EDWIN B. FISHER, *Chapel Hill, NC, Chicago, IL, Washington, DC*

As reported by the CDC, 46% of people with diabetes are estimated not to receive the diabetes self management education and support they need and this number is higher among ethnic minorities. Most published research in the field reports that patient education and support interventions are reaching only select samples of patients. Here we report population focused peer support strategies designed to reach and engage all diabetes patients at a federally qualified health center in Chicago serving a predominantly Latino population. Peer support is delivered through a tiered program in which all patients with diabetes receive Regular Care that includes quarterly contacts, group classes, activities, "point of care marketing" by which peer supporters are present in the waiting rooms and at clinic visits, all promoting pursuing self management goals as well as regular clinical care. A High Need group (n=469; HbA1c>8%, elevated psychosocial needs, or physician referral) receives biweekly contact for 6 months and then monthly until they no longer meet criteria or progress has stabilized. Flexible, nondirective strategies are used to engage patients in peer support and include: 1) low demand - an initial call to describe and offer services, not push to accept, 2) repeat calls in 2-4 weeks to "check in with" not "check up on" patient, 3) two-year availability to patient - not considered refusal unless they clearly request no further contact, 4) after patient is engaged, begin working on individually chosen goal from set of key self management behaviors such as health eating, etc. Results to date (after 18 months since program initiation): of the High Need patients, we have reached 375 (80%) with 260 (69%) up-to-date on contacts. In the Regular Care group, we have reached 1,731 (48%) with 1,463 (85%) up-to-date on contacts. These preliminary results demonstrate that peer supporters can reach and engage an entire patient population into educational, support and clinical services.

Supported By: Bristol-Myers Squibb Foundation

46-LB

The Effect of Lifestyle Modification Program Reduces Fasting Plasma Glucose in Overweight Children: A Systematic Review and Meta-analysis

ANGELA SHIN-YU LIEN, BIH-SHYA GAU, YI-DER JIANG, JIA-LING TSAI, *Taoyuan, Taiwan, Taipei, Taiwan*

The increase in childhood obesity and young type 2 diabetes mellitus has been determined globally. Lifestyle modification may be helpful for weight and glycemic control. We aimed to determine the effects of lifestyle modification program on fasting plasma glucose (FPG) in overweight children. Data was obtained in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis statement, including 4 relevant electronic databases searched from 1965 to June 2013 of the publication date. We included overweight children between the age of 5 and 18 years from whom measurements for FPG were obtained and lifestyle modifications such as diet control, healthy nutrition, exercise or fitness, or physical activities were attempted. After an initial search and full text reviewed, 5 studies were identified containing FPG for inclusion into qualitative synthesis and meta-analysis. A total of 1291 children in the intervention and 1236 in the control group completed. The point estimate for the mean difference in effect size

For author disclosure information, see page LB91.

was –2.03 (95% CI, –3.51 to –0.55, Z = –2.68, p = 0.007), which indicated that lifestyle modifications would decrease significantly 2.0 mg/dl of FPG. This study concludes that lifestyle modification is effective for reducing FPG in overweight children. A large cohort study can be expected to prevent the onset of adolescent type 2 diabetes.

EXERCISE

47-LB

Exercise Effects on Postprandial Glucose Metabolism and Insulin Mobilization in Type 1 Diabetes

ASHWINI MALLAD, MICHELE SCHIAVON, LING HINSHAW, CHIARA DALLA MAN, RITA BASU, CLAUDIO COBELLI, YOGISH C. KUDVA, ANANDA BASU, *Rochester, MN, Padova, Italy*

A better understanding of effects of exercise on postprandial glucose metabolism, insulin availability and action in type 1 diabetes (T1D) would help inform next generation closed loop control algorithms. We therefore studied 14 recreationally active T1D subjects (age 44.9±12.5 yrs., BMI 28.6±5.5kg/m^2, HbA1c 7.6±0.7%) on insulin pump before, during and after 75 min of moderate intensity exercise (50% VO_2 max) that started 120 min after a mixed meal containing 75 g glucose. Prandial insulin bolus was administered as per each subject's customary insulin: carbohydrate ratio adjusted for the level of physical activity. Basal insulin infusion rates were not altered. There were no episodes of hypoglycemia during the study. Over the next six hours, glucose turnover was measured with the triple tracer technique. Rates of endogenous glucose production (EGP) fell 98% within 75 min then rose rapidly during exercise to baseline levels. Whole body glucose uptake (Rd) peaked at 75 min after the meal. During exercise, rates of Rd rose gently before returning to baseline levels within 45 min after completion of exercise. Interestingly, plasma insulin concentrations rose by 31% during exercise despite no changes in insulin pump infusion rates implying increased mobilization of insulin from subcutaneous depots. In contrast to healthy subjects undergoing the same protocol, Rd and glucose clearance were lower ($p<0.01$) and integrated rates of EGP higher, despite higher plasma glucose ($p<0.01$) concentrations in T1D during exercise. Also, the rise in plasma glucagon concentrations during exercise was lower in T1D (33% vs. 210%) than healthy subjects implying a combined effect of hyperglycemia and persistent alpha cell dysfunction in T1D. Closed loop control algorithms will need to account for the effects of exercise on glucose turnover, insulin mobilization and suboptimal glucagon response in next generation artificial pancreas systems to improve outcomes related to both hypoglycemia and hyperglycemia.

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48-LB

Clinical Results of Smart Detection of Physical Activity in Adults with Type 1 Diabetes

ISURU S. DASANAYAKE, WENDY BEVIER, KRISTIN CASTORINO, EYAL DASSAU, DALE SEBORG, FRANCIS J. DOYLE III, *Santa Barbara, CA*

Physical activity has a significant effect on glucose metabolism in individuals with type 1 diabetes (T1D), and often results in hypoglycemia. Consequently, early detection and classification of activity will improve glucose control and minimize the risk for immediate and latent hypoglycemia. The purpose of this study was to develop a novel activity detection method based on CGM, activity and heart rate sensors to detect and classify events as part of future smart glucose management system.

Eight T1D adults (4F: 4M; 44±18 y; 80±13 kg) were monitored for a total of four days using a detailed diary, tri-axial accelerometer, heart-rate monitor and CGM. After 24 hours of home data collection, subjects participated in an 8-hour in-clinic exercise session: 60 and 30 minutes at 30% and 50% predicted maximal heart rate reserve (HRR), respectively, using a treadmill or a recumbent bicycle. Subjects then continued in-home data collection for 48 hours. In-home data were used to develop the detection method based on principal component analysis, while in-clinic data were used to identify false positives. The proposed detection method flags an activity if consecutive samples exceed the threshold (6σ confidence limit), determined for the non-exercise data.

The detection method was able to identify the 30% HRR exercise at a median of 8 min [range 3-17 min], and the 50% HRR exercise at a median of 4 min [range 3-7 min]. The glucose drop from the start of exercise to the detection time ranged between -2.2 mg/dl to +17.8 mg/dl with a median of 3 mg/dl for 30% HRR exercise. For 50% HRR exercise it ranged from -4.0 to +9.6 mg/dl with a median of 2.4 mg/dl. This detection method based on different types of sensors provided good robustness to sensor dropouts and data outliers.

The novel personalized method for reliable fast detection of exercise was validated on clinical data. Early detection of exercise is a critical factor in minimizing immediate and nocturnal hypoglycemia episodes in people with T1D.

Supported By: NIH (R01DK085628, DP3DK094331)

49-LB

Physical Activity Raises HDLc and Protects from CVD in Male Medalists

STEPHANIE A. D'EON, STEPHANIE M. HASTINGS, ZHIHENG H. HE, GEORGE L. KING, HILLARY A. KEENAN, *Boston, MA*

Cardiovascular disease (CVD) is the primary cause of mortality in people with type 1 diabetes (T1D). We have recently documented a significant difference in the rates of CVD between males (51.8%) and females (35.1%) with 50 or more years of T1D (Joslin 50-Year Medalists) (p=0.02). HDLc levels above 60 mg/dL conferred the most significant protection among women in Medalists, which was not found in males. Interestingly, the prevalence of self-reported CVD does NOT differ (PA: males 37.0% v females 31.4% (p=0.3, n=350)) between males and females who are physically active (PA), collected by the Paffenbarger questionnaire (no PA: males 67.5% v females 35.8% (p=0.0025, n=93)). HDLc levels were significantly higher among males who exercised (57.9 v 53.9 mg/dL, p=0.03) and BMI levels lower (26.3 v 28.8 kg/m^2, p=0.007). PA males were less likely to report antihypertensive use (67% v 82.5%, p=0.06). No significant difference was found between age (66.5 v 66.7 y), duration (54.0 v 56.4 y), HbA1c (7.1% v 7.0%), daily insulin dose/kg (0.50 v 0.49 u/kg) and total cholesterol (151.7 v 148.2 mg/dL) between PA males and those not (p>0.05). Exercise did not significantly affect HDLc's association with CVD in females, however, the increase in HDLc levels in PA males contributed to protection from CVD (OR:0.97 95% CI:0.96, 0.99). This demonstrates a potentially strong effect of exercise on male risk for CVD. Age at visit, antihyperlipidemic use and HbA1c varied significantly between males with and without CVD, and these factors were adjusted for in the final model. In summary, PA conferred a greater than three-fold protection (adjusted OR:0.26; 0.13, 0.6) from CVD among male Medalists, with HDLc partially contributing to the effect. Possibly, as PA significantly increases HDLc levels, and reduces the risk of CVD among male Medalists, these finding suggest exercise may equilibrate the gender difference in rates of CVD among males and females with T1D.

Supported By: NIH; JDRF

49A-LB

A Novel Method of Electrical Pulse Stimulation Mimics the Effects of Exercise in Human Myotubes

NATALIE A. STEPHENS, TRACEY WOODLIEF, MARIA PINO, LAUREN M. SPARKS, *Orlando, FL*

Human satellite cells retain the phenotypic characteristics of the skeletal muscle from which they have been derived, and as such are well-established models for *in vitro* manipulations and cell studies. Here, we describe a novel method of *in vitro* exercise mimetics and demonstrate that the effects of this method recapitulate the effects of exercise observed in the whole body organism. Human myoblasts derived from lean, healthy individuals were cultured and differentiated over a 7 day differentiation time course. On days 5 - 7 of differentiation, myotubes were subjected to electrical pulse stimulation (EPS) using the C PACE, Cell Culture Stimulator by ION OPTIX©. Cells were pulsed for 3 hours/day with 11.5 V at a frequency of 0.2Hz, in a 2 ms field. Myotubes were also switched to antibiotic-free differentiation media, which was replaced just prior to the start of EPS on each day of stimulation. This low frequency, 3 hour-long bout of EPS, repeated over a 3 day period most closely mimics a low intensity training program. On Day 7 of differentiation, cells were harvested at 0, 1, 2, 3, 4, 12 and 24 hour time-points at the end of the 3-hour EPS time period. Samples were also collected from a control plate not subjected to EPS at these same time-points. RNA was isolated from each sample and analyzed by qRT-PCR.

We have shown that the exercise-linked cytokine, IL-6, as well as several genes involved in muscle metabolism and exercise, including PGC1-alpha and PPAR alpha were significantly upregulated in the myotubes subjected to EPS, compared to the control cells. In addition, we found that PDK4, which is associated with lipid metabolism, was also significantly upregulated. These findings strongly indicate that this novel method of myotube stimulation is an effective exercise mimetic. With variations in frequency and intensity of stimulation, EPS may also be modified to examine the effects of different types of exercise programs *in vitro,* and is therefore a valid and useful means of examining the effects of exercise in cells.

NUTRITION—CLINICAL

50-LB

Treatment with High-Dose Ergocalciferol Does Not Improve Insulin Resistance in Obese Individuals with Vitamin D Inadequacy

PRAPIMPORN CHATTRANUKULCHAI SHANTAVASINKUL, PARIYA PHANACHET, ORAWAN PUCHAIWATTANANON, TANARAT LEPANANON, LA-OR CHAILURKIT, BOONSONG ONGPHIPHADHANAKUL, DARUNEEWAN WARODOMWICHIT, *Bangkok, Thailand*

Obesity is a key risk factor of type 2 diabetes and the effect of vitamin D supplementation to glucose homeostasis has been controversial. This randomized double blinded controlled trial study was aimed to investigate the effect of high dose ergocalciferol treatment to insulin resistance and body composition change in obese individuals with vitamin D inadequacy.

A total of 101 obese individual with total 25(OH) < 30 ng/mL, were recruited. 52 subjects were randomized to receive ergocalciferol 50,000 IU, 5 times/week and 49 subjects received placebo for 12 weeks. Serum 25(OH)D level, body composition analysis, fasting plasma glucose, insulin, A1C were also measured at baseline and at 12-week. The homeostasis model assessment of insulin resistance (HOMA-IR) was assessed.

At 12-week after treatment, all subjects with ergocalciferol treatment, but not with placebo, had normalized vitamin D level (25(OH)D > 30 ng/mL). Total 25(OH)D level was significantly higher in subjects with vitamin D treatment (54.8 + 14.7) compare to placebo group (25.7 + 8.5). Interestingly, after vitamin D2 level supplementation, the level of 25(OH)D3 level decreased significantly in subjects with ergocalciferol treatment(before; 20.8 + 4.2 and after; 8.3 + 4.1) but increased significantly in placebo group(before; 21.3 + 4.2 and after; 24.0 + 6.0). As expected, 25(OH) D2 level was significantly higher in treatment group (46.5 + 16.8) compared to placebo (1.64 + 5.1). After intervention BW, BMI, FPG, insulin and HOMA-IR were not significantly different between 2 groups.

Treatment of vitamin D inadequacy with ergocalciferol 250,000 IU per week in obese individual was able to normalize total 25(OH)D level by increasing 25(OH)D2 level. Nevertheless the serum level of 25(OH)D3 level decreased significantly and HOMA-IR was not improved after treatment. Further study is needed to investigate whether the reduction of vitamin D 3 has negative effect to the glucose homeostasis.

51-LB

Honokiol Attenuated Insulin Resistance by Regulating Glucose Metabolism and Insulin Signaling in C57BL/KsJ-db/db Mice

MYUNG-SOOK CHOI, YOUNG-JE KIM, YONG BOK PARK, UN JU JUNG, *Daegu, Republic of Korea*

Honokiol, ingredient of Magnolia officinalis, which is used in Chinese and Japanese traditional medicine, has been reported to have antioxidant, anticancer, and antiangiogenic effects. In recent, many studies have shown that various phytochemical compounds such as resveratrol and curcumin have the therapeutic potential to protect against diabetes. However, the ability of honokiol to improve diabetes is unknown. Thus, we evaluated the anti-diabeteic effect of honokiol in C57BL/KsJ-*db/db* (*db/db*) mouse and its underlying mechanisms based on insulin signaling.

Twenty male four-weeks-old C57BL/KsJ-db/db mice were randomly divided into two groups and fed a AIN-76 semisynthetic diet (DB) or AIN-76 semisynthetic diet with 0.02% Honokiol (HON) for 5 weeks.

As expected, *db/db* mice showed hyperphagia, hyperglycemia, hyperinsulinemia and insulin resistance. Level of blood HbA1c, a marker of long-term glycemic control, was significantly lower in the HON group than in the DB group. Plasma insulin and homeostasis model assessment of insulin resistance levels were also significantly lower in the HON group than in the DB group. Activities of hepatic gluconeogenic enzymes, glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, were significantly decreased in the HON group compared to the DB group. Moreover, mRNA expression of insulin receptor and insulin receptor substrate was decreased in the epididymal fat of HON group compared to DB group.

These results indicate that honokiol improves glucose metabolism and insulin sensitivity by regulating hepatic gluconeogenic enzyme activities and epididymal insulin signaling- related gene expression. Thus, honokiol may have potential as source of anti-diabetic agents that improve insulin resistance.

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52-LB

Effects of Fish or Meat Intake Before and After Rice on Postprandial Glucose Excursions and Incretin Secretion in Type 2 Diabetes: Meal Sequence as a Novel Target in Dietary Therapies for Diabetes

DAISUKE YABE, HITOSHI KUWATA, MASAHIRO IWASAKI, RYOTA USUI, TAKESHI KUROSE, YUTAKA SEINO, *Osaka, Japan*

We investigated the effects of fish or meat intake before and after rice intake on postprandial glucose excursions as well as incretin secretion in patients with type 2 diabetes (T2DM). In experiment A, untreated T2DM patients were subjected to 2 way-crossover tests on two separate days, in which they received, with a 15-min interval, steamed rice before or after canned mackerels in brine. Postprandial glucose was significantly reduced when they received mackerels before rice. Strikingly, GLP-1 was significantly elevated when they received the mackerels before the rice, while GIP was hardly affected by changing the order of intake. In experiment B, untreated T2DM patients were subjected to 3 way-crossover tests on three separate days, in which they received, with a 15-min interval, rice before or after grilled beef or rice after mackerels. Postprandial glucose was significantly reduced when they received beef before rice. GLP-1 was significantly elevated when they received beef before rice. The profiles of postprandial glucose and GLP-1 were similar when they received beef or mackerels before rice. Interestingly, GIP secretion was significantly elevated when the patients received the beef, but not the mackerels, before the rice. Experiment C, a nutrition component analysis, revealed that the beef was rich in oleate and stearate, strong enhancers of GIP secretion, while the mackerels were rich in eicosapentaenoic acid and docosahexaenoic acid, which are poor enhancers of GIP secretion. Our results show that meal-sequence can play an important role in controlling postprandial glucose and incretin secretion. While eating meat before rice in T2DM might ameliorate postprandial glucose and enhance GLP-1 secretion in a fashion similar to eating fish before rice, beef's concomitant enhancement GIP secretion could promote obesity when such meal sequence is taken chronically.

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PSYCHOSOCIAL, BEHAVIORAL MEDICINE

53-LB

Complementary and Alternative Medicine Use among Diverse, Low-Income Patients with Diabetes: A Practice with Clinical Significance

MARGARET A. HANDLEY, MARIA CHAO, JUDY QUAN, NEDA RATANAWONGSA, URMIMALA SARKAR, DEAN SCHILLINGER, *San Francisco, CA*

The degree to which diabetes patients employ complementary and alternative medicine (CAM) is poorly understood, and whether CAM is associated with health outcomes is not known. We report prevalence of CAM use and disclosure to clinicians among diverse diabetes patients, and explore independent associations between CAM and HbA1c. A Medicaid managed care plan enrolled 362 patients in a self-management program from 2009-11. Six month phone interviews collected self-reported CAM use in the prior 30 days using a 12-item validated instrument in English, Spanish and Cantonese. Oral hypoglycemic medication adherence was measured using pharmacy claims. HbA1c was obtained from electronic records. 278 patients (77%) completed follow-up interviews, and were predominantly Asian (60.1%), Latino (22.6%) and non-English-speaking (71.9%). Mean age was 55 yrs, with mean of 7 yrs with diabetes. Any CAM use was reported by 51.4%. One third (30.0%) used CAM for diabetes. Specific modalities included vitamins/ nutritional supplements (25.9%), natural remedies/herbs (24.5%, massage/acupressure (11.5%), and meditation/yoga/tai chi (10.4%, at a median monthly cost of $33 (range 0-$1200). While 47.2% did not disclose CAM to a clinician, 24% of CAM users reported putting off buying medications to pay for food, vs. 13% of non-CAM users ($p<.05$). Based on pharmacy claims, 21% of CAM users had poor adherence vs. 12% of non-CAM users ($p<.05$). CAM users were more likely to have poor glycemic control (A1c 8% or more)compared to non-CAM users (34% vs. 16%, $P<0.05$). CAM use is common among diverse, low income patients with diabetes, but disclosure to clinicians is inconsistent. CAM use appears to be clinically relevant, being associated with poor glycemic control. While CAM use may be a marker for disease burden or non-Western beliefs, that CAM use was associated with cost-related non-adherence suggests there may be a causal path between CAM and poor glycemic control.

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For author disclosure information, see page LB91.

54-LB

Review of Smartphone Applications Designed to Improve Latino(a) Diabetics' Self-Care Behaviors: "Opportunity" or Risk?

LILIANA AGUAYO, PABLO TORRES, SUSANA URQUIZA, DIANA GRIGSBY-TOUSSAINT, *Champaign, IL*

Diabetes disproportionately affects Latinos in the U.S. Latinos are 1.7 times more likely to have diabetes compared to Whites. Increased diabetes risk among Latinos may be attributed to challenges in access to quality health care, language barriers, & genetic makeup. Latinos are significantly more likely than other groups to download apps to track their health. Consequently, Smartphone apps present a low cost opportunity to improve diabetes self-care among Latino diabetics. However, little is known about whether apps follow evidence-based guidelines or are grounded in behavioral theory. Using AADE7TM measures for diabetes self-care behaviors & tools for evidence-based evaluations of health apps, we examined Spanish language apps for diabetes self-care for iPhones™. On February 11, 2014, all apps (n=926) that resulted from the search of "diabetes" in the iTunes™ store were screened for Spanish language options. 130 apps that indicated availability in Spanish, & were classified as "Medical" or "Health & Fitness" were included in this review. All apps were first reviewed by three independent reviewers to determine whether content was designed for diabetes self-care. A total of 54 apps meeting this criterion were downloaded & evaluated. Overall, we found many discrepancies between the information in the description of each app, & their attributes upon downloading. Only 30 (55%) of the apps downloaded were in Spanish. Reliability between the number of AADE7TM behaviors found in the description & upon downloading was poor, only 20% of the number of behaviors claimed were available on the apps (kappa=.032). Results suggest the need for a revision on content or language availability for apps targeting Spanish-speaking individuals with diabetes. Diabetes apps available in Spanish are not grounded in behavioral theory or follow evidence-based guidelines, limiting their long-term impact for diabetes self-care, & potentially putting users at risk.

55-LB

Illness Identity and Self-Management of T1DM in Adolescents

PERSIS V. COMMISSARIAT, JOSLYN KENOWITZ, JENIECE TRAST, RUBINA A. HEPTULLA, JEFFREY S. GONZALEZ, *Bronx, NY*

As glycemic control tends to deteriorate during adolescence, the purpose of the current study was to investigate how the process of identity development is related to self-management in adolescents with Type 1 diabetes (T1DM). Semi-structured interviews and validated measures of self-esteem, social competency, and self-care were completed with 81 adolescents with T1DM, ages 13 to 21. Participants were predominantly ethnic minorities (47% Latino, 28% Black) had a mean age of 15.9 (SD=2.1) and had been diagnosed for 6.7 (SD=3.7) years; 53% were female and 55% were on an insulin pump. Overall, glycemic control was poor (HbA1c: M=10.0, SD=2.4). Thematic content analysis determined whether adolescents had successfully "incorporated" T1DM in their identity, based on criteria informed by Charmaz's (1999) theory of identity development in chronic illness. Those classified as "incorporating" described: acceptance of illness/treatment as a necessary part of daily life, sharing of T1DM status and knowledge with peers, and success in managing stigma. Ranesults of an ANCOVA, controlling for age, gender, insulin method, and duration of illness, indicated that those successfully incorporating had significantly lower HbA1c (difference: -1.4%, p=.007), better self-care (p=0.006), higher self-esteem (p=.001), and greater perceived social competency (p=.015). Logistic regressions controlling for the same covariates were used to test HbA1c, self-care, self-esteem, and social competency as predictors of successful incorporation. In separate models, all predictors were significant (ps<.02). However, a multivariate model showed that only social competency was a significant independent predictor of incorporation of T1DM into identity (p=.04), with self-esteem trending toward significance (p=.06). These results suggest that social competency is a significant predictor of successful incorporation of T1DM into the sense of self, and positive integration of T1DM may lead to better self-management and clinical outcomes.

56-LB

Willingness to Initiate/Intensify Medications in the Second Diabetes Attitudes, Wishes, and Needs (DAWN2) Study

MARK PEYROT, SØREN E. SKOVLUND, *Baltimore, MD, Bagsværd, Denmark*

Delaying initiation or intensification of antihyperglycemic medication is a barrier to achieving optimal outcomes of diabetes care. DAWN2 examined the beliefs of people with diabetes (PWD) in 17 countries about medication and their willingness to initiate antihyperglycemic medications and increase insulin injections. Respondents included those with: type 1 diabetes mellitus (DM) (T1 = 1332), type 2 DM insulin-medicated (T2i = 2471), type 2 DM oral medication (T2o = 2771), type 2 DM no medication (T2n = 1700). Unweighted data were analyzed with no adjustment for country-level effects or individual-level respondent characteristics.

Among T2n, 27% were unwilling to initiate oral medication if recommended by their healthcare provider (HCP), but significantly (p< .05) more reported that they would not be willing to start insulin (43%) or other injectable medication (46%). Among T2o, 38% were unwilling to initiate insulin or other injectable medication (41%) if recommended by HCP. Significantly (p< .05) fewer insulin users (T1 = 39%, T2i = 38%) were unwilling to initiate injectable medication other than insulin; their unwillingness to increase insulin injections was similar (39% and 38%, respectively).

In multivariate analysis, T2o were less willing and T2i more willing than T1 to initiate/intensify insulin or initiate other injectable medication. Several beliefs such as, ability to avoid complications, current medication effectiveness, and understanding of current medication were associated (p< .05) with increased willingness to initiate/intensify both types of medication. Perceived injection pain was associated with lower willingness to initiate both types of medication. Weight worry and dietary restrictions were associated with an increased willingness to initiate injectable medication other than insulin.

Our results suggest that psychological barriers to medication enhancement represent a significant barrier to effective diabetes care.

57-LB

Understanding the Influence of Low Income and Education Level on Glycemic Control: A Mediation Analysis

JANIE HOULE, MARIE-DOMINIQUE BEAULIEU, SOPHIE MEUNIER, JEAN-LOUIS CHIASSON, FRANÇOIS LESPÉRANCE, JOSÉ CÔTÉ, IRENE STRYCHAR, JEAN LAMBERT, *Montréal, QC, Canada*

Living in poverty and low educational level have consistently been associated with poorer glycemic control. It is important to better understand how these two determinants of health influence diabetes control if we want to successfully intervene with these client groups. This study examines the contribution made by of a variety of mediating factors known to be important in diabetes control: cognitive variables (illness representations, motivation, self-efficacy, cognitive functioning), behavioral variables (coping strategies, self-management), social variables (support from family, friends and peers) and medical variables (working alliance, care concordant with the Chronic Care Model). We conducted a 1-year cohort study in which 237 patients with type 2 diabetes were evaluated at baseline, 6 months and 12 months, using self-administered and HbA1C measures. Using the Preacher and Hayes approach, statistical analyses were performed to test the indirect effect of each mediator on the dependent variables: living in poverty and educational level. Mediation analyses revealed that depressive symptoms, avoidance coping strategies, and the representation that diabetes is unpredictable all mediate the relationship between living in poverty and glycemic control. Educational level has a negative association with glycemic control, mediating through lower levels of cognitive functioning and avoidance coping strategies. Social and medical variables were not identified as mediators in our analyses. Our results suggest that illness representations and coping strategies need to be explored and addressed, paying more attention to individuals with diabetes who live in poverty or have a lower education level.

Supported By: CIHR

58-LB

Hyperamylinemia Promotes Amylin Deposition in the Brain and Affects Brain Function

SARAH SRODULSKI, SAVITA SHARMA, ADAM BACHSTETTER, JENNIFER BRELSFOARD, CONRADO PASCUAL, XINMIN XIE, KATHRYN SAATMAN, NELSON PETER, LINDA VAN ELDIK, FLORIN DESPA, *Lexington, KY, Redwood, CA*

Chronic hypersecretion of the pancreatic hormone amylin is common in humans with prediabetes and leads to amyloid deposition and proteotoxicity in pancreas. We recently showed that amylin deposits are also present in failing diabetic hearts and brain samples from patients with type-2 diabetes (T2D) and dementia. Here, we investigated whether amylin deposition impacts brain function.

Because rodent amylin is neither amyloidogenic nor cytotoxic, we used rats that overexpress human amylin in the pancreas (HIP rats) and wild-type (WT) rats as controls to assess mechanistically how a "human" hyperamylinemia affects brain function. Cage activity, rotarod and novel object recognition tests were performed on all animals. Brain amylin deposition was documented by immunochemistry with an amylin antibody. We also assessed the level of lipid peroxidation in cortical arteries by confocal microscopy and cerebral inflammation by immunohistochemistry, qRT-PCR and cytokine protein levels.

HIP rats, but not WT littermates, display deposition of amylin in the brain. Compared to WT rats, HIP rats show i) changes in active/inactive rhythm, motor coordination and balance, ii) impaired recognition memory and iii) no ability to improve the performance on the rotarod. Neurologic deficits in HIP rats may be due to oligomerized amylin-induced oxidative stress and inflammation. We

For author disclosure information, see page LB91.

found elevated lipid peroxidation in smooth muscle cells isolated from HIP rat cortical arteries. Amylin deposits are co-localized with macrophages and activated microglia. Multiple inflammatory markers are expressed in HIP rat brains as opposed to WT rats, confirming that amylin deposition in the brain induces a neuroinflammatory response.

We therefore conclude that accumulation of aggregated amylin in the brain leads to neurological deficits through mechanisms that involve oxidative stress and inflammation. Brain amylin pathology could be a mechanism by which T2D predisposes to brain injury and cognitive decline.

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59-LB

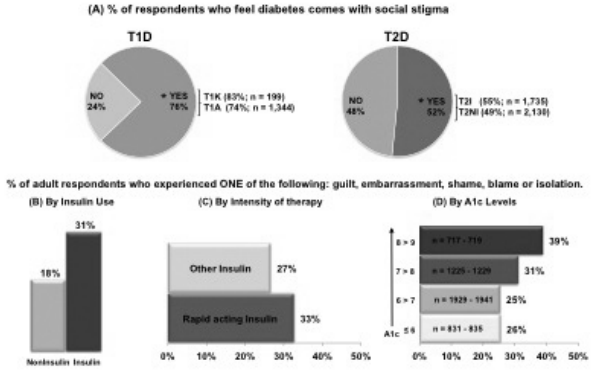
Investigation of the Presence and Impact on Patients of Diabetes Social Stigma in the USA

ALEXANDRA FOLIAS, ADAM S. BROWN, JASMINE CARVALHO, VINCENT WU, KELLY L. CLOSE, RICHARD WOOD, *San Francisco, CA*

Does diabetes come with social stigma? Is diabetes management affected? Diabetes requires monitoring of blood glucose, adherence to demanding therapies, and regulated lifestyle regimes: difficult and unwelcome additions to patients' lives. How patients feel socially about their diabetes can significantly impact adherence to - and efficacy of - their therapies.

To measure how perceptions affect people with diabetes, we surveyed 5,410 patients in the USA with type 1 diabetes (T1D) and type 2 diabetes (T2D) in December 2013, to learn whether they felt diabetes came with social stigma. The answer was a strong 'yes' from those with T1D (76%), particularly in parents of children with diabetes (83%). Respondents with T2D were equivocal, at 52% overall, and 55% amongst those taking insulin (A).

How social stigma is experienced did not vary by demographics (age, income, education, location). However, insulin patients were 72% more likely than patients on oral agents only (31% vs. 18%), to experience either guilt, embarrassment, shame, blame or isolation (B). This likelihood increased with intensive therapy (83% more likely for rapid-acting insulin users) (C), and with poor glucose control (116% more likely for patients with an A1c>8%) (D) (33% and 39%). These data highlight where the social stigma associated with diabetes is felt most, and presents opportunities to better support subpopulations of patients who are most in need.



60-LB

U.S. Physicians' Challenges When Presenting and Discussing the Type 2 Diabetes (T2D) Diagnosis with Patients: Insights from the Cross-National IntroDia™ Study

WILLIAM H. POLONSKY, ANNE BELTON, SUSAN DOWN, MATTHEW CAPEHORN, VICTORIA GAMERMAN, FRIEDERIKE NAGEL, JISOO LEE, DOUGLAS CLARK, STEVEN V. EDELMAN, *San Diego, CA, Toronto, ON, Canada, Bridgwater, United Kingdom, Rotherham, United Kingdom, Ridgefield, CT, Ingelheim, Germany*

Physician-patient communication at T2D diagnosis may affect patients' attitudes to disease, self-care, and outcomes. As part of a global survey of T2D physician-patient communication (IntroDia™), we evaluated challenges faced by U.S. primary-care physicians (PCPs) at diagnosis.

1057 PCPs (74% male; median age 46 yrs) completed an online survey including a novel 12-item questionnaire of potential challenges when presenting the T2D diagnosis as well as the validated Jefferson Scale of Physician Empathy.

Most (87%) agreed that the diagnosis conversation has a big impact on how well patients accept the diagnosis and adhere to treatment over time. Of the PCPs, 64% encountered ≥1 challenge in most diagnosis conversations. Factor analysis yielded 2 factors (comprising 11 of the 12 items): Discouraged with Patients at Diagnosis (DPD; e.g., "It is frustrating to work with T2D patients that don't follow my recommendations"; 7 items, $\alpha = 0.88$) and Frustrated with the Situation at Diagnosis (FSD; e.g., "I don't have enough time"; 4 items, $\alpha = 0.78$). Correlation between the 2 factors DPD and FSD was moderate ($r = 0.63$, $p < 0.0001$), suggesting related, but distinct, groups of challenges. Mean ± SD for DPD was higher than FSD: 2.9 ± 0.7 vs. 2.4 ± 0.8 ($p < 0.0001$).

Upon adjusting for demographic and clinical practice variables, regression models showed a negative relationship between physician empathy and perceived challenges for total score (all 12 items) as well as DPD and FSD (all $p < 0.0001$).

The diagnosis is a critical moment that can impact the patient's future, but many PCPs, especially those who score lower on empathy, report significant challenges and frustrations with these conversations. This suggests that supporting the use of empathy-related skills to address patients' emotional stresses at diagnosis might make this a less frustrating task for PCPs and perhaps contribute to better patient outcomes.

Supported By: Boehringer Ingelheim/Eli Lilly and Company

61-LB

Dose-Response Relationship of Nap Time with the Risk of Type 2 Diabetes: A Meta-analysis

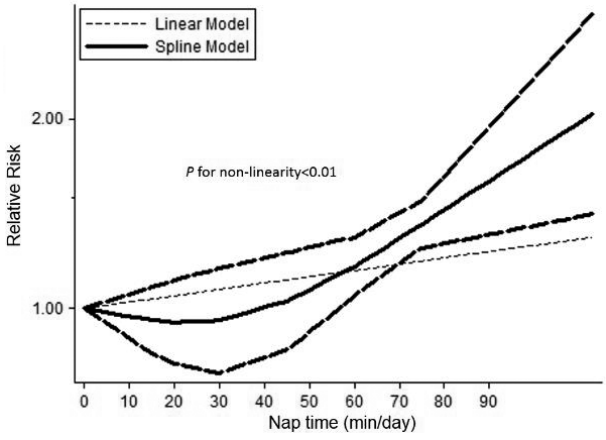
TOMOHIDE YAMADA, KAZUO HARA, NOBUHIRO SHOJIMA, HAYATO HOSOE, TAKASHI KADOWAKI, *Tokyo, Japan*

We performed a meta-analysis of evidence on the association between napping and the risk of type 2 diabetes and attempted to quantify the potential dose-response relation.

We searched Medline, Web of Science, and Science Direct for articles published up to March 2014 using the keywords nap and diabetes. Observational studies reporting risk estimates for type 2 diabetes were assessed. The adjusted relative risk and 95% confidence interval were calculated with the random effect model. Dose-response relations were evaluated using data from different nap categories in each study.

Among 1,018 studies, 225,717 Asian and Western subjects stratified into 5 categories were identified. The analyses performed in each study were well adjusted for several confounders for diabetes. Pooled analysis revealed that a longer nap time (≥60 min/day) significantly increased the risk of type 2 diabetes (relative risk 1.46 (1.23-1.74, p<0.001)), while shorter nap time (<60 min/day) did not (0.95 (0.75-1.21, p=0.68)).

Meta-analysis showed a significant non-linear dose-response relation between nap time and the risk of diabetes (P for non-linearity<0.01) (Figure), with no effect of nap time up to about 40 minutes/day followed by a sharp increase in the risk of diabetes at longer times. In conclusion, there was a J-curve relation between nap time and the risk of type 2 diabetes, with longer nap times being associated with an increased risk.



62-LB

Physicians' Challenges When Discussing the Type 2 Diabetes (T2D) Diagnosis with Patients: Insights from a Cross-National Study (IntroDia™)

WILLIAM H. POLONSKY, ANNE BELTON, SUSAN DOWN, MATTHEW CAPEHORN, VICTORIA GAMERMAN, FRIEDERIKE NAGEL, JISOO LEE, DOUGLAS CLARK, STEVEN V. EDELMAN, *San Diego, CA, Toronto, ON, Canada, Bridgwater, United Kingdom, Rotherham, United Kingdom, Ridgefield, CT, Ingelheim, Germany*

IntroDia™ investigates early physician-patient (pt) communication and its potential impact on pt self-care and outcomes, involving ~17000 T2D pts and physicians in 26 countries. Within this, we surveyed 6753 physicians from Asia, Europe, America, Africa, and Australia using a novel questionnaire of 12

For author disclosure information, see page LB91.

challenges physicians may encounter at T2D diagnosis and the Jefferson Scale of Physician Empathy.

Across countries, 76-100% agreed that diagnosis conversations impact on pts' disease acceptance/treatment adherence. Factor analysis of the 12 challenges yielded 2 factors (Table): Discouraged with Pts at Diagnosis (DPD; α = 0.87) and Frustrated with Situation at Diagnosis (FSD; α = 0.72). Correlation between factors suggested related but distinct groups of challenges ($r = 0.64$, $p < 0.0001$). Factor scores varied globally (DPD highest in France; FSD in Japan). Upon adjusting for demographic/clinical practice variables, regression models showed a negative relationship between physician empathy and perceived challenges for total score (all 12 items) as well as DPD and FSD (all $p < 0.0001$).

Thus many physicians, especially those scoring lower on empathy, report significant challenges and frustrations with diagnosis conversations. 92% wanted tools to help pts sustain behavioral change. Supporting use of empathy-related skills may contribute to better pt outcomes.

12-item Questionnaire: "Challenges at Diagnosis"						
How often are you encountering the challenges described by these statements during your diagnosis conversations?	(n=6753) % physicians answering In ... diagnosis conversations					
	...no	...a few	...some	...most	...all	Factor
Shortly after diagnosis, patients fail to keep up with the required behavioral changes and return to old habits	3	22	47	26	2	DPD
The patients do not understand the seriousness of the situation	4	25	48	21	2	DPD
It is frustrating to work with T2D patients that don't follow my recommendations	14	34	33	15	5	DPD
It is difficult to convince patients that they can take control of their health	7	33	42	16	2	DPD
It is difficult to develop a treatment plan with patients that they will follow	11	39	36	13	2	DPD
It is difficult to convince patients to stay positive	9	41	37	12	2	DPD
Patients do not see the benefits/need to collaborate with me to manage the disease	12	42	34	10	2	DPD
Patients leave the visit without having a clear idea of what they are supposed to do	20	43	26	9	1	DPD
I don't have enough time	25	25	27	17	6	FSD
I do not receive enough support from others (my team, nurses, etc.)	49	25	15	8	3	FSD
It is difficult to deal with patients' emotional responses to the diagnosis	17	41	31	9	1	FSD
It is difficult to explain diabetes to these patients	25	38	27	8	2	FSD

Supported By: Boehringer Ingelheim/Eli Lilly and Company

63-LB

Examining the Relationship between Physical Activity, Psychological Mediators of Physical Activity, and Negative Symptoms in Individuals with Psychosis and Diabetes

PAUL GORCZYNSKI, HIREN PATEL, ROHAN GANGULI, *Toronto, ON, Canada*

Individuals with psychosis and Type 2 Diabetes Mellitus (T2DM) are physically inactive and are at risk for cardiovascular disease and premature mortality. Becoming physically active can mitigate this risk. Researchers have suggested that behavioral interventions designed to increase physical activity in this population should be theoretically sound and account for the symptoms of psychosis. This study examined the relationship between physical activity, psychological mediators of physical activity, and negative symptoms in people with psychosis and pre-diabetes or T2DM to better understand what variables to target in future interventions. Forty-nine individuals with psychosis and pre-diabetes or T2DM participating in a randomized controlled trial examining a weight loss intervention were included in the analysis. Negative symptoms were evaluated using the Scale for the Assessment of Negative Symptoms (SANS); physical activity was assessed using the International Physical Activity Questionnaire; while psychological mediators of physical activity, including self-efficacy, barriers to and benefits of physical activity, were assessed using the Patient-Centered Assessment and Counseling for Exercise questionnaire. Spearman's correlations showed a significant association between physical activity and negative symptoms ($r = -.35$, $p < .05$). Significant correlations existed between physical activity and self-efficacy ($r = .37$, $p < .01$) and perceived barriers to physical activity ($r = -.35$, $p < .05$), but not perceived benefits of physical activity ($r = -.11$, $p = .45$). The best predictor of physical activity was self-efficacy ($\beta = .31$, $p < .05$). Results suggest that interventions should aim to increase an individual's confidence to be active in an attempt to improve physical activity. For individuals with high negative symptom scores, personalized engagement approaches may be necessary.

64-LB

Relationship of Self-Esteem to Glycemic Control amongst Minority Adolescents with Type 1 Diabetes

JOSLYN KENOWITZ, PERSIS COMMISSARIAT, JENIECE TRAUST, RUBINA HEPTULLA, JEFFREY S. GONZALEZ, *Bronx, NY*

The purpose of this study was to examine relationships between psychosocial factors and self-management in adolescents with type 1 diabetes.

Eighty-five adolescents ages 13-21 years (54% female; 47% Latino, 28% Black; 55% used insulin pump) completed validated self-report measures of self-esteem, quality of life and self-care. Diabetes-specific self-esteem (DSSE) and three subscales on the Diabetes-Specific Quality of Life (QoL) Scale (life satisfaction, disease impact and disease worry) were examined in relation to self-care and HbA1c using Pearson correlation and linear regression.

The group had a suboptimal HbA1C (10+2.4%). Better self-care was associated with all QoL subscales (ps<0.003) and DSSE ($p < 0.001$). Males reported higher satisfaction, lower impact, and lower worry than females (ps <0.002). Lower HbA1c was significantly correlated with lower disease impact ($p < 0.008$), greater life satisfaction ($p < 0.003$) and higher DSSE ($p < 0.001$). Regression analyses, controlling for age, gender, duration of illness and insulin method, indicated that DSSE was the strongest predictor of better self-care ($B = .63$, $p < 0.001$) and lower HbA1c ($B = -.54$, $p < 0.001$). When self-care was added into the model, only DSSE was a significant predictor of HbA1c ($B = -.35$, $p < 0.004$), while self-care, was not ($B = -.199$, $p = .086$).

These findings suggest gender differences in diabetes-specific QoL and demonstrate that QoL and DSSE are important correlates of self-care and glycemic control among ethnically diverse adolescents. Assessment of adolescents' subjective sense of how well they are meeting their diabetes self-management goals (DSSE) may identify those at risk for poor glycemic control. Results suggest that DSSE may be more closely linked with glycemic control than assessments of self-care behavior frequency.

65-LB

How Do Depressive Symptoms Influence Diabetes Self-Management and Glycemic Control? The Contribution of Mediating Variables

JANIE HOULE, MARIE-DOMINIQUE BEAULIEU, SOPHIE MEUNIER, JEAN-LOUIS CHIASSON, FRANÇOIS LESPÉRANCE, JOSÉ CÔTÉ, IRENE STRYCHAR, JEAN LAMBERT, *Montréal, QC, Canada*

It is well known that depressive symptoms have a negative impact on diabetes self-management behaviors and glycemic control. This study seeks to provide a better understanding of this influence by examining mediating variables: illness representations, diabetes self-efficacy, motivation, social support, the physician-patient relationship, care concordant with the Chronic Care Model, coping strategies, and general health condition. In an observational prospective study, we assessed 237 adult patients with type 2 diabetes at baseline, 6 months and 12 months. Using the Preacher and Hayes approach, statistical analyses were performed to test the indirect effect of each mediator on both dependent variables: self-management behaviors, as measured by the Summary of Diabetes Self-Care Activities - Revised, and glycemic control, using HbA1c level. Our results indicate that diabetes self-efficacy, working alliance, chronic illness care, self-management support from family and friends, and coping strategies all mediate the relationship between depressive symptoms and self-management behaviors. However, the belief that diabetes is cyclical and unpredictable as well as a negative emotional reaction to diabetes mediate the relationship between depressive symptoms and glycemic control. The results suggest specific targets for intervention to achieve better self-management behaviors and glycemic control in patients with type 2 diabetes and depressive symptoms. The negative impact of depressive symptoms on diabetes outcomes may be lessened by improving self-efficacy and coping strategies, further developing the working alliance, and providing care concordant with the Chronic Care Model.

Supported By: CIHR

66-LB

Association of Medication Adherence with Psychological Distress in Relation to Types of Antidiabetic Medications among Patients with Uncontrolled Type 2 Diabetes

MELANIE SIAW, YU KO, DANIEL MALONE, YIIJEN LEW, ELAINE TAN, JOYCE YU-CHIA LEE, *Singapore, Singapore, Tucson, AZ*

Although studies have focused on medication adherence and diabetes distress, little is understood about how different types of antidiabetic medications may play a role in this intricate relationship between adherence and diabetes distress. In this cross-sectional, multicenter study, we aimed to examine the association of medication adherence with psychological distress among patient taking different types of antidiabetic agents. All patients with HbA1c > 7% were included in this study while patients with limited language proficiency were excluded. A questionnaire which included an 8-item Morisky Medication Adherence Score (MMAS) and a 20-item Problem Areas in Diabetes Scale (PAID) were administered to all eligible patients. Of the 349 patients approached, 312 (89.4%) were eligible for the study. The mean age was 59.4 ± 8.1 years with 42.9% female and 57.1% male. The average HbA1c was 8.4 ± 1.3%. In addition, 211 (67.6%) were on oral hypoglycemic agents while 101 (32.4%) were on insulin-containing regimen. Overall, PAID scores

For author disclosure information, see page LB91.

were 23.3 ± 16.5 while the adherence rate for low, medium and high were 121 (38.8%), 123 (39.4%) and 67 (21.5%) respectively. Using general linear model, adjusted for age, gender, ethnicity, education level, marital and employment status, duration of diabetes and number of comorbidities, our study showed that lower adherence to medications was associated with higher psychological distress (β = -0.033; p = 0.001). Interestingly, types of antidiabetic medications did not significantly influence the relationship between medication adherence and psychological distress (p > 0.05). In conclusion, the association of medication adherence with psychological distress was not related to the types of antidiabetic medications taken by patients.

67-LB

A New Validated Measure of Diabetes Distress for Adults with Type 1 Diabetes

LAWRENCE FISHER, WILLIAM POLONSKY, DANIELLE HESSLER, LISA STRYCKER, UMESH MASHARANI, IAN BLUMER, ANNE L. PETERS, VICKY BOWYER, *San Francisco, CA, San Diego, CA, Eugene, OR, Whitby, ON, Canada, Los Angeles, CA*

Several measures have been used to assess diabetes distress (DD) but none has targeted the unique worries and fears of T1D adults that are linked to clinical outcomes. We developed and validated a new survey instrument to address this need.

Items (59) were developed from interviews with 25 T1D adults and 10 providers. The validation sample consisted of 478 eligible patients identified from local clinics and diabetes registries in the U.S. and Canada, 412 completed an online survey (86%) that also included measures of Quality of Life (WHO5), depression (PHO8), number of complications, Hypo Fear Survey-Worry, and HbA1C. The final sample contained 303 U.S. and 109 Canadian patients. Each received a $15 gift card.

Patient age (U.S./Canada) = 43.2 / 41.9, % female 55.4 / 54.1, years with T1DM = 22.5 / 26.0, HbA1C = 7.45 / 7.99 (9.3/10.1). Exploratory principal components analysis with promax rotation was undertaken with the U.S. sample, and a confirmatory analysis was performed with the Canadian sample. The same stable and clinically meaningful 7-factor solution (28 items) emerged in both analyses, and internal reliability and construct validity coefficients were highly significant (Table 1).

The T1-DDS is a reliable and valid measure of DD for use with adults with T1D. The 7 subscales reflect a comprehensive profile of worries and concerns that target the unique demands and burdens of T1D, which are linked with disease management and glycemic control.

T1-DDS sub scales	No. items	Alpha	PHQ 8 *r*	No. complications *r*	WHO 5 *r*	HbA1C *r*	Hypo. worry scale *r*
Powerlessness	5	.87	.45[3]	.15[2]	.43[3]	.10	.56[3]
Managemt. distress	4	.78	.25[3]	.15[2]	.29[3]	.41[3]	.27[3]
Hypo. distress	4	.78	.34[3]	.24[3]	.29[3]	-.01	.69[3]
Negative social perceptions	5	.85	.35[3]	.04	.37[3]	.03	.47[3]
Eating distress	3	.73	.30[3]	.21[3]	.36[3]	.19[3]	.32[3]
Physician distress	4	.80	.16[2]	.10[1]	.16[2]	.15[2]	.25[3]
Family/ friend distress	4	.79	.20[3]	.12[1]	.29[3]	.10[1]	.40[3]

[1]$p < .05$, [2]$p < .01$, [3]$p < .001$

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68-LB

Emergence of Emotional Support in Peer Support Interventions: A Cross-Cultural Study

SARAH KOWITT, DIANA URLAUB, LAURA GUZMAN-CORRALES, MELISSA MAYER, JUANA BALLESTEROS, DAVID SIMMONS, EDWIN B. FISHER, *Chapel Hill, NC, Chicago, IL, Cambridge, United Kingdom*

Emotional support is commonly reported in peer and social support interventions to assist diabetes management. However, individuals often initially deny wanting to obtain emotional support and modes of emotional support vary across cultures. This study examined how emotional support emerged in interactions between peer supporters and participants in two distinct cultural settings. 7 Latino peer supporters serving a low-income, Hispanic population in Chicago, and 9 retired, middle class supporters in a program for an older, predominately Caucasian population in the United Kingdom (UK) completed semi-structured interviews focusing on their relationships with those they help. Coding field notes used deductive and inductive codes and consensus among 3 coders to ensure accuracy. Consistencies across both cultures included a) gradual emergence of emotional support and b) emphasis on implicit support. Type of support varied over time. Initially, peer supporters provided information for diabetes management; over time, they came to provide substantial emotional support. Emotional support was frequently conveyed not explicitly (e.g., by reassurance or discussing stressors) but implicitly, in the manner in which information was shared. Implicit modes of support include non-verbal actions that convey emotional acceptance, e.g., a walk together, but do not involve discussion of problems. Cross-cultural differences did appear for barriers to diabetes management. Social concerns were more likely in the U.S. than the UK. Regarding the role of peer support, those in the U.S. were more likely informally to include family and provide directive support whereas UK peer supporters reported more nondirective support. These findings suggest that peer supporters gradually provide emotional support through similar strategies across cultures, but that support is tailored to problems facing participants and to cultural factors, including the role of family and style (nondirective, directive) of support.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—GLUCOSE MONITORING AND SENSING

69-LB

Continuous Sensing of Glucose at the Site of Insulin Delivery in Swine

WILLIAM K. WARD, SHEILA BENWARE, MATTHEW BREEN, KRISTIN MORRIS, XIAOSONG DU, CHRISTOPHER DURGAN, DAVID MATTHEWS, JOHN CONLEY, GREGORY HERMAN, ROBERT CARGILL, *Portland, OR, Corvallis, OR*

People with type 1 diabetes (T1D) who use an insulin pump and a continuous sensor must insert two devices. To address the issue of whether glucose can be measured at the site of insulin delivery, we developed a catheter on which sensing elements are disposed, allowing continuous glucose measurement directly at the site of subcutaneous (SC) insulin infusion.

Microfabrication and photolithographic techniques were used on a flat substrate to create multiple redundant indicating electrodes and a single, common reference electrode. Each substrate was then wrapped around, and adhered to, a 21- gauge steel needle. Compounds required for amperometric sensing were applied after wrapping.

Sensing catheters were tested in octreotide-treated, anesthetized Yucatan pigs. Several sensing catheters, connected to transceivers, were placed in the SC tissue. After initial stabilization, a euglycemic glucose clamp was carried out for 3.5 h. High dose insulin was infused through some of the sensing catheters (total rate, 0.7 u/h). The final hour consisted of a hyperglycemic clamp. A notebook computer remotely collected transmitted data. A one-point calibration was performed at the start of insulin delivery. Data were available for 10 sensors through which insulin was infused and for 15 sensors in which no insulin was given.

Despite an increasing and large insulin effect, there was no clear time-related decline of the glucose signal from the sensing catheters that delivered insulin. There was a non-significant trend for sensed glucose levels to be slightly lower in the insulin catheters vs. non-insulin catheters. Insulin and non-insulin sensors performed similarly during hyperglycemia. Accuracy was improved by 30% with redundant sensing (2-6 sensing units per catheter) as compared to individual sensing units.

Our data suggest that it is possible to measure glucose continuously from the site at which insulin is delivered into SC tissue. Multiple sensing units on a single catheter appear to improve sensing accuracy.

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70-LB

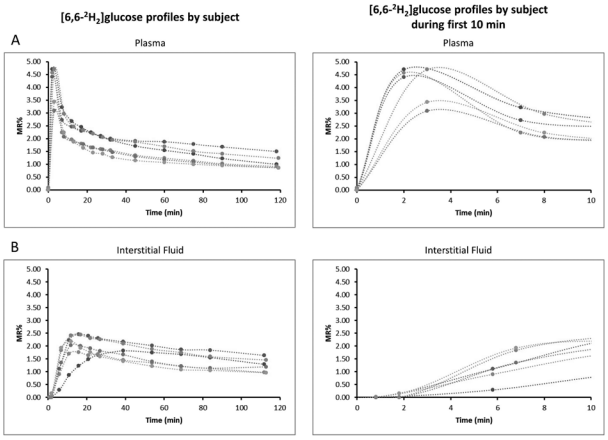
Time Lag of Glucose Transport from Intravascular to Interstitial Compartment in Type 1 Diabetes

SIMMI DUBE, SONA VEETTIL, MICHAEL SLAMA, YOGISH C. KUDVA, CLAUDIO COBELLI, ANANDA BASU, RITA BASU, *Rochester, MN, Padova, Italy*

In the overnight fasted state, the physiological delay of glucose transport from vascular to interstitial space is ~6 min in healthy adults. The current studies were undertaken to assess the time lag in glucose appearance from intravascular to interstitial compartment in type 1 diabetes mellitus (T1D). Microdialysis catheters were placed in the abdomen of six T1D (age 44 ± 14 years; BMI 25.2 ± 3.6 kg/m^2; HbA1c 7.8 ± 0.9%) following an overnight fast.

For author disclosure information, see page LB91.

[1-^{13}C], [6,6-$^{2}H_2$], [2-^{13}C] glucose were administered sequentially at two hour intervals to achieve ~4% enrichment. Plasma/microdialysate samples were collected periodically for isotopic enrichments. Regular insulin was infused starting at 9 PM to maintain glucose concentrations (~113 mg/dl) throughout the study period. Figure 1 illustrates subject-specific profiles for [6,6-$^{2}H_2$] glucose enrichments in plasma (A) and microdialysate (B) after tracer bolus (left panels) and with more resolution (right panels). Profiles of [1-^{13}C] and [2-^{13}C] glucose were similar to [6,6-$^{2}H_2$] glucose. After accounting for catheter dead space transit time (6.2 min) and assay noise (MR > 0.3%), mean time lag of tracer appearance in the interstitial space was ~6 min, which is similar to healthy adults. Model derived equilibration time needs to be estimated for T1D. This data will help optimize future generation glucose sensor algorithms for the artificial endocrine pancreas systems.



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71-LB

Dulce Wireless Tijuana: A Randomized Control Trial Studying the Impact of the Project Dulce™ Model and Mobile Technology on Metabolic Outcomes, Quality of Life, and Behaviors

MARIA CECILIA ANZALDO-CAMPOS, SONIA CONTRERAS, ADRIANA CAROLINA VARGAS-OJEDA, RUFINO MENCHACA-DIAZ, ATHENA PHILIS-TSIMIKAS, *Tijuana, Mexico, National City, CA, La Jolla, CA*

The prevalence of type 2 diabetes mellitus (T2DM) is rapidly rising in the U.S./Mexico border regions (15.7% in adults). Efficient and cost-effective programs are needed to improve care. This study evaluates the effectiveness of the Project Dulce model using peer educators enhanced with wireless technology on glycated hemoglobin (HbA1c), quality of life (QoL), and lifestyles (LS) of patients with poorly controlled T2DM.

A randomized controlled study was conducted in the 27-Family Medical Unit of Intituto Mexicano del Seguro Social (IMSS) in Tijuana, México. A total 301 adults with T2DM, HbA1c ≥8% and no current insulin use were recruited and randomly assigned to three intervention groups: Project Dulce (PD), Project Dulce enhanced with wireless technology (PD-TE) and the standard of care (SC). Participants were followed for 10 months for effect on HbA1c levels, QoL and LS. Means and standard deviations (s) were calculated between groups and differences analyzed by one-way ANOVA.

At baseline no differences were detected. Analysis at 10th month demonstrated significant changes in PD-TE and PD groups compared with SC. (Table 1).

The Project Dulce model, with and without wireless technology, was effective in reducing HbA1c levels and improving QoL and LS in high-risk T2DM patients in a major IMSS Family Clinic along U.S./Mexico border region.

Table 1. HbA1c, QoL, and LS at 10th month.

	SC*	PD**	PD-TE***	
Outcomes	Mean(s) n	Mean(s) n	Mean(s) n	p value†
HbA1c(%)	9.36 (2.85) 81	8.21 (2.38) 70	8.08 (2.10) 82	.002
Quality of Life	24.81 (18.23) 79	16.68 (14.81) 62	19.28 (16.88) 77	.018
Lifestyles	69.90 (12.00) 79	77.60 (9.21) 62	76.90 (11.80) 77	.001

** The standard of care was the usual treatment for T2DM in the clinic.

*** Project Dulce is a trademark of a chronic care multidisciplinary model for diabetes treatment and education.

****Wireless technology included an electronic glucose meter with value-sensitivity database and capacity to send notifications to patients and medical staff, and thru 3G cell phones, interactive motivational surveys, culturally appropriate videos, and educational materials.

† Significant differences between groups at 10th month.

72-LB

Systematic Performance Evaluation of Five Blood Glucose Meters at Stable Low, Normal, and High Blood Glucose Levels

ERIC ZIJLSTRA, ANNELIE FISCHER, CHRISTOPH KAPITZA, *Neuss, Germany*

Accuracy of a blood glucose (BG) meter is determined by the system's random error (measurement variability) and systematic error (measurement bias). We performed a systematic evaluation of 5 commercially available BG meters to investigate their measurement performance at 3 different stable BG levels, 60 - 100 - 200 mg/dL.

Sixteen subjects with type 1 diabetes participated in this open label, single center trial. The subjects' BG was clamped at each of the 3 levels by variable rate infusions of glucose and insulin. Once BG was stabilized, medical staff performed regular fingerpricks (up to 10 per BG level) to obtain capillary blood samples for paired BG meter and YSI reference measurements. Each sample was measured in duplicate (on 2 devices) to investigate the precision absolute relative difference (PARD). One subject was excluded from the analysis due to problems with repeated capillary blood sampling.

Key results are shown (Table). At each BG level and overall, the BGStar, iBGStar and Accu-Chek meters showed the lowest bias and the highest measurement accuracy. Measurement variability, as well as PARD was similar for most meters at the 3 BG levels and overall.

In conclusion, the random error of the tested BG meters is comparable, but a lower systematic error for BGStar, iBGStar and Accu-Chek gives these meters a highly accurate performance at low, normal and high BG levels.

Measurement Performance 5 BG Meters.

	BGStar	iBGStar	Accu-Chek Aviva Nano	One Touch Verio IQ	Freestyle Insulinx
Measurement accuracy—MARD (%)					
60	5.7	6.3	6.3	13.2	9.5
100	3.9	4.1	4.6	10.6	6.7
200	4.1	4.0	3.8	6.1	6.7
Overall	4.6	4.8	4.8	9.9	7.6
Measurement variability—SD					
60	4.2	4.7	4.3	3.6	4.0
100	4.7	5.1	5.6	5.3	4.5
200	10.4	9.8	9.4	8.7	9.8
Overall	6.4	6.5	6.4	5.9	6.1
Measurement bias (%)					
60	-1.9	0.5	4.3	12.0	-8.9
100	-1.6	0.4	0.9	9.8	-6.5
200	0.9	2.3	-1.4	5.4	-6.1
Overall	-0.9	1.0	1.3	9.0	-7.1

Supported By: Sanofi

73-LB

Accuracy of BG Detection in Diabetes Alert Dogs (DADs)

JACLYN SHEPARD, JESSE GRABMAN, DALLAS DUCAR, ANAND TRIPATHI, ZACHARY MCELGUNN, LINDA GONDER-FREDERICK, *Charlottesville, VA*

Use of DADs to monitor BG extremes in type 1 diabetes is growing, but there is little data on their accuracy. This study investigated DAD accuracy using owner diaries of daily BG levels and DAD alerts.

Participants were 18 DAD owners (44.4% female; 77.8% children) with T1D, all of whom obtained a DAD from the same training organization. Adults ranged in age from 40- 47 yrs (M = 44.3 ± 4.4) and children ranged from 2-15 yrs (M = 9.1 ± 4.9). Participants (or parents) completed diaries, recording all daily BG readings and DAD alerts. Number of days of completed diaries ranged from 5-134 and number of entries ranged from 34-569. For each DAD, % Hits (alert with BG 11.1 mmol/L), % Misses (no alert with BG 11.1 mmol/L), and % False Alarms (alert with BG > 5.0 and < 11.1 mmol/L) were computed.

Table 1 shows an overview of results. Comparison of DAD Hits to Misses found significantly more Hits for both low and high BGs. There were significantly more Hits than False Alarms ($\chi 2$ = 65.8, p 65% and 44.4% hit >70%. For high BG, 16.7% of DADs hit >65% and 5.6% hit >70%.

Results indicate that DADs may be an effective tool for detecting out of range BG values. However, more research is needed to establish DAD accuracy and identify factors influencing variability of DAD accuracy in BG detection.

Table 1. Overview of Results.

	Average Hit %	Minimum Hit %	Maximum Hit %	Total Number of Entries	Chi Square (Hits to Misses)	p Value
Overall	54.4%	39.0%	73.7%	2014	43.34	< .0005
Low BG	65.6%	33.3%	100.0%	584	19.24	< .0005
High BG	52.1%	29.4%	76.9%	1430	24.19	< .0005

74-LB

Use of Structured Self-Monitoring of Blood Glucose Improves Glycemic Control in Australians with Non-Insulin-Treated Type 2 Diabetes: First Results of the STeP IT UP Trial

JANE SPEIGHT, JESSICA L. BROWNE, GEORGE KOUMANTAKIS, ALAN BARCLAY, HILTON SHAPIRO, GARY DEED, TRACY HUNTER, WALTER KOEHLER, CHRISTOPHER PARKIN, LUISA CAPEZIO, MATTHIAS A. SCHWEITZER, BETTINA PETERSEN, *Melbourne, Australia, Castle Hill, Australia, Padstow Heights, Australia, Mascot, Australia, Coorparoo, Australia, Indianapolis, IN, Frankfurt, Germany, Boulder City, NV, Mannheim, Germany*

Structured self-monitoring of blood glucose (SMBG) is an approach in which blood glucose data are gathered according to a defined regimen, interpreted and utilized to make appropriate pharmacologic and/or lifestyle adjustments. Its benefits have been demonstrated in efficiency and effectiveness studies in the U.S. and European but the generalizability of these findings have not yet been shown in Australia. The Structured Testing Program Implementation Trial (STeP IT UP) assessed the impact of structured SMBG on HbA1c and diabetes-related distress in 136 adults with non-insulin-treated type 2 diabetes managed in primary care settings across Australia: mean [SD] HbA1c 8.7[1.2]%, age 60.8[12.2] years, 39.7% women, BMI 32.1[6.3]. In this 24-week, multi-center, uncontrolled, observational study, Australian clinicians with structured SMBG experience trained patients to use and interpret structured SMBG (3-day, 7-point profiles), using the Accu-Chek 360° View paper tool. Patients completed the tool prior to their visits at weeks 4, 12 and 24; results were discussed at each visit. Data from preliminary analyses of >50% of enrolled patients (n=77) showed reductions in HbA1c from week 4 at weeks 12 and 24 (-0.9[1.2]%, P<0.0001; -1.1[1.4]%, p<0.0001, respectively), with no increase in hypoglycemia (<72 mg/dL / <4 mmol/L). Reductions in percentage of high glucose values (>180 mg/dL / >10 mmol/L) were seen at weeks 12 and 24 (-7.2[21.5]%, p=0.0114; -11.1[25.8]%, P=0.0049, respectively). Diabetes-related distress showed no increase at weeks 12 or 24 (-0.12[0.77], p=0.2294; -0.16[0.93], p=0.1811, respectively). In this preliminary analysis, use of structured SMBG by Australian adults with non-insulin-treated type 2 diabetes supported by primary care clinicians is associated with signficant improvements in glycemic control without increasing hypoglycemia or diabetes-related distress.

75-LB

CGM Is Not a Limiting Factor in Artificial Pancreas Systems

TIMOTHY S. BAILEY, KATHERINE NAKAMURA, ANNA CHANG, MARK CHRISTIANSEN, DAVID A. PRICE, ANDY BALO, *Escondido, CA, San Diego, CA, Concord, CA, Walnut Creek, CA*

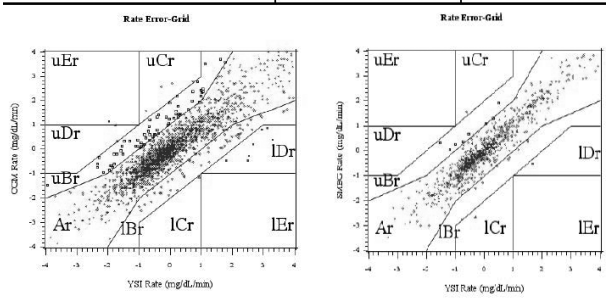
CGM used for Artificial Pancreas (AP) systems requires low glucose accuracy for safety, euglycemic and hyperglycemic accuracy to optimize insulin dosing determinations, and consistent performance across sensors and over time. A modified CGM designed specifically for the AP project was assessed in a clinical research study.

The study enrolled 51 subjects from 3 U.S. centers, 86% with T1D. Subjects wore sensors for up to 7 days and used self-monitored blood glucose to calibrate their CGM twice daily. Each subject was in-clinic for 12 hours on day 1, 4, or 7 to collect YSI reference venous glucose every 15 minutes and capillary SMBG test every 30 minutes; glucose was manipulated to provide sufficient data in low and high glucose ranges.

The study concluded that the CGM readings were highly correlated with YSI with correlation coefficient of 0.97 comparing 0.99 of that for SMBG. Using YSI reference, the CGM performed similarly as the SMBG meter. The study showed that the overall point accuracy,clinical accuracy, accuracy over the duration of wear, accuracy across the glycemic ranges, and reliability (98% of sensors lasted 7 days) are unmatched by current CGM systems. Accordingly, the CGM accuracy should not limit AP system development.

Figure 1. Performance Comparison of CGM-YSI vs. SMBG-YSI.

Performance vs. YSI	CGM	SMBG
Temporal matched pairs (N)	2263	994
Pearson Correlation Coefficient	0.97	0.99
Mean Absolute Relative Difference (ARD)	9.0%	4.6%
MARD within Day 1|Day 4|Day 7	10.7%|8.0%|8.5%	5.3%|4.9%|6.6%
Mean Absolute Difference (MAD), at Hypoglycemia BG <= 70 mg/dl	6.4 mg/dL	4.2 mg/dL
MARD at Euglycemia70 < BG <= 180	9.7%	6.1%
MARD at Hyperglycemia BG > 180 mg/dl	8.0%	4.8%
Overall CEG A+B Zones|A Zone	99.5%|92.4%	99.6%|98.5%
CG-EGA Zone Accurate Readings Hypoglycemia/Euglycemia/Hyperglyceima	95.6%|99.1%|99.2%	97.3%|99.7%|99.6%



76-LB

A Multicenter Evaluation of the Accuracy of the Contour© XT Glucose Meter Following ISO 15197:2013 Accuracy Criteria

JOSE LUIS BEDINI, JANE WALLACE, THORSTEN PETRUSCHKE, BARBARA STOLL-FUSS, SCOTT PARDO, *Barcelona, Spain, Mishawaka, IN, Leverkusen, Germany, Whippany, NJ*

A multicenter study was carried out in 21 Spanish Hospitals to evaluate the performance of the Contour® XT (Bayer) glucose meter, under daily routine conditions, in comparison with the hexokinase method.

As a first step, the comparability of glucose hexokinase results between the different sites' analyzers was assessed by measuring three different levels of control material (BioRad) twice a day during five days.

Thereafter, each site measured the glucose level in 100 surplus venous blood samples (range from 33 mg/dL to 562 mg/dL) with a Contour® XT and the laboratory clinical chemistry analyzer using the hexokinase method.

The time between the Contour® XT measurement and the centrifugation to obtain plasma for the analyzer was strictly controlled to be of less than 10'.

At each site, the Contour® XT results were compared to those of the respective hexokinase method, to determine whether they were within either ± 15 mg/dL of the analyzer result, for samples <100 mg/dL, or within ± 15% for samples ≥100 mg/dL. A Consensus Error Grid analysis was performed.

Overall blood testing results showed that 99.43% (2088 out of 2100) of the Contour® XT results met the ISO 15197:2013 accuracy criteria. As for individual sites, 14/21 sites had 100% of results within the criteria; five had 99%, one had 98% and one had 95%.

2096 out of 2100 results (99.8%) were inside the Consensus Error Grid zone A, while the remaining four results (0.2%) were in zone B.

This is one of the few multicenter studies performed with a blood glucose meter. Despite the inclusion of a high number of samples and sites, and the use of different hexokinase analyzers for the comparative glucose measurements, overall results exceed the system accuracy requirements of the ISO 15197:2013 regulation (99.43%). Moreover, individual results from each site also met these requirements. In conclusion, Contour XT tested under daily routine conditions was found to be a highly accurate and robust blood glucose monitoring system.

77-LB

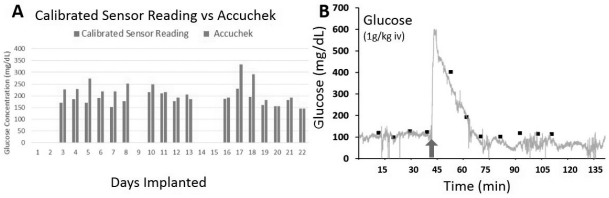
A Wireless Continuous Glucose Monitoring System for Subcutaneous Implantation in Rodents

DANIEL V. AILLON, ERIK NAYLOR, HANS P. HARMON, BRIAN S. BARRET, DONNA A. JOHNSON, DAVID A. JOHNSON, PETER A. PETILLO, *Lawrence, KS*

Continuous monitoring of glucose concentrations is critical for the study and management of diabetic models in animals. We have developed a continuous glucose monitoring system specifically designed for use in rats. Subcutaneous implantation of the glucose biosensor is achieved using a minimally invasive surgical procedure and the telemetry system is attached to a jacket. Five biosensors were implanted in wild-type Sprague-Dawley rats for at least two-

For author disclosure information, see page LB91.

weeks (Figure 1A). Each sensor was calibrated daily to Accu-Chek readings of tail-vein blood. Daily injections of glucose (1 g/kg ip) were administered. No statistical difference was noted between the calibrated sensor reading and the Accu-Chek value taken during the bolus (calibrated value: 174 +/- 14 mg/dL, Accu-Chek Value: 189 +/- 12 mg/dL, P>0.05, two-tailed t-test) after two weeks of continuous monitoring. In a second cohort of animals, the femoral vein was catheterized and blood samples were taken every 8 minutes over the course of either a glucose (1 g/kg iv) or insulin bolus (2 U/kg iv). Using a two-point calibration, responses were accurately tracked by the biosensor (e.g. Figure 1B). The telemetry system integrates seamlessly with a software suite that provides both real-time monitoring of the CGMS signal and the ability to readily process the data.



CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULINS

78-LB

The Ultra-Rapid BioChaperone Insulin Lispro (BC LIS) Shows a Faster Onset of Action and Stronger Early Metabolic Effect than Insulin Lispro (LIS)

GRIT ANDERSEN, BERTRAND ALLUIS, GRÉGORY MEIFFREN, AYMERIC RANSON, OLIVIER SOULA, GÉRARD SOULA, RÉMI SOULA, ANNELIE FISCHER, LESZEK NOSEK, FREIMUT SCHLIESS, TIM HEISE, *Neuss, Germany, Lyon, France*

In this double-blind, crossover study we investigated the pharmacodynamic characteristics of BC LIS, a novel insulin lispro formulation with BioChaperone aimed at accelerating the absorption from the subcutaneous tissue. Thirty-six people with type 1 diabetes completed this study and received 0.2 U/kg of BC LIS or LIS under automated euglycemic clamp conditions (ClampArt®, target blood glucose 100 mg/dL, clamp duration 6h post-dosing). Mean glucose infusion rates (GIR) are given in the figure. Compared with LIS, BC LIS showed ultra-rapid properties with a faster onset of action (23.1±7.0 (mean±SD) vs. 34.4±15.3 min, p<0.0001), an earlier maximum effect ($T_{GIR\ max}$ 99±42 vs. 133±45 min, p=0.0002) and a stronger early metabolic effect in the first hour ($AUC_{GIR\ 0\text{-}1h}$ 218±88 vs. 129±63 mg/kg, p<0.0001) and first 2 hours ($AUC_{GIR\ 0\text{-}2h}$ 627±235 vs. 525±214 mg/kg, p=0.0041). Total ($AUC_{GIR\ 0\text{-}6h}$ 1409±494 vs. 1434±506 mg/kg, p=0.72) and maximum metabolic effect (GIR_{max} 7.85±2.87 vs. 7.96±2.81 mg/kg/min, p=0.76) were comparable. Both insulin formulations were well tolerated. In conclusion, BC LIS shows a faster onset of action, an earlier maximum action and stronger metabolic effect in the first 2 hours than native insulin lispro. BC LIS has the characteristics of an ultra-fast acting insulin with the potential to be injected at mealtime with excellent glycemic control.

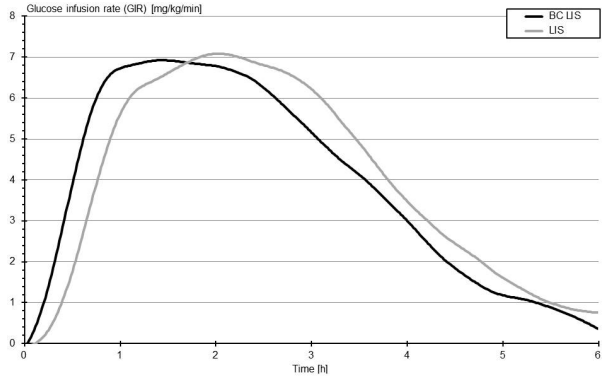


Figure: Smoothed pharmacodynamic (GIR) profiles of BioChaperone lispro (BC LIS) and native insulin lispro (LIS)

79-LB

Pharmacokinetic and Pharmacodynamic Profiles of BIOD-531 vs. Insulin Lispro U-100 or U-500R Following Pump Bolus or Subcutaneous Administration in Miniature Diabetic Swine

RODERIKE POHL, MING LI, BRYAN R. WILSON, MARY GUINNESS, ALAN KRASNER, ERROL DE SOUZA, *Danbury, CT*

BIOD-531, a U-400 formulation of recombinant human insulin, EDTA, citrate and $MgSO_4$, is associated with an accelerated onset of action compared to Humulin® R U-500 (U-500R) and Humalog® Mix75/25™ and a basal duration profile in obese non-diabetic subjects and in diabetic swine. In order to assess the potential of BIOD-531 for CSII therapy for subjects who require high doses of insulin and utility in artificial pancreas systems, we evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of BIOD-531 vs. U-500R and Humalog® U100 (insulin lispro; IL) following pump bolus administration or subcutaneous (SC) injection in miniature diabetic swine. Key PK parameters and onset of action PD parameters such as $T\text{-}BG_{50\%Minimum}$ (time to 50% glucose nadir) and $T\text{-}BG_{Minimum}$ (glucose nadir) are shown in Table below. The rate of absorption and onset of action of BIOD-531 are not significantly different from IL and faster than U-500R following pump bolus administration. In addition, the PK and PD profiles comparing BIOD-531 vs. IL look similar following pump bolus or SC injection. These data suggest the potential utility of BIOD-531 as CSII therapy for highly insulin resistant type 2 diabetes patients who require high doses of insulin. Furthermore, BIOD-531 may be useful to help conserve space in future Artificial Pancreas systems.

Pharmacokinetic and Pharmacodynamic Profiles of BIOD-531 Vs. Insulin Lispro U-100 or U-500R Following Pump Bolus Administration or Subcutaneous Injection in Miniature Diabetic Swine

Pharmacokinetic (PK) or Pharmacodynamic (PD) Parameter		Pump Bolus Administration				Subcutaneous Injection
		Study 1		Study 2		Study 3
		BIOD-531	U-500R	BIOD-531	IL	BIOD-531	IL
PK	$T_{50\%max}$ (min)	12±4	26±7	13±3	17±3	11±2	21±4*
	T_{max} (min)	31±9	74±17	73±19	29±5	76±18	55±8
	$AUC_{0\text{-}20min}$ ((µU/mL)*min)	863±86	581±125*	758±78	961±285	1081±182	904±245
	C_{max} (µU/mL)	93±14	126±28	96±10	129±17	125±17	153±16
PD	$T\text{-}BG_{50\%Minimum}$ (min)	40±23	71±24	20±5	30±7	17±2	28±4
	$T\text{-}BG_{Minimum}$ (min)	302±82	249±69	163±36	98±20	216±63	78±15
	$BG_{Minimum}$ (mg/dl)	-245±27	-244±26	-208±34	-250±36	-244±25	-244±17

Studies were carried out using a cross-over design. Fasted swine were given 0.25 U/kg insulin via an Animas Ping pump or subcutaneous injection and fed. Blood was sampled from -30 to 480 min post dose. Plasma insulin was measured by insulin ELISA and glucose by YSI.

Data represent Mean ± SEM; n = 8 (pump), n=9 (sc) * Significant difference from BIOD-531 at p< 0.05

Supported By: NIH (R43DK096604)

80-LB

Glycemic Control and Hypoglycemia with New Insulin Glargine 300U/mL in People with T1DM (EDITION 4)

PHILIP D. HOME, RICHARD M. BERGENSTAL, MATTHEW C. RIDDLE, MONIKA ZIEMEN, MARIA ROJESKI, MELANIE ESPINASSE, GEREMIA B. BOLLI, *Newcastle upon Tyne, United Kingdom, Minneapolis, MN, Portland, OR, Frankfurt, Germany, Bridgewater, NJ, Paris, France, Perugia, Italy*

EDITION 4 studied the efficacy and safety of new insulin glargine (300 U/mL; Gla-300) vs. glargine 100 U/mL (Gla-100) in people with T1DM. In this 6-month, multinational, multicenter, open-label study, participants (n=549, BMI 27.6 kg/m^2, T1DM duration 21.0 yr, HbA_{1c} 8.12%) were randomized 1:1:1:1 to once-daily Gla-300 or Gla-100, morning or evening, while continuing meal-time insulin. Overall, Gla-300 was non-inferior to Gla-100 for HbA_{1c} change from baseline (primary endpoint) (LS mean change [SE] –0.40 [0.05] % and –0.44 [0.05] %; LS mean difference 0.04 [95% CI: –0.10 to 0.19] %). Event rate of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia at any time of day (24 h) was similar for the two groups, while nocturnal hypoglycemia was lower in the Gla-300 vs. Gla-100 group in the first 8 weeks of the study (Table). Neither glycemic control nor hypoglycemia differed between morning and evening injection groups. Severe hypoglycemia was observed in 6.6% (Gla-300) and 9.5% (Gla-100) of participants. Total insulin dose increased to a somewhat greater extent for Gla-300 vs. Gla-100 (change from baseline +0.19 vs. +0.10 U/kg). Weight gain was significantly lower with Gla-300 (difference –0.56 [–1.09 to –0.03] kg, p=0.037). There was no difference in adverse events. In conclusion, Gla-300 provided comparable glycemic control vs. Gla-100 and nocturnal hypoglycemia was reduced during the first 8 weeks.

Table – Hypoglycemic events per participant-year in the two insulin groups

	Gla-300 (N=274)	Gla-100 (N=275)	RR (95% CI)
Total participant-years	**124.10**	**126.83**	
Nocturnal (00:00–05:59 h) confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe			
Baseline to month 6	8.00	8.95	0.90 (0.71 to 1.14)
Baseline to week 8	7.75	11.20	0.69 (0.53 to 0.91)
Week 9 to month 6	8.13	7.85	1.04 (0.80 to 1.36)
Any-time (24 h) confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe			
Baseline to month 6	78.42	72.53	1.09 (0.94 to 1.25)
Baseline to week 8	87.39	89.49	0.98 (0.85 to 1.13)
Week 9 to month 6	73.93	64.18	1.16 (0.98 to 1.37)

RR, risk ratio; CI, confidence interval

Supported By: Sanofi (NCT01683266)

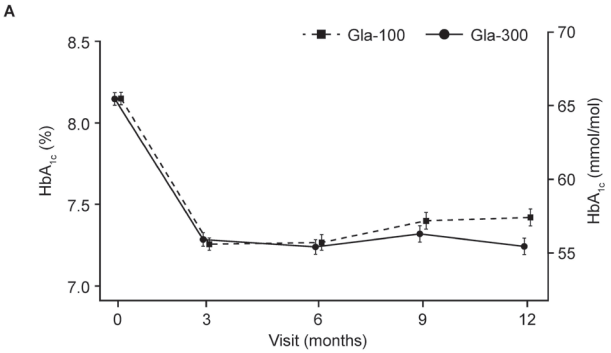
81-LB

Sustained Glycemic Control and Less Hypoglycemia with New Insulin Glargine 300 U/mL Compared with 100 U/mL: One-Year Results in People with T2DM Using Basal + Mealtime Insulin (EDITION 1)

MATTHEW C. RIDDLE, GEREMIA B. BOLLI, HANNELE YKI-JÄRVINEN, MONIKA ZIEMEN, ISABEL MUEHLEN-BARTMER, SOPHIE CISSOKHO, PHILIP D. HOME, *Portland, OR, Perugia, Italy, Helsinki, Finland, Frankfurt, Germany, Levallois-Perret, France, Newcastle upon Tyne, United Kingdom*

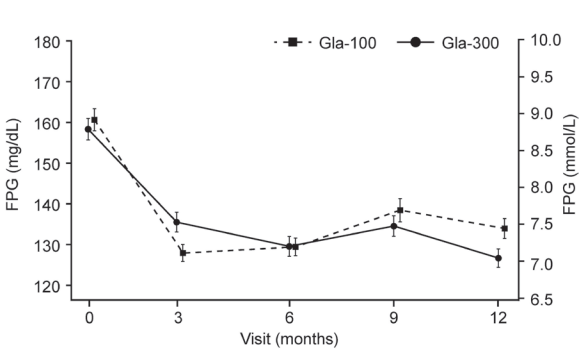
In EDITION 1, 807 people with elevated HbA_{1c} using basal + mealtime insulin were randomized to titrated insulin glargine 300 U/mL (Gla-300) or glargine 100 U/mL (Gla-100) once daily in the evening for 6 months, continuing the mealtime insulin. In a 6-month open-label extension, participants continued Gla-300 or Gla-100; 89% and 88% completed 12 months of treatment. Improved glycemic control was maintained over 12 months in both groups (LS mean difference Gla-300 vs. Gla-100: –0.17 [95% CI –0.30 to –0.05] % for HbA_{1c} and –0.34 [95% CI –0.69 to 0.01] mmol/L for FPG) (Figure). Basal insulin doses were higher with Gla-300 than Gla-100 after 12 months (1.03 vs. 0.90 U/kg). During the 12 months of treatment, a similar % of participants had ≥1 confirmed (≤70 mg/dL) or severe hypoglycemic event at any time of the day (85.9% with Gla-300 vs. 91.5% with Gla-100; RR 0.94 [95% CI 0.89 to 0.99]). During the night this percentage was lower in Gla-300 (54.5% vs. 64.7% in Gla-100; RR 0.84 [95% CI 0.75 to 0.94]). Severe hypoglycemia was reported by 6.7% of Gla-300- and 7.5% of Gla-100-treated participants. No between-treatment differences in adverse events were seen. In conclusion, over 1 year of treatment in people with T2DM using basal + mealtime insulin, Gla-300 provided sustained glycemic control with a lower incidence of hypoglycemia compared with Gla-10.

Figure: Glycemic control over 12 months in EDITION 1 study. (A) HbA_{1c} (B) FPG



HbA_{1c} [%] mean

Gla-100	8.15	7.26	7.27	7.40	7.42
Gla-300	8.15	7.29	7.24	7.32	7.24



FPG [mg/dL] mean

Gla-100	160.6	128.1	129.6	138.5	134.1
Gla-300	158.3	135.6	129.7	134.7	126.8

Supported By: Sanofi (NCT01499082)

82-LB

Concentrated Insulin BIOD-531 Is Associated with Accelerated Onset of Action Compared to Humulin® R U-500 and Humalog® Mix75/25™ and a Basal Duration Profile

LINDA MORROW, LORI CANNEY, PHILIP PICHOTTA, MARCUS HOMPESCH, ALAN KRASNER, ERROL DE SOUZA, *Chula Vista, CA, Danbury, CT*

Formulations of insulin containing citrate and EDTA have been shown to be more rapidly absorbed than conventional formulations of recombinant human insulin (RHI) or rapid acting insulin analogs. BIOD-531, a concentrated (400 U/ml or U-400) formulation of RHI containing EDTA, citrate and $MgSO_4$, has been shown in diabetic swine to be associated with rapid onset and extended duration of action. In this single-center, randomized, double-blind four-period crossover study employing 24-hour euglycemic clamps, the pharmacokinetics (PK) and pharmacodynamics (PD) of BIOD-531 at two doses (1 U/kg and 0.5 U/kg) were compared to Humulin® R U-500 (1.0 U/kg) and Humalog® Mix75/25™ (0.5 U/kg) in 13 obese non-diabetic subjects. All study drugs were well tolerated. Key PK and PD parameters are summarized in Table 1. This study demonstrates that BIOD-531 has a more rapid onset of action and rises to higher peak effect than either comparator. The duration of action of BIOD-531 (~ 18 hours) while slightly shorter than that of either comparator is commensurate with a basal insulin. In addition, BIOD-531 delivers significantly greater glucose lowering activity over a 24 hour period than Humalog® Mix75/25™. These PK/PD profiles suggest BIOD-531 has the potential to deliver ultra-rapid prandial and basal insulin coverage in small injection volumes.

Table 1. Data Represent the Mean ± SEM; Median Values are Presented in [Parentheses].

Parameter	BIOD-531 (1 U/kg) N=12	Humulin® R U-500 (1 U/kg) N=12	p-value of BIOD-531 vs. U-500	BIOD-531 (0.5 U/kg) N=12	Humalog® Mix75/25™ (0.5U/kg) N=12	p-value of BIOD-531 vs. 75/25
Early ½ T_{max} (min)	11.0±1.9 [8.2]	135.3±34.9 [99.6]	0.001	16.4±4.9 [10.4]	47.9±2.6 [46.3]	0.002
T_{max} (min)	223.8±62.3 [195.0]	393.3±58.3 [360.0]	0.006	131.3±43.4 [37.5]	160.0±11.9 [150.0]	0.846
$AUCGIR_{0\text{-}60min}$ (mg/kg)	108.5±22.0 [101.1]	40.4±10.0 [44.5]	0.001	68.9±13.4 [52.8]	14.5±4.7 [6.4]	<0.001
Onset of Action (min)	7.2±4.1 [1.0]	21.4±6.7 [12.5]	0.023	14.6±6.0 [11.0]	35.9±7.9 [33.0]	0.033
Duration of Action (min)	1165.0±56.9 [1188.5]	1383.6±38.0 [1440]	0.002	1076.2±50.7 [1028.5]	1284.0±47.3 [1321.5]	0.002
Peak Effect (GIR_{max}) (mg/kg/min)	6.28±0.66 [6.21]	5.54±0.67 [5.60]	0.032	4.89±0.72 [5.40]	3.10±0.55 [2.29]	0.009
Total glucose lowering activity ($AUCGIR_{0\text{-}1440min}$) (mg/kg)	4229.9±329.0 [4593.7]	4477.1±512.4 [4800.9]	0.765	2913.3±315.2 [3061.9]	2148.3±284.7 [2137.7]	0.016

For author disclosure information, see page LB91.

83-LB

Pharmacokinetic (PK) and Pharmacodynamic (PD) Characteristics of BioChaperone Combo (BC Combo), the First Fixed Combination of Glargine and Lispro, in Type 1 Diabetes

ULRIKE HÖVELMANN, BERTRAND ALLUIS, GRÉGORY MEIFFREN, AYMERIC RANSON, OLIVIER SOULA, GÉRARD SOULA, RÉMI SOULA, BIRGIT KRONSHAGE, LESZEK NOSEK, SUSANNE FAMULLA, TIM HEISE, *Neuss, Germany, Lyon, France*

In this double-blind, crossover study we investigated the PK/PD characteristics of BC Combo, a novel insulin combining lispro (25%) and glargine (75%) in a limpid pH-neutral formulation. Twenty people with type 1 diabetes participated in automated euglycemic clamps (ClampArt®, target blood glucose (BG) 100 mg/dL, clamp duration 30h) and received 0.8 U/kg of BC Combo or Humalog Mix25 (MIX). Mean glucose infusion rate (GIR) curves (Figure) illustrate an earlier onset of action (25±11 vs. 40±13 min) consistent with earlier T_{max} (2.8±0.8 vs. 3.4±0.8 h) of BC Combo vs. MIX. Likewise, the early metabolic effect ($AUC_{GIR\ 0\text{-}2h}$ 504±210 vs. 325±183 mg/kg) and the early PK exposure ($AUC_{PK\ 0\text{-}1h}$ 86±39 vs. 34±19 h*mU/L) were higher, and BC Combo showed a more pronounced late metabolic effect ($AUC_{GIR\ 12\text{-}30h}$ 1480±900 vs. 961±553 mg/kg) consistent with a higher basal exposure ($AUC_{PK\ 12\text{-}30h}$ 563±409 vs. 286±233 h*mU/L). Duration of action (time to BG > 118 mg/dL, 29.8±0.7 vs. 25.5±4.3 h) and half-life (17.6±8.7 vs. 7.7±3.0 h, p<0.05 for all comparisons) were longer with BC Combo indicating the potential for once daily dosing. Both formulations were well tolerated, no local reactions occurred. Both PK and PD demonstrate faster prandial and longer basal action for BC Combo supporting the potential for improved BG control vs. MIX with only one daily injection.

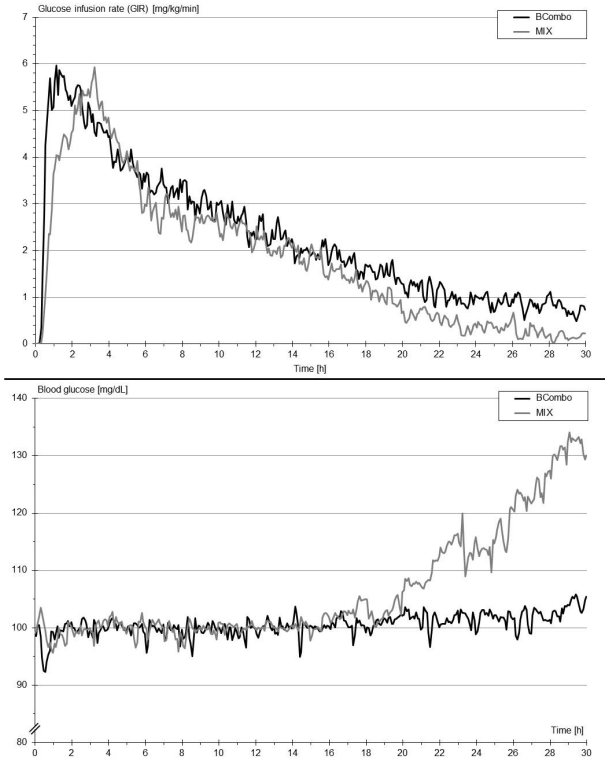


Figure:Pharmacodynamic (GIR, upper panel) and blood glucose (BG, lower panel) profiles (5 min mean values, respectively) of BioChaperone Combo and Humalog Mix25

84-LB

The INITIATOR Study: Real-World Treatment Patterns and Outcomes in Patients with Type 2 Diabetes Mellitus (T2DM) Initiating Insulin Glargine (GLA) or Liraglutide (LIRA)

PHILIP LEVIN, WENHUI WEI, ERIN BUYSMAN, SARAH THAYER, LEE BREKKE, WILLIAM CROWN, MICHAEL GRABNER, XUEHUA KE, RALPH QUIMBO, MARK CZIRAKY, WENLI HU, ROBERT CUDDIHY, JAMES CHU, *Baltimore, MD, Bridgewater, NJ, Eden Prairie, MN, San Francisco, CA, Wilmington, DE, Monterey, CA*

As the first large real-world study of T2DM patients Initiating New Injectable Treatment Introduced after Anti-diabetic Therapy with Oral-only Regimens (INITIATOR), this analysis aimed to describe baseline (BL) characteristics and 1 year follow-up outcomes.

Medical charts and claims data were extracted for adult T2DM patients previously on oral antidiabetic drugs, initiating GLA disposable pen or LIRA, and with continuous plan enrollment 6 months before (BL) and 1 year after initiation (follow up). Differences in BL characteristics were compared and 1 year follow-up outcomes were assessed descriptively.

A total of 4,490 patients were included with significant BL differences (Table). GLA patients had higher A1C and comorbidity scores. LIRA patients weighed more, were more often women, and 1 in 4 had A1C < 7%. At follow up both groups had significant A1C reductions with GLA gaining and LIRA patients losing weight. Diabetes healthcare costs increased significantly in LIRA but not in GLA.

These results showed clinically relevant differences in BL characteristics and follow-up outcomes in T2DM patients initiating GLA or LIRA. The study highlights challenges in translating clinical trial findings into the real world, and conducting comparative effectiveness studies when important BL group differences exist.

Table. INITIATOR Characteristics and Outcomes.

	OP[a] GLA (n = 1,278)	OP[a] LIRA (n = 1,469)	HC[a] GLA (n = 838)	HC[a] LIRA (n = 905)
BL Age (years), Mean (SD)[b] BL Female, n (%)[b] BL Quan-Charlson Comorbidity Score, Mean (SD)[b]	53.3 (8.8) 553 (43.3) 0.89 (1.53)	52.2 (8.9)** 714 (48.6)* 0.61 (1.14)**	53.2 (9.0) 341 (40.7) 0.87 (1.53)	52.4 (8.6) 434 (48.0)* 0.65 (1.21)**
BL A1C/ Follow-up A1C[c] change (%), Mean (SD)[b]	9.73 (2.08)/ -1.24 (2.26)	8.23 (1.76)**/ -0.53 (1.59)	9.72 (2.07)/ -1.23 (2.09)	8.12 (1.55)**/ -0.48 (1.65)
BL Weight/ Follow-up Weight[c] change (lbs), Mean (SD)[b]	222.1 (51.3)/ 2.5 (13.5)	244.9 (54.5)**/ -5.7 (15.8)	223.1 (52.0)/ 2.7 (18.9)	243.9 (52.2)**/ -6.6 (14.2)
Diabetes-related Hospitalization, n(%)[d]	BL: 115 (9.0) HY2: 65 (5.1) **	BL: 39 (2.7) HY2: 56 (3.8)	BL: 52 (6.2) HY2: 57 (6.8)	BL: 40 (4.4) HY2: 46 (5.1)
Diabetes-related Healthcare Cost, Mean (SD)[d]	BL: $3,301 ($8,623) HY2: $3,474 ($10,410)	BL: $1,947 ($4,538) HY2: $3,026 ($6,145)**	BL: $3,783 ($19,359) HY2: $3,665 ($16,474)	BL: $2,320 ($4,157) HY2: $3,636 ($8,192)**
Diabetes Drug Costs, Mean (SD)[d]	BL: $641 ($703) HY2: $1,199 ($1,013)**	BL: $661 ($708) HY2: $1,520 ($1,025)**	BL: $739 ($806) HY2: $611 ($830)**	BL: $764 ($793) HY2: $1,587 ($1,164)**

* P≤0.01; ** P≤0.001. [a]Data collected from two health insurance plans, associated with Optum™ (OP) and HealthCore® (HC). [b]Statistical significance denotes differences between treatment cohorts within each health plan. [c]Among patients with ≥1 A1C result or ≥1 weight reading in the follow-up period. [d] Within each treatment group, hospitalizations and costs during the second half year of follow-up (HY2) were assessed and compared with BL; statistical significance denotes change from BL to follow-up within each treatment arm. SD, standard deviation.

Supported By: Sanofi

85-LB

Recombinant Human Hyaluronidase Pretreatment of CSII Cannula Sites Provides Comparable Glycemic Control with Reduced Hypoglycemia in T1DM Compared to Usual CSII

IRL B. HIRSCH, BRUCE W. BODE, JAY S. SKYLER, SATISH K. GARG, JOHN B. BUSE, XIONGHUA W. WU, DANIEL E. VAUGHN, DOUGLAS B. MUCHMORE, *Seattle, WA, Atlanta, GA, Miami, FL, Aurora, CO, Chapel Hill, NC, San Diego, CA*

Recombinant human hyaluronidase (rHuPH20) is FDA-approved to increase dispersion and absorption of injected drugs. In CSII, a single pretreatment of the cannula site with rHuPH20 accelerates exposure and action of bolus doses of rapid analogs for up to 3 days of catheter use. 456 subjects with T1DM (age 48±13 years, BMI 28.5±5.1, screening A1C 7.8±0.7) were randomized 3:1 to rapid acting analog (RAI) CSII with rHuPH20 pretreatment or usual RAI CSII for 6 months. A1C fell 0.14% from baseline 7.69% with rHuPH20 and 0.18% from baseline 7.70% for CSII alone. The primary endpoint of A1C noninferiority (0.4% margin) was achieved with a treatment difference of 0.05% (95% CI -0.08 to 0.18) with similar % of subjects reaching A1C <7.0% (20.9% with rHuPH20 and 17.5% for CSII alone, p=.45). Mean overall 90 min post-meal glucose excursion was 18.6 mg/dL with rHuPH20 and 19.6 for CSII alone (p=.76). There were fewer hypoglycemic events (HEs) with rHuPH20 than for CSII alone. The protocol specified primary HE analysis was based on event rates after a month of active titration following randomization. Documented HEs ≤70 mg/dL (obtained from SMBG uploads of 259,666 records) were reduced 11% from 13.7/subject-month for standard CSII vs. 12.2 with rHuPH20 (p=.11), while documented HEs <56 mg/dL were reduced 21% from 4.0/mo to 3.1 (p=0.033). Nocturnal HEs (≤70 mg/dL between 23:00 and 06:00 hrs) were reduced 20%

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(p=.032). Severe HEs occurred at a rate of 0.17 per subject-year for standard CSII and 0.07 with rHuPH20 (60% reduction, p=.12). Adverse event rates were generally comparable between treatments, although rHuPH20 pretreatment was associated with an increased incidence of infusion site pain (typically mild transient burning) from 5.3% to 14.0%. We conclude that pretreatment of CSII cannulas with rHuPH20 is well tolerated and results in similar glycemic control in T1DM with reduction of hypoglycemia.

86-LB

Efficacy and Safety of Once-Daily Biphasic Insulin Aspart 70/30 (BIAsp 30) with Sitagliptin and Twice-Daily BIAsp 30 With or Without Sitagliptin in Patients with Type 2 Diabetes: The Sit2Mix Trial

SULTAN LINJAWI, RADHAKRISHNA SOTHIRATNAM, RAMAZAN SARI, HENNING ANDERSEN, LINE CONRADSEN HIORT, PATURI V. RAO, *Coffs Harbour, NSW, Australia, Seremban, Malaysia, Antalya, Turkey, Søborg, Denmark, Hyderabad, India*

Sit2Mix is a 24-week, randomized, controlled, open-label trial comparing efficacy and safety of twice-daily BIAsp 30 + sitagliptin (BIAsp BID+Sit, n=195), once-daily BIAsp 30 + sitagliptin (BIAsp QD+Sit, n=193) and twice-daily BIAsp 30 without sitagliptin (BIAsp BID, n=194), all with metformin, in patients with type 2 diabetes (T2D) inadequately controlled on sitagliptin and metformin. At baseline, age, diabetes duration, BMI, FPG, and A1C 8.4% [68 mmol/mol]) were similar across groups. After 24 weeks, A1C reduction (% [mmol/mol]) was statistically superior with BIAsp BID+Sit vs. BIAsp QD+Sit (-1.51 [-16.5] vs. -1.15 [-12.6], difference: -0.36 [-3.89], 95% CI -0.54;-0.17 [-5.91;-1.88], $p<0.001$) and vs. BIAsp BID (vs. -1.27 [-13.8], diff: 0.24 [2.65], 95% CI 0.06;0.43 [0.62;4.68], $p=0.01$); BIAsp QD+Sit and BIAsp BID were not significantly different. A similar trend was seen for A1C responders <7.0%: 59.8% of patients achieved target with BIAsp BID+Sit, 46.5% with BIAsp QD+Sit and 49.7% with BIAsp BID. Severe or minor hypoglycemia (plasma glucose <56 mg/dL ± symptoms) was significantly different with BIAsp QD+Sit vs. BIAsp BID ($p=0.015$); rates were 1.17 events/patient-year with BIAsp QD+Sit, 1.50 with BIAsp BID+Sit and 2.24 with BIAsp BID. Other adverse events were similar across groups. Treatment difference in body weight change significantly favored BIAsp QD+Sit vs. both BID groups (vs. BIAsp BID+Sit 1.51 [0.82;2.21], $p<0.001$; vs. BIAsp BID 2.19 [1.49;2.89], $p<0.001$). Final total daily insulin dose was 0.39, 0.66 and 0.72 U/kg, respectively (baseline 0.16 U/kg). To conclude, addition of BIAsp 30 to patients with T2D inadequately controlled with sitagliptin and metformin is efficacious and has a good tolerability profile; however, while BIAsp BID+Sit was superior in glycemic control, BIAsp QD+Sit had a lower hypoglycemia risk vs. BIAsp BID and less weight gain vs. both BID groups.

Supported By: Novo Nordisk A/S

87-LB

Bedtime Oral Insulin Lowers Fasting Blood Glucose Levels in T2DM Patients

JOEL NEUTEL, MIRIAM KIDRON, EHUD ARBIT, KENNETH HOMER, *Tustin, CA, Jerusalem, Israel, Cedar Knolls, NJ*

Bedtime insulin administration has been suggested to best counteract abnormal morning fasting blood glucose (FBG) levels, a harbinger of diabetes and a key obstacle to optimal glycemic management in T2DM patients. However, many early-stage patients resist introduction of insulin injections into their routine. The pursuit of an orally bioavailable insulin formulation has been driven by the notion that it can both increase patient compliance, and better mimic the physiological route of naturally secreted insulin, consequently lowering risk of hypoglycemia. In this randomized, double-blind, placebo-controlled study, the pharmacokinetics and pharmacodynamics of bedtime administration of the ORMD-0801 oral insulin were assessed in 30 adult T2DM patients inadequately controlled with diet and exercise and/or metformin. Following a 5-day placebo run-in period, a blinded continuous glucose monitor (CGM) was implanted and patients received a single placebo dose on day 1, followed by a 7-day, bedtime placebo or ORMD-0801 (460 IU or 690 IU) treatment in an inpatient setting. Plasma insulin and c-peptide levels were monitored for 5-hours postdosing. A manufacturing fault limited 690 IU dose efficacy; the data were excluded from the analysis. No hypoglycemic events were recorded throughout the entire study period. ORMD-0801-treated patients showed consistently higher mean plasma insulin levels throughout the 180 min Day 8 postdosing period, when compared to baseline. Moreover, in the first 60 min postdosing, plasma insulin exposure was 20.53 µIU*h/mL greater among ORMD-0801-treated patients when compared to the placebo arm and followed a concentration-time course similar to that of plasma c-peptide. Fasting CGM data demonstrated a mean -30.24 mg/dL difference between the last two days of active versus placebo treatment. Overall, ORMD-0801 led to a stable, consistent and short-acting rise in plasma insulin levels, which positively impacted FBG concentrations in the treated T2DM patients.

88-LB

New Insulin Glargine 300 U/mL: Glycemic Control and Hypoglycemia in Japanese People with T1DM (EDITION JP 1)

MUNEHIDE MATSUHISA, MASAYOSHI KOYAMA, XI CHENG, SHIN SHIMIZU, TAKAHISA HIROSE, ON BEHALF OF THE EDITION JP 1 STUDY GROUP, *Tokushima, Japan, Tokyo, Japan, Beijing, China*

EDITION JP 1 was a 6-month multicenter, open-label, phase 3 study to compare the efficacy and safety of new insulin glargine 300 U/mL (Gla-300) vs. glargine 100 U/mL (Gla-100) in Japanese people with T1DM using basal plus mealtime insulin. Participants (n=243; mean age 45.2 yr; T1DM duration 13.0 yr; HbA1c 8.1%) were randomized to Gla-300 or Gla-100 in combination with mealtime insulin. Basal insulin was titrated to target FPG 4.4-7.2 mmol/L (80 to 130 mg/dL). Primary endpoint was HbA1c change from start of treatment to month 6; similar HbA1c decreases were seen with both Gla-300 and Gla-100 (LS mean [SE] -0.30 [0.06] % and -0.43 [0.06] %; LS mean difference 0.13 [CI: -0.03 to 0.29] %). Fewer participants who received Gla-300 experienced confirmed or severe nocturnal hypoglycemic events vs. Gla-100 over the 6-month study period with the greatest difference observed during the first 8 weeks (Table). Rate of hypoglycemic events per participant-year at any time of the day was lower with Gla-300 vs. Gla-100. Severe hypoglycemia was infrequent in either group. Comparable numbers of adverse events were recorded in both groups. In conclusion, in Japanese people with T1DM using basal and mealtime insulin, Gla-300 provides comparable effective glycemic control with less nocturnal hypoglycemia, particularly in the first 8 weeks, and no increase in daytime hypoglycemia vs. Gla-100.

Table: Confirmed or severe hypoglycemia in the EDITION JP 1 study (safety population)

		Nocturnal hypoglycemia (00:00–05:59)		Hypoglycemia at any time of day (24 h)	
		Gla-300 (N=122)	Gla-100 (N=121)	Gla-300 (N=122)	Gla-100 (N=121)
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia					
Baseline to month 6	*% people ≥1 event*	68.9	81.0	96.7	97.5
	RR (95% CI)	0.85 (0.73 to 0.99)		0.99 (0.95 to 1.04)	
	Rate per participant-year	7.46	11.24	75.31	94.76
Baseline to week 8	*% people ≥1 event*	43.4	61.2	86.9	95.0
	RR (95% CI)	0.71 (0.56 to 0.91)		0.91 (0.84 to 0.99)	
	Rate per participant-year	7.48	12.79	82.77	119.10
Week 9 to month 6	*% people ≥1 event*	61.7*	73.7†	94.2*	93.2†
	RR (95% CI)	0.84 (0.70 to 1.00)		1.01 (0.95 to 1.08)	
	Rate per participant-year	7.45	10.53	71.86	83.58
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycemia					
Baseline to month 6	*% people ≥1 event*	36.9	53.7	78.7	90.9
	RR (95% CI)	0.69 (0.52 to 0.91)		0.87 (0.78 to 0.96)	
	Rate per participant-year	2.00	4.07	18.91	23.28
Baseline to week 8	*% people ≥1 event*	22.1	37.2	59.0	80.2
	RR (95% CI)	0.60 (0.40 to 0.89)		0.74 (0.62 to 0.87)	
	Rate per participant-year	2.12	5.72	21.95	30.33
Week 9 to month 6	*% people ≥1 event*	27.5*	44.9†	71.7*	85.6†
	RR (95% CI)	0.61 (0.43 to 0.87)		0.84 (0.73 to 0.96)	
	Rate per participant-year	1.94	3.31	17.50	20.02

RR, relative risk; CI, confidence interval; *n=120; †n=118

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89-LB

A Novel Very Long-acting Insulin Analog (HM12470) with Potential for Once-Weekly Dosing Has a Favorable PK, PD, and Mitogenic Profile

SANG YOUN HWANG, IN YOUNG CHOI, JIN YOUNG KIM, SUNG-YOUB JUNG, DAE JIN KIM, YOUNG-MI LEE, YOUNG HOON KIM, MICHAEL TRAUTMANN, MARCUS HOMPESCH, JEEWOONG SON, SE CHANG KWON, *Gyeonggi, Republic of Korea, Hwaseong-si, Republic of Korea, Hamburg, Germany, Chula Vista, CA, Seoul, Republic of Korea*

Long-acting insulins have the potential to improve treatment compliance and opportunities to start an insulin therapy earlier in the disease. To develop insulins with a longer half-life various formulations of insulin, and various insulin analogues are under investigation. The long-acting basal insulin, HM12470 is developed for once-weekly injection by conjugating an insulin analog with the constant region of a human immunoglobulin fragment via non-peptidyl linker. The objective of this study was to investigate the *in vitro* properties, pharmacokinetics and pharmacodynamics of HM12470 in normal and diabetic animal models to evaluate the once-weekly dosing and the metabolic/mitogenic effects. In a pharmacokinetic study, subcutaneously injected HM12470 exhibited a half life of ~ 43 hr in normal rats, while insulin degludec showed 2.9 hr of half-life. The extended half-life was also confirmed in

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other species such as mice, dogs, and monkeys. The improved pharmacokinetic profile had contributed to prolonged glucose lowering efficacy in *db/db* mice. Moreover the prolonged glucose lowering efficacy was even observed at lower dose levels when compared with a native human insulin conjugate (HM12460A). Based on the results from three different species, human pharmacokinetics was projected by the Wajima C_{ss}-MRT method. The half-life in humans is expected to be 132 hr and the peak-to-though ratio was calculated to be 1.6 on once weekly dosing. *In vitro* mitogenic potency of HM12470 was assessed by using cell proliferation in MCF-7 and SaOs-2 cells. Compared to its lipogenic efficacy assessed in adipocyte-induced 3T3-L1 cells, the mitogenic to lipogenic potency ratio was significantly lower than that of human insulin. These observations suggest that HM12470 has a once-weekly dosing potential with a sufficiently extended half-life and a low mitogenic risk.

90-LB

New Insulin Glargine 300 U/mL: Glycemic Control and Hypoglycemia in a Meta-analysis of Phase 3a EDITION Clinical Trials in People with T2DM

ROBERT RITZEL, RONAN ROUSSEL, GEREMIA B. BOLLI, LAETITIA VINET, HANNELE YKI-JÄRVINEN, *München, Germany, Paris, France, Perugia, Italy, Nanterre, France, Helsinki, Finland*

The EDITION 1, 2 and 3 studies compared the efficacy and safety of new insulin glargine 300 U/mL (Gla-300) with insulin glargine 100 U/mL (Gla-100) in people with T2DM on basal and mealtime insulin, basal insulin and OADs, and no prior insulin, respectively. A meta-analysis of these three studies enabled glycemic control and hypoglycemia to be examined over 6 months in a large, heterogeneous T2DM population (Gla-300, N=1247; Gla-100, N=1249). Mean change in HbA_{1c} was comparable for Gla-300 and Gla-100 (each –1.02 [SE 0.03]%). Gla-300 was associated with a reduced risk of experiencing a hypoglycemic event vs. Gla-100 (nocturnal and at any time of day; Table). Rates of nocturnal hypoglycemia were consistently lower with Gla-300 than Gla-100. Severe hypoglycemia was rare in both treatment groups (2.3% with Gla-300 vs. 2.6% with Gla-100). Weight gain with Gla-300 and Gla-100 was slight (mean change: 0.49 [SE 0.10] kg, 0.75 [0.10] kg, respectively), with a trend for less weight gain with Gla-300 (–0.26 [95% CI –0.52 to 0.01] kg, p=0.058). In conclusion, Gla-300 provides comparable glycemic control to Gla-100 in T2DM, with consistently less hypoglycemia at any time of the day and less nocturnal hypoglycemia.

Table – Glycemic control and hypoglycemic events over 6 months in a meta-analysis of the EDITION 1, 2 and 3 studies

		HbA_{1c} (%)*	
mITT population		**Gla-300 (N=1239)**	**Gla-100 (N=1235)**
Baseline	*Mean*	8.30	8.31
Change from baseline to Month 6	*LS mean (SE)*	–1.02 (0.03)	–1.02 (0.03)
		Weight (kg)**	
Safety population		**Gla-300 (N=1242)**	**Gla-100 (N=1246)**
Baseline	*Mean*	99.89	99.94
Change from baseline to Month 6	*LS mean (SE)*	0.49 (0.10)	0.75 (0.10)

		Nocturnal hypoglycemia (00:00–05:59)		Hypoglycemia at any time of day (24 h)	
Safety population		**Gla-300 (N=1242)**	**Gla-100 (N=1246)**	**Gla-300 (N=1242)**	**Gla-100 (N=1246)**
Any hypoglycemia					
Baseline to month 6	*% people ≥1 event*	31.7	41.3	67.8	73.8
	RR[a] (95% CI)	0.77 (0.69 to 0.85)		0.92 (0.87 to 0.96)	
	Rate per participant-year	2.25	3.30	15.87	18.62
	RR[b] (95% CI)	0.68 (0.57 to 0.82)		0.85 (0.76 to 0.96)	
Confirmed (≤3.0 mmol/L [≤54 mg/dL]) or severe hypoglycemia					
Baseline to month 6	*% people ≥1 event*	9.7	13.2	26.9	33.3
	RR[a] (95% CI)	0.73 (0.59 to 0.91)		0.81 (0.72 to 0.90)	
	Rate per participant-year	0.37	0.56	1.93	2.08
	RR[b] (95% CI)	0.67 (0.50 to 0.91)		0.93 (0.76 to 1.13)	
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia					
Baseline to month 6	*% people ≥1 event*	30.0	39.8	65.5	72.0
	RR[a] (95% CI)	0.75 (0.68 to 0.83)		0.91 (0.87 to 0.96)	
	Rate per participant-year	2.10	3.06	15.22	17.73
	RR[b] (95% CI)	0.69 (0.57 to 0.84)		0.86 (0.77 to 0.97)	
Severe hypoglycemia					
Baseline to month 6	*% people ≥1 event*	0.6	1.0	2.3	2.6
	RR[a] (95% CI)	0.71 (0.32 to 1.59)		0.85 (0.52 to 1.39)	
	Rate per participant-year)	0.02	0.03	0.11	0.11
	RR[b] (95% CI)	0.70 (0.35 to 1.42)		0.98 (0.51 to 1.86)	

CI, confidence interval; mITT, modified intention-to-treat; RR[a], relative risk; RR[b], rate ratio. *MMRM, mixed model for repeated measurements; **LOCF, last observation carried forward.

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91-LB

WITHDRAWN

92-LB

Transition Therapy for Inpatient to Outpatient Glycemic Control: Results of the Veterans Inpatient Insulin Study and Transition Algorithm (the VIISTA Study)

DENNIS G. KAROUNOS, VIISTA STUDY GROUP, *Lexington, KY*

Little data exists regarding optimal transition from inpatient (inpt) to outpatient (outpt) insulin therapy after hospitalization for acute noncritical illness. The purpose of this phase IV, randomized, open-label study of 120 patients with T2DM was to determine the efficacy of both basal-bolus insulin (detemir & aspart) during the inpt hospitalization for treatment of hyperglycemia as well as the transition to pre-mixed insulin after discharge, randomized to receive either NPH/regular 70/30 insulin Group A (Grp A) or NPH/aspart 70/30 insulin analog (Grp B) twice daily. There were 6 screen failures or withdrawals during inpt phase, leaving an intention-to-treat cohort of 112 males and 2 females, age 63.8 ± 8.8 y, duration of DM 13.4 ± 9.3 y with 50 randomized to group A and 64 to group B. The 20 week outpt phase consisted of bi-weekly phone calls and monthly clinic visits using blood glucose (BG) profiles to adjust therapy. Of 104 completing the study, mean total daily insulin dose was 0.72 ± 0.49 U/kg, which was a 15% increase since hospital discharge. In Grp A there was a 6.7% improvement in glycemic control (HbA1c 8.91% ± 2.0 at baseline to 8.32% ± 1.5 at 16 weeks, p=0.0514 & BG improving from 198 ± 2.9 to 185 ± 0.8 mg/dl, p<0.0001). There was a greater effect in Grp B with a 12.2% improvement in glycemic control (HbA1c 9.51% ± 2.3 at baseline to 8.35% ± 1.95 at 16 weeks, p=0.0004 & BG improving from 208 ± 3 mg/dl to 184 ± 0.7 mg/dl, p<0.0001). With 70/30 aspart analog (Grp B) there was better glycemic control compared to NPH/regular 70/30 (Grp A) with no difference in occurrence of hypoglycemia, body wt, serious adverse events or patient-reported distress. Thus, we provide new data on transition therapy from inpatient to outpatient care. This strategy of transitioning from basal bolus therapy to premixed twice daily insulin is particularly useful when treating older individuals with type 2 diabetes after hospitalization for an acute non-critical illness.

93-LB

Less Nocturnal Hypoglycemia and Weight Gain with New Insulin Glargine 300 U/mL Compared with 100 U/mL: 1-Year Results in People with T2DM Using Basal Insulin with OADs (EDITION 2)

HANNELE YKI-JÄRVINEN, RICHARD M. BERGENSTAL, GEREMIA B. BOLLI, MONIKA ZIEMEN, MAREK WARDECKI, ISABEL MUEHLEN-BARTMER, MAGALI MAROCCIA, MATTHEW C. RIDDLE, *Helsinki, Finland, Minneapolis, MN, Perugia, Italy, Frankfurt, Germany, Warsaw, Poland, Levallois-Perret, France, Portland, OR*

EDITION 2 investigated glycemic control and hypoglycemia in 811 adults with T2DM and inadequate control of HbA_{1c} using basal insulin and OADs randomized to receive either insulin glargine 300 U/mL (Gla-300) or glargine 100 U/mL (Gla-100) for 6 months. In this 6-month open-label extension, participants continued to receive Gla-300 or Gla-100 once daily plus OADs; 315 (78%) in Gla-300 and 314 (77%) in Gla-100 completed 12 months of treatment. Improved control of HbA_{1c} was maintained at 12 months with each regimen. Over 12 months, per participant-year event rates of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe nocturnal hypoglycemia were 37% lower with Gla-300 than Gla-100 (1.74 vs. 2.77, RR 0.63; 95% CI 0.42 to 0.96). Fewer participants experienced ≥1 confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe nocturnal hypoglycemia with Gla-300 than Gla-100 (RR 0.84; 95% CI 0.71 to 0.99). Severe hypoglycemia was infrequent. Body weight increase was observed in both groups, and was significantly less with Gla-300 than Gla-100 (mean: 0.42 [0.04 to 0.80] vs. 1.14 [0.76 to 1.52] kg, p=0.0091). No between-treatment differences in adverse events were seen. Over 1 year of treatment, people with T2DM using Gla-300 and OADs had comparable glycemic control, experienced fewer nocturnal hypoglycemic events and less weight gain compared with those using Gla-100.

Table – Glycemic control and hypoglycemia over 12 months in the EDITION 2 study

		HbA1c (%)	
mITT population		Gla-300 (N=403)	Gla-100 (N=405)
Baseline	*Mean (SD)*	8.26 (0.86)	8.21 (0.77)
Change from baseline to Month 12 (OC)	*Mean (95% CI)*	−0.55 (−0.67 to −0.44)	−0.50 (−0.61 to −0.39)
	LS mean difference (95% CI)	0.06 (−0.22 to 0.10)	

		Nocturnal hypoglycemia (00:00–05:59)		Hypoglycemia at any time of day (24 h)	
		Gla-300 (N=403)	Gla-100 (N=406)	Gla-300 (N=403)	Gla-100 (N=406)
Any hypoglycemia					
Baseline to month 12	*% people ≥1 event*	39.7	46.1	79.9	83.0
	RR[a] (95% CI)	0.86 (0.73 to 1.01)		0.96 (0.90 to 1.03)	
	Event rate per participant-year	1.80	2.94	11.87	13.70
	RR[b] (95% CI)	0.61 (0.41 to 0.92)		0.87 (0.70 to 1.07)	
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia					
Baseline to month 12	*% people ≥1 event*	37.5	44.6	78.4	82.0
	RR[a] (95% CI)	0.84 (0.71 to 0.99)		0.96 (0.89 to 1.02)	
	Event rate per participant-year	1.74	2.77	11.60	13.18
	RR[b] (95% CI)	0.63 (0.42 to 0.96)		0.88 (0.71 to 1.09)	

CI, confidence interval; mITT, modified intention-to-treat; OC, observed case; RR[a], relative risk; RR[b], rate ratio

Supported By: Sanofi (NCT01499095)

94-LB

Glycemic Control and Hypoglycemia in Japanese People with T2DM Receiving New Insulin Glargine 300 U/mL in Combination with OADs (EDITION JP 2)

YASUO TERAUCHI, MASAYOSHI KOYAMA, XI CHENG, SHIN SHIMIZU, TAKAHISA HIROSE, ON BEHALF OF THE EDITION JP 2 STUDY GROUP, *Yokohama, Japan, Tokyo, Japan, Beijing, China*

In this multicenter, randomized, open-label, phase 3 study (EDITION JP 2), people with T2DM on basal insulin plus OAD(s) (n=241; mean age 60.8 yr; mean BMI 25.3 kg/m2; mean duration of T2DM 14.0 yr; mean HbA1c 8.0%) were randomized to receive new insulin glargine 300 U/mL (Gla-300) or glargine 100 U/mL (Gla-100) plus OAD(s). Insulin was titrated to target FPG 4.4-5.6 mmol/L (80-100 mg/dL). Primary endpoint was HbA1c change from baseline to month 6. HbA1c decreased similarly in both groups (LS mean [SE] -0.45 [0.06]% for Gla-300 and -0.55 [0.06] % for Gla-100; LS mean difference 0.10 [CI: -0.08 to 0.27]%). Fewer participants experienced any hypoglycemic events during 6 months with Gla-300 vs. Gla-100. The number (%) of participants with ≥1 confirmed (≤3.9 mmol/L) or severe hypoglycemic event (24 h and nocturnal) was consistently lower with Gla-300 vs. Gla-100 and rate per participant-year was lower with Gla-300 vs. Gla-100 (Table). Severe hypoglycemia was infrequent in either group. LS mean (SE) weight change was -0.62 (0.19) kg for Gla-300 and 0.37 (0.19) kg for Gla-100. Similar safety profiles were observed in both groups. In conclusion, in Japanese people with T2DM using basal insulin plus OAD(s), Gla-300 provides comparable effective glycemic control with fewer hypoglycemic events, particularly during the first 8 weeks, vs. Gla-100.

Table: Hypoglycemia in the EDITION JP 2 study (safety population)

		Nocturnal hypoglycemia (00:00–05:59)		Hypoglycemia at any time of day (24 h)	
		Gla-300 (N=120)	Gla-100 (N=120)	Gla-300 (N=120)	Gla-100 (N=120)
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia					
Baseline to month 6	*% people ≥1 event*	28.3	45.8	65.0	76.7
	RR (95% CI)	0.62 (0.44 to 0.88)		0.86 (0.73 to 1.01)	
	Rate per participant-year	2.18	4.98	10.48	16.52
Baseline to week 8	*% people ≥1 event*	13.3	16.7	37.5	55.0
	RR (95% CI)	0.83 (0.45 to 1.52)		0.69 (0.52 to 0.91)	
	Rate per participant-year	2.25	2.67	9.00	15.66
Week 9 to month 6	*% people ≥1 event*	25.4*	43.7†	60.2*	72.3†
	RR (95% CI)	0.58 (0.40 to 0.85)		0.84 (0.70 to 1.01)	
	Rate per participant-year	2.15	6.03	11.17	16.91
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycemia					
Baseline to month 6	*% people ≥1 event*	10.0	10.8	16.7	19.2
	RR (95% CI)	0.94 (0.44 to 2.00)		0.86 (0.50 to 1.48)	
	Rate per participant-year	0.24	0.35	0.61	0.64
Baseline to week 8	*% people ≥1 event*	3.3	5.8	6.7	10.0
	RR (95% CI)	0.61 (0.19 to 1.94)		0.66 (0.28 to 1.55)	
	Rate per participant-year	0.21	0.53	0.48	0.86
Week 9 to month 6	*% people ≥1 event*	6.8*	6.7†	11.9*	12.6†
	RR (95% CI)	1.01 (0.39 to 2.62)		0.93 (0.47 to 1.83)	
	Rate per participant-year	0.25	0.27	0.67	0.54

RR, relative risk; CI, confidence interval; *n=118; †n=119

Supported By: Sanofi (NCT01689142)

95-LB

Inspire Diabetes: A Pulse of Basal Bolus Analog Insulin as the First Treatment of T2DM

JAY H. SHUBROOK, AIRANI SATHANANTHAN, MASATO NAKAZAWA, NISHITA PATEL, RUCHA J. MEHTA, FRANK L. SCHWARTZ, *Athens, OH, Pomona, CA*

Most people with type 2 diabetes (T2DM) require increasing medication over time to maintain glucose control due to progressive beta cell failure. INSPIRE Diabetes is a multicenter randomized open label clinical trial that evaluated the treatment of adults with newly diagnosed T2DM. Participants (10 men, 13 women. Mean age of 44.5 yrs) were randomized to: (1) a pulse of basal bolus analog insulin (glargine, glulisine) that was used for a total of 12 weeks with weight based initiation and twice weekly titration with forced down titration (EIT) versus; (2) routine care (RC) as recommended by the 2009 ADA treatment recommendations. Primary end points were need for and time to rescue therapy. There was no difference in time to rescue (16.4 weeks RC vs. 24.0 weeks EIT) or need for rescue therapy (2/10 RC vs. 6/13 EIT). The A1c were improved in both groups significantly overtime. The A1c at baseline was 10.1% +/- 1.2% RC vs. 9.9% +/- 1.2% EIT. This improved to 7.01% +/- 0.8 RC vs. 6.7% +/- 0.8 EIT. At 12 weeks the routine care group continued oral anti-glycemic therapy, but the insulin group stopped all diabetes treatments until rescue was needed. At 15 months A1c for RC was 6.7% +/-0.8 and EIT 6.8% +/-0.4%. The EIT group lost weight (2.4 kg) vs. weight gain of 2.1 kg for RC (NS). When excluding participants with a BMI >50 the EIT arm lost significantly more weight than RC ($p<0.05$). The EIT group also had significantly higher fasting and stimulated c-peptide levels ($p<0.001$). There were only 10 hypoglycemic episodes in the study (7 EIT, 3 RC) and zero severe hypoglycemic episodes. Twelve weeks of EIT was as effective as RC for people with newly diagnosed T2DM and is not associated with the weight gain we typically see later in the disease. Further, there is some evidence that EIT improves beta cell function over 15 months. This study is limited by its size and the fact that the RC group did substantially better than what is normally seen in real clinical practice. EIT produced not only rapid control of glucose but may have a legacy effect on beta cell function.

Supported By: Sanofi

96-LB

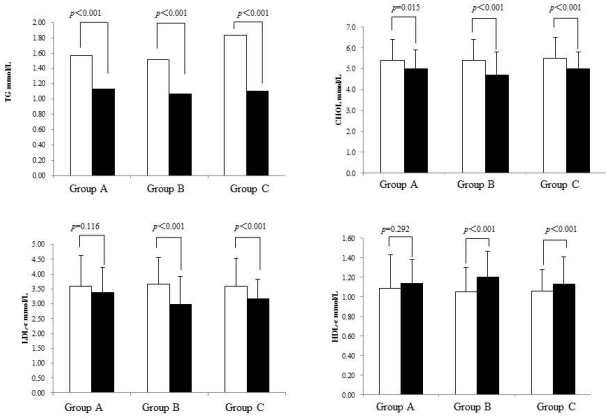
The Effects on Lipid Profiles in Patients with Newly Diagnosed Type 2 Diabetes Treated with Short-term Continuous Subcutaneous Insulin Infusion Combined with Different Antihyperglycemic Agents

HAI LI, WEIJIAN KE, JUAN LIU, LIEHUA LIU, YANBING LI, *Guangzhou, China*

According to our previous study, shot-term intensive insulin therapies by continuous subcutaneous insulin infusion (CSII) can eliminate lipotoxicity in newly diagnosed type 2 diabetic patients. This study was to investigate whether CSII combined with different antihyperglycemic agents can improve lipid profiles better than CSII alone.

139 newly diagnosed type 2 diabetic patients were enrolled. All patients were randomly assigned to therapy with CSII alone (Group A, n=47), or CSII combined with metformin 1.5/d and pioglitazone 30mg/d (Group B, n=46), or CSII combined with sitagliptin 100mg/d (Group C, n=46). The treatment was stopped after normoglycaemia maintained for 2 weeks.

The clinical characteristics, glucose levels and lipid profiles at baseline were similar between the three groups. After 2 weeks treatment, the total cholesterol (TC), and triglyceride (TG) levels were decreased significantly in three groups. There were significant reduction of low-density lipoprotein cholesterol (LDL-C) and significant increase of high-density lipoprotein cholesterol (HDL-C) compared to baseline in group B and C, however, this improvement was not observed in the group A. In conclusion, CSII combined with different antihyperglycemic agents can improve lipid profiles better than CSII alone.



For author disclosure information, see page LB91.

97-LB

Improved Oral Insulin Bioavailability when Delivered in Soft Capsules

MIRIAM KIDRON, CAMIL FUCHS, EHUD ARBIT, SHOSHI SHPITZEN, DANIEL SCHURR, *Jerusalem, Israel, Tel Aviv, Israel*

One of the established clinical advantages of soft gel capsules is the potential to enhance active ingredient bioabsorption and bioavailability, which often translates to lower required drug doses. In this study, the bioavailability of insulin orally administered to five Type 1 diabetes mellitus (T1DM) patients by way of a hard versus soft gelatin capsule was compared. Patients received an 8 mg or 16 mg (2 x 8 mg capsules) dose of insulin packaged in either soft or hard gelatin, enteric-coated capsules, 15 min before a standard meal. Plasma insulin and glucose concentrations were monitored over the ensuing 5 hour period and the ratios of responses in the baseline (0-20 min postdose) vs. treatment (20-300 min postdose) periods were computed. The soft gelatin capsules generated consistently higher concentration-time insulin curves when compared to the hard gelatin capsules, and demonstrated a dose-dependent effect on blood glucose levels. More specifically, the 8 mg and 16 mg doses delivered in a soft capsule were associated with 31% and 38% respectively higher mean plasma insulin concentration and area under the curve (AUC) baseline vs. response ratios, when compared to identical doses delivered in hard capsules. Moreover, upon dose doubling, mean plasma insulin concentration and AUC ratios increased by 13.8% and 14.5%, respectively, when delivered in soft capsules, but only by 7.4% when delivered in hard gelatin capsules. In parallel, the mean plasma glucose concentration ratio following treatment with the 8 mg insulin soft gel capsule was 19.1% higher than that measured after a similar dose delivered in a hard capsule, while a 31% difference was observed following dosing with 16 mg insulin in a soft vs. hard gelatin capsule. The improved bioavailability and bioefficacy observed upon insulin delivery in soft gelatin capsules will be valuable in further clinical development of oral insulin.

98-LB

Evaluation of Safety of Insulin Degludec on Undergoing Total Colonoscopy Using Continuous Glucose Monitoring

SOICHI TAKEISHI, AKIHIRO MORI, NOBUTOSHI FUSHIMI, HIROKI HACHIYA, TAKAYUKI YUMURA, SHUN ITO, TAKASHI SHIBUYA, NORITSUGU OHASHI, HIROMI KAWAI, *Ichinomiya, Japan*

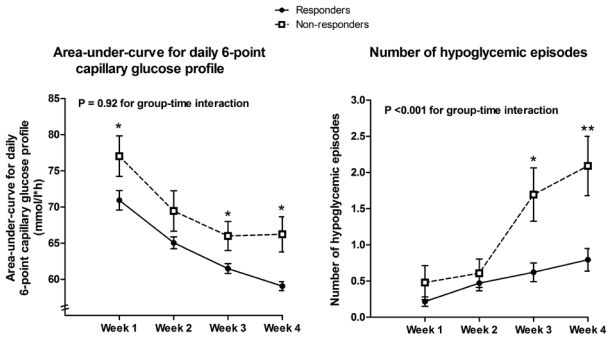
Screening of colon cancer with total-colonoscopy (TCS) in type 2 diabetic patients is significant clinical approach. Anti-diabetic agent should be reduced or discontinued because preparation for TCS forces the patient to be long fasting. However, there is little information regarding how to adjust insulin degludec (D) having an ultra-long action profile. Therefore, we investigated glucose variability of twelve patients with type 2 diabetes mellitus treated with D scheduled to undergo TCS, using continuous glucose monitoring (CGM). In admission, CGM was attached from the previous day to the following day of TCS. Patients had been fasting for 24 hours after the supper (6 p.m.) on the previous day. At breakfast and lunch on the day of TCS, patients discontinued all anti-diabetic agents and took polyethylene glycol electrolyte solution. Primary endpoints were to evaluate the frequency of hypoglycemia (below 70 mg/dl), Hypoglycemic Index, mean glucose level (MEAN) and standard deviation (SD) in daytime fasting duration (between 8 a.m. and 6 p.m. on the day of TCS) (F duration). Secondary endpoints were to compare each parameters between F duration and daytime non-fasting duration (between 8 a.m. and 6 p.m. on the previous day) (NF duration) and to estimate the relation between ΔMEAN (F duration - NF duration) and MEAN of NF duration. As a result, in F duration, there was no hypoglycemia and Hypoglycemic Index, MEAN and SD were 0, 141.3±31.5 mg/dl and 15.6 ±6.5 mg/dl. MEAN and SD in F duration were significantly lower than them in NF duration ($P < 0.006$, $P < 0.003$). ΔMEAN and MEAN of NF duration were significantly correlated ($r = -0.80$, $P = 0.008$). Therefore, we consider that patients treated with D can undergo TCS despite unavoidable F duration with discontinuation of D once on the day of TCS. In even patients with normal glucose control, adjustment of D dose on the previous day seems to be unnecessary, because degree of decreased glucose level with fasting was lower in patients with nearer normal glucose level.

99-LB

Clinical Predictors of the Improvement in Beta-Cell Function with Short-term Intensive Insulin Therapy (IIT) in T2DM

COREY STEIN, CAROLINE K. KRAMER, BERNARD ZINMAN, HAYSOOK CHOI, CHRISTINE OPSTEEN, RAVI RETNAKARAN, *Toronto, ON, Canada*

In patients with T2DM, a short course of IIT can improve beta-cell function and even induce transient remission of diabetes. However, not all patients respond to this therapy. While the achievement of fasting glucose <7.0 mmol/L one day after stopping IIT can identify patients in whom beta-cell function has improved, we sought to identify clinical predictors for early detection of such responders before or during IIT. We pooled data from 2 studies in which 97 patients with T2DM of mean 4.0±4.4 yrs duration and A1c 6.8±0.8% underwent 4-8 weeks of IIT (basal detemir and pre-meal aspart). There were 74 responders and 23 non-responders. At baseline, responders had shorter duration of T2DM (3.0 vs. 6.0 years, p=0.002) and lower fasting glucose (6.5 vs. 7.9 mmol/L, p<0.001) than non-responders. On logistic regression analyses, duration of diabetes (OR=0.72, 95% CI 0.56-0.92, p=0.009) and baseline fasting glucose (OR=0.40, 0.24-0.68, p=0.001) emerged as independent predictors of the likelihood of responding. Despite having lower glucose levels, responders had less hypoglycemia than non-responders (median 0.3 vs. 1.6 episodes/week, p<0.0001), with hypoglycemia rates diverging from the 3rd week onwards (Fig). In summary, shorter duration of diabetes, lower baseline fasting glucose and less hypoglycemia by the 3rd week on therapy can identify patients most likely to benefit from short-term IIT.



Supported By: Novo Nordisk A/S; Merck & Co., Inc.

100-LB

The Relationship between Insulin Dosing and Patient Outcomes among Patients with Diabetes: Evidence from a Commercially Insured Cohort

ELIZABETH EBY, BRADLEY H. CURTIS, CYNTHIA S. BRUSKO, KATE VAN BRUNT, MAUREEN J. LAGE, *Indianapolis, IN, Windlesham, United Kingdom, Bonita Springs, FL*

The objective of this study was to examine costs, resource utilization, adherence, and hypoglycemic events among increasing doses of U-100 insulin regimens.

Truven's Health Analytics Commercial Claims and Encounters database from 1/1/08 through 12/31/11 were utilized. General linear models with a gamma distribution and log link were used to examine costs, logistic and negative binomial regressions were used to examine resource utilization and hypoglycemic events. Analyses controlled for patient characteristics, pre-period comorbidities general health, use of antidiabetic medications, and index dose of insulin.

Results indicate that, in general, costs and resource utilization are highest among patients treated with the highest dose of insulin (>300 units per day). For example, all-cause and diabetes-related hospitalizations, ER visits, and outpatient visits were highest in the highest dose cohort. Costs generally followed the same pattern. Furthermore, the odds of achieving an adherence threshold of at least 80%, based upon initial dose range, was significantly lower for all index dose categories, compared to index dose of 10-100 units per day. There was generally no significant difference in rates of hypoglycemic events based upon index dose.

These results suggest significant differences in patient outcomes based upon dosing of insulin.

Resource Utilization.

	Dose 10-100 (N=70,625)	Dose 101-150 (N=24,500)	Dose 151-200 (N=11,259)	Dose 201-300 (N=7,772)	Dose >300 (N=2,933)	P Value
Resource Utilization	Mean [SD]	Mean [SD]	Mean [SD]	Mean [SD]	Mean [SD]	t-test for all pairwise comparisons
Hospital Length of Stay (LOS)	2.57 [6.31]	1.70 [3.08]	1.95 [3.88]	2.40 [4.48]	3.29 [7.98]	<0.05
Number of Hospitalizations	0.36 [0.48]	0.25 [0.28]	0.27 [0.32]	0.32 [0.36]	0.43 [0.54]	<0.05
Number of ER Visits	0.74 [0.65]	0.61 [0.49]	0.64 [0.52]	0.69 [0.59]	0.83 [0.70]	<0.05
Number of Office Visits	12.64 [4.82]	13.11 [5.17]	14.02 [5.60]	15.74 [6.40]	17.30 [6.57]	<0.05
Diabetes-Related Hospital LOS	1.62 [3.42]	1.08 [1.77]	1.21 [2.09]	1.46 [2.55]	2.11 [4.16]	<0.05
Number of Diabetes-Related Hospitalizations	0.25 [0.30]	0.18 [0.19]	0.18 [0.20]	0.21 [0.23]	0.28 [0.31]	<0.05

101-LB

The Relationship between Insulin Dosing and Patient Outcomes among Patients with Diabetes: Evidence from a Medicare Cohort

ELIZABETH EBY, BRADLEY H. CURTIS, CYNTHIA S. BRUSKO, KATE VAN BRUNT, MAUREEN J. LAGE, *Indianapolis, IN, Windlesham, United Kingdom, Delray Beach, FL*

Examine costs, resource utilization, adherence, and hypoglycemic events among various doses of U-100 insulin regimens.

Truven's Health Analytics Medicare database from 1/1/08 through 12/31/11 were utilized. General linear models with a gamma distribution and log link were used to examine costs, while logistic and negative binomial regressions were used to examine resource utilization and hypoglycemic events. Analyses controlled for patient characteristics, pre-period comorbidities, general health, and use of antidiabetic medications, as well as index dose of insulin.

All-cause inpatient, emergcency room (ER) and outpatients costs, as well as and diabetes-related inpatient costs were highest among individuals who were treated with an index dose of 10-100 followed by >300 units per day, while drug costs and total costs generally increased as index dosage increased. Resource utilization generally followed the same pattern as costs. Compared to patients who initiated with an index dose of 10-100 units per day, all other patients were significantly less likely to achieve an adherence threshold of 80% based upon index dose range, and while those with an index dose of 101-150 units per day were significantly more likely experience a hypoglycemic event .

These results suggest higher patient burden among those with the lowest and highest insulin doses.

All-Cause Direct Medical Costs.

All-Cause Costs	Dose 10-100 (N=32,325)	Dose 101-150 (N=9,552)	Dose 151-200 (N=4,125)	Dose 201-300 (N=2,716)	Dose >300 (N=952)	P Value* Pairwise Comparisons
	Mean [SD]	Mean [SD]	Mean [SD]	Mean [SD]	Mean [SD]	
Inpatient	8906.00 [6346.05]	7315.25 [4639.33]	7072.09 [4498.18]	7566.68 [4886.75]	8264.78 [4941.49]	<0.05
Emergency Room	824.45 [519.58]	751.31(G) [455.48]	797.97 [492.65]	723.48(J) [444.33]	741.18(GJ) [448.16]	<0.05
Outpatient	13220.70(CD) [9267.83]	11733.52 [7262.25]	12009.37 [7471.67]	13104.53(CJ) [8073.92]	13632.82(DJ) [7687.40]	<0.05
Drug	5881.23 [1339.08]	7577.91 [1646.63]	9025.43 [1958.76]	10688.58 [2260.48]	14799.49 [3065.14]	<0.05
Total	28688.45(B) [15277.71]	27425.45 [12672.45]	29120.13(B) [13615.24]	32468.40 [14986.41]	38526.56 [16421.75]	<0.05

*All pairwise comparisons statistically significant unless denoted by letter in parentheses.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULIN DELIVERY SYSTEMS

102-LB

Efficacy and Safety of Insulin Pump Therapy in Type 2 Diabetes: The Opt2mise Study

YVES REZNIK, OHAD COHEN, IGNACIO CONGET, RONNIE ARONSON, SARAH RUNZIS, JAVIER CASTANEDA, SIMONA DE PORTU, SCOTT W. LEE, OPT2MISE STUDY GROUP, *Caen, France, Tel Hashomer, Israel, Barcelona, Spain, Toronto, ON, Canada, Tolochenaz, Switzerland, Northridge, CA*

Prior randomized controlled studies comparing continuous subcutaneous insulin infusion (CSII) vs. multiple daily injections (MDI) in type 2 diabetes (T2D) patients have been limited and results were conflicting. This study is the first large multicenter, randomized, controlled trial aiming to compare the efficacy and safety of CSII vs. MDI in insulin-using patients with T2D. Subjects with poor glycemic control (n=495) on multiple doses of insulin (MDI, basal-bolus using insulin analogs) were enrolled into a run-in period for insulin dose optimization (≥0.7 and ≤1.8 U/kg/d). Subjects showing persistent hyperglycemia (HbA1c ≥8% and ≤12%) were then randomly assigned to switch to CSII or to continue with MDI regimens for 6 months. Both groups underwent double-blinded continuous glucose monitoring (CGM) assessments at baseline and 6 months. The primary endpoint was the between-group difference in mean change in HbA1c from baseline to 6 months. A total of 331 subjects were randomized (45.6% women, mean±SD age 56.0±9.6 yr, BMI 33.4±7.3 kg/m^2, diabetes duration 15.1±8.0 yr, HbA1c 9.0±0.8%). Subjects assigned to CSII achieved significantly greater HbA1c reduction than MDI arm (-1.1±1.2% vs. -0.4±1.1%, p<0.001), with no difference in time spent <70 mg/dL as determined by CGM. The percentage of subjects achieving HbA1c <8.0% was 57% in CSII arm vs. 27% in MDI arm (OR=1.9, 95% CI 1.47 to 2.46, P<0.001) At the end of the study, total daily insulin dose was 20.4% lower in the CSII group than in the MDI group, and there was no significant between-groups difference in body weight change. No ketoacidosis occurred in either group, and one episode of severe hypoglycemia occurred in the MDI group. CSII treatment in suboptimally controlled type 2 diabetes provides significant improvement in glycemic control compared to intensive MDI therapy with lower insulin dose requirement and without impacting safety or hypoglycemia.

Supported By: Medtronic, Inc.

103-LB

Automated Predictive Suspend and Resume of Insulin Delivery in a Randomized Multicenter Ambulatory Clinical Trial

RAVI GONDHALEKAR, EYAL DASSAU, SUE A. BROWN, KRISTIN CASTORINO, ANANDA BASU, YOGISH C. KUDVA, STEPHEN D. PATEK, HOWARD C. ZISSER, FRANCIS J. DOYLE III, *Santa Barbara, CA, Charlottesville, VA, Rochester, MN*

The prevention of hypoglycemia, especially nocturnal hypoglycemia, is one of the early achievements of the Artificial Pancreas (AP) and Low Glucose Suspend systems. However, when, and for how long, to suspend basal delivery, and when to resume it, are very much open questions; typical systems rely on heuristics, ad-hoc supervisory systems, and/or users. An AP that performs fully automated insulin delivery and suspension, via Continuous Glucose Monitor (CGM) feedback, based on Model Predictive Control (MPC) employing an asymmetric insulin penalty function to facilitate independent tuning of the AP's responses to hypo- and hyperglycemia, was evaluated in an ambulatory multi-center randomized crossover study. The ability of the AP to suspend/resume insulin delivery when facing hypoglycemia was evaluated.

Twenty outpatient closed-loop trials ~25 h were completed by 12 adults with type 1 diabetes (8F, age 25-62 (av. 50), 4-45 (av. 28) years T1D, 60-119 (av. 78) kg) at 3 sites. Participants had 3 announced meals (30-90g), unannounced exercise (30-60 min), and an overnight period.

The system: On average attenuated insulin delivery by 1.5 U (2.85%) from basal over 24 h, and 0.49 U (5.41% of basal) at night; performed 112, 30 and 6 pump suspensions of duration >15 min, >60 min, and >120 min, respectively; performed pump suspensions (>15 min) of average duration 49 [15-175] min; fully suspended insulin delivery (>15min) for impending hypoglycemia on average at 119 [51-233] mg/dL; automatically resumed insulin delivery on average at 99 [64-191] mg/dL. Hypoglycemia predictions 45 min ahead were performed; pump (suspension and) resumption may occur at very high CGM values when CGM decrease is rapid but slowing.

The proposed AP performs predictive pump suspensions, and subsequent, timely predictive pump resumptions to ameliorate glucose rebounds, based on MPC according to clinical needs as per CGM feedback, without relying on heuristics, auxiliary safeguards, or user interaction.

Supported By: NIH (DP3DK094331)

104-LB

Multinight "Bedside" Artificial Pancreas for Patients with T1D Improves Glycemic Control

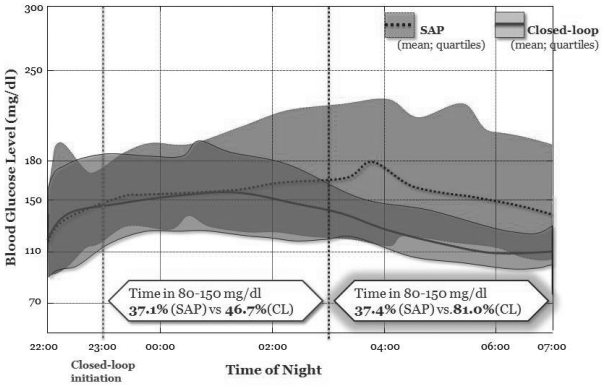
SUE A. BROWN, DANIELA BRUTTOMESSO, MARC D. BRETON, SIMONE DEL FAVERO, STACEY ANDERSON, CLAUDIO COBELLI, BORIS P. KOVATCHEV, *Charlottesville, VA, Padova, Italy*

Objective: Test the feasibility of multi-night closed loop control (CLC) aiming for tight glycemic control in the morning to effectively "reset" the patient to normoglycemia before waking up.

Methods: N=10 subjects with T1D were enrolled in a randomized cross-over trial: sensor-augmented pump therapy (SAP) vs. CLC of 5 consecutive nights (23:00 to 07:00) in outpatient setting. Subjects wore a DexCom Platinum CGM, Roche Accu-Chek Combo Pump and the Diabetes Assistant (DiAs) - a cell-phone CLC platform running the USS Virginia control-to-range algorithm.

Results: Subjects (mean age 46±9, A1c 7.0±1.1%) completed 49 nights of CLC and 49 nights of SAP. The system functioned 98.3% of time with no adverse events. CLC vs. SAP improved significantly: mean glucose at 07:00am (119.3 ± 24 vs. 152.9 ± 59.5 mg/dL, p<0.001); overnight mean glucose (139 vs. 170.3 mg/dL, p<0.001); and percent time in 80-150 mg/dL (64.3 vs. 38.3%, p<0.001), 70-180 mg/dL (85.4 vs. 59.1%, p<0.001) - see Figure - using similar amount of insulin (6.1 vs. 6.8U, p=0.1). Time in hypoglycemia <70 mg/dL was low: 0.55% in CLC vs. 1.65% in SAP; 0.12 episodes/night in each. Overnight control correlated with following daytime control (r=0.47, p=0.002).

Overnight CLC results in significant improvement in morning and overnight glucose levels, and time in target range, with the potential to improve day-time control when glucose levels were "reset" to normoglycemia each morning.



Supported By: NIH

105-LB

Provincially-Funded Insulin Pump Therapy and Health Care Utilization in Adults with Type 1 Diabetes in Ontario, Canada

SELINA L. LIU, BAIJU R. SHAH, STEWART B. HARRIS, *London, ON, Canada, Toronto, ON, Canada*

In September 2008, Ontario became the first province to publicly fund insulin pump therapy (IPT) for adults with type 1 diabetes (T1DM), via the Assistive Devices Program (ADP). This study characterized the ADP-funded adults on IPT and assessed the clinical impact of ADP enrollment on selected health care utilization outcomes.

Data from all adult ADP applicants from September 1, 2008 to December 31, 2012 were linked to provincial administrative databases detailing all hospitalizations and physician service claims.

There were 7,220 adults who started IPT. At enrollment, the mean age was 40.5 years, the mean A1C was 8.0%, 44.5% were male, 74.8% had T1DM duration ≥ 10 years, 75.0% had endocrinologist care, and few had any diabetic ketoacidosis (2.4%) events the year prior. Of note, 49.1% were from the 2 highest income quintiles.

The frequency of health care utilization within 1 year pre- and post-ADP enrollment was compared (Table 1). Post enrollment, DM-related emergency room visits and family physician visits significantly decreased.

In Ontario, provincially-funded IPT in adults with T1DM was associated with positive changes in health care utilization, but there was evidence of disparity in access to funding in those of lower income.

Table 1. Frequency of Selected Health Care Utilization Outcomes Pre- and Post-ADP Enrollment.

	Pre-ADP Enrollment	Post-ADP Enrollment	p-value
MEDIAN NUMBER (IQR)OF VISITS PER SUBJECT Family physician office visits	4 (2,7)	3 (1,6)	<0.0001
DM-related endocrinologist/internist office visits	2 (1,3)	2 (1,3)	<0.0001
Outpatient laboratory visits	2 (1,3)	2 (1,3)	0.076
MEDIAN NUMBER (%) OF VISITS FOR TOTAL COHORT (n=7,220) DM-related emergency room visits	533 (7.4%)	431 (6.0%)	0.010
Eye exams	2,892 (40.1%)	2,988 (41.4%)	<0.001
Inpatient admissions for DKA	188 (2.6%)	205 (2.8%)	0.323
Non-glycaemia-related inpatient admissions	580 (8.0%)	618 (8.6%)	0.219

106-LB

Real Time Remote Monitoring with Artificial Pancreas: A Family-Centered Pilot Trial

NATHAN LAU, MOLLY MCELWEE, CHRISTIAN WAKEMAN, MARK DEBOER, DANIEL R. CHERNAVVSKY, *Charlottesville, VA*

Adolescents with Type 1 Diabetes (T1D) struggle with blood glucose (BG) control while assuming more responsibility for their health. Supporting this transition with real-time remote monitoring (RM) enables joint parent-child review of BG levels and insulin delivery.

We evaluate the parent-child dyad's acceptance and confidence using RM in a randomized, crossover artificial pancreas (AP) trial which studied 17 adolescents ages 13-18 on 2 separate days: sensor-augmented pump vs. AP. Parents remotely monitor their child's BG control and rated their experience before and after the AP session. They also filled a Potential Action Questionnaire (PAQ) every 30 minutes during AP day to comment on how or if they would intervene given RM indications. In post-trial focus groups (FG), parents and adolescents provided feedback on their experiences and envisioned future uses of RM and AP.

The PAQ indicated that parents would intervene less frequently if their child was wearing the AP ($\chi 2$ (.05,4)=102.6, p<0.01). The post-trial survey ratings on a scale from 1 (Very Uncomfortable) to 5 (Very Comfortable) suggested that the dyads were comfortable using the AP (N=17, M=4.25, SD=0.44) and the RM (N=17, M=4.32, SD=.60) respectively. The FG highlighted that the systems were easy to learn and trusted and also indicated that customization features would be useful.

Parents wished to have RM when their child was at college while adolescents wanted to customize alerts for roommates, significant others, and healthcare providers. All expressed desire to adopt the AP and RM immediately, and noted that bringing the current technology to market should take precedence over any potential future improvements.

This first family-centered study indicates ease of use and trust in the AP and RM, demonstrates promise for transferring health responsibilities for adolescent independence, and shows potential for improvement of glycemic control. Future studies with larger patient populations will be necessary to confirm these findings.

Supported By: University of Virginia

107-LB

"Learning" Can Improve the Closed-Loop Blood Glucose (BG) Control Performance

CHAOFENG YAN, JINPING ZHANG, CLAUDIO COBELLI, DONG ZHAO, NA WANG, XIAOPING CHEN, BO ZHANG, SHAOLONG WEI, CONG HAO, WENYING YANG, YOUQING WANG, *Beijing, China, Padova, Italy*

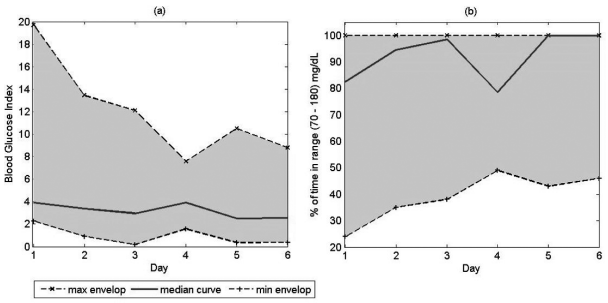
There exists repetitiveness in glucose-meal-insulin dynamics, but no clinical trial considers the possibility of learning from one day to another. To clinically evaluate the capability of "learning", a learning-type closed-loop BG control algorithm, termed as L-MPC, has been tested on ten T1DM adult (age>16) subjects in China-Japan Friendship Hospital (6M & 4F; age: 35.8±13.2; BMI: 68.7±14.4).

With insulin therapy optimization and model identification in advance, the closed-loop clinical trials last six days for each subject. In each day, the trail starts at 8am and ends at noon with 50g CHO diet at 9am. To study the influences of alcohol and exercise, subjects drink 50mL beer and/or ride 15-min bike on the fourth and/or sixth day. The order of drinking and riding was determined randomly. The learning gain in L-MPC was chosen as 0.5.

Test results show that L-MPC can learn from an individual's lifestyle and improve the blood glucose control performance from day to day. By comparing

the third with the first day, the BGI value decreases from 5.4 to 4.2 and the percentage of time when BG within [70, 180]mg/dL increases from 76.6 to 83.7 in average. There is no significant hypoglycemia (BG<60 mg/dL).

To the authors' best knowledge, this is the first clinical study verifying the learning's capability. L-MPC is effective for T1DM and has excellent robustness to alcohol and exercise disturbances. The subsequent clinical trials are under way.



Supported By: EFSD/CDS/Eli Lilly and Company; NSFC (61374099)

108-LB

Engineering a Thin-Film Cell Encapsulation Device for Treating Type 1 Diabetes

RYAN CHANG, CRYSTAL NYITRAY, GAETANO FALEO, QIZHI TANG, TEJAL DESAI, *San Francisco, CA*

Replacement of insulin-producing cells using islet transplantation is a proven effective therapy for Type 1 Diabetes. The use of an encapsulation device as a physical barrier between the recipients and xenogeneic islets or hESC-derived beta cells may enable the safe use of these therapies while eliminating the need of immunosuppression. Here we present a novel thin-film cell encapsulation device with stringently defined porosity for immunoprotection as well as a favorable microenvironment that promotes cell survival.

Polycaprolactone (PCL) thin films were fabricated by casting PCL and Polyethylene Glycol (PEG) dissolved in 2,2,2-trifluoroethanol and casted onto nanotemplated silicon wafers. PEG particles were dissolved away in deionized water to release the thin film from the wafer. The device is assembled by heat sealing two PCL thin-films together with firefly luciferase expressing islets encapsulated in the inner lumen. Devices containing islets or free islets were transplanted in the subcutaneous space of syngeneic and allogeneic mice models. Islet viability was assessed by monitoring bioluminescence over time while therapeutic efficacy was evaluated by measuring blood glucose concentration.

Free islets and encapsulated islets survived equally well in the 30-day post-transplantation period. Syngenic free islet transplants survived while allogeneic free islet transplants failed. However, encapsulated islets survived in both syngeneic and allogeneic transplants. Blood glucose levels dropped from 400 mg/dL to under 200 mg/dL in mice transplanted with the cell encapsulation device. The implanted devices demonstrated superior vascularization along the outer surface of the membrane as seen after 30 days in vivo.

These studies demonstrate proof of principle using our cell encapsulation technology to treat diabetes in allogeneic models. We look forward to further evaluate our technology by characterizing the immunoprotection capability in more stringent autoimmune animal models.

Supported By: JDRF

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—NON-INSULIN INJECTABLES

109-LB

ISIS-GCGRRX, an Antisense Glucagon Receptor Antagonist, Caused Rapid, Robust, and Sustained Improvements in Glycemic Control without Changes in BW, BP, Lipids, or Hypoglycemia in T2DM Patients on Stable Metformin Therapy

ERIN MORGAN, ANNE SMITH, LYNNETTA WATTS, SHUTING XIA, WEI CHENG, RICHARD GEARY, SANJAY BHANOT, *Carlsbad, CA*

Excessive glucagon &/or dysregulation of postprandial glucagon secretion contributes to hyperglycemia in pts with T2DM. ISIS-$GCGR_{RX}$ (GR) is an antisense drug that reduces hepatic GCGR mRNA expression. We reported that GR was safe and produced significant increases in total GLP-1 levels without affecting BP or lipids in healthy volunteers (*Diabetologia (2013) 56: Suppl 1: 691P*). In this double-blind study, T2DM pts on stable MET therapy were randomized to placebo, 100 or 200 mg GR injected SC as a loading dose (4 inj. in 14 days) then once wkly for 11 wks. Mean baseline (BSLN) glycemic values were HbA1c (8.3 - 9.1%), FPG (180.6 - 227.5 mg/dL) and fructosamine (290 - 311 µmol/L). GR treatment caused robust improvements in glycemic control that were sustained for many weeks after the last dose. Significant increases were observed in total GLP-1 (up to 4-fold), accompanied by OGTT improvements consistent with a GLP-1 effect. No hypoglycemia, no changes in vital signs, ECG, renal function, TGs, LDL-c, BW or BP were observed. As reported with GCGR small molecules, some GR 200 mg pts had mild increases in ALT/AST without elevation in bilirubin, alk phos or clinical symptoms. The GR efficacy and safety profile supports further development in T2DM pts uncontrolled on existing therapies.

Efficacy Results.

		Mean Change from BSLN to Week 14					At Wk 14
Treatment Group	N	HbA1c (%)	FPG (mg/dL)	Fructosamine (µmol/L)	Glucose AUC (mg*min/dL) during 2 hr OGTT	C-peptide AUC (ng*min/mL) during 2 hr OGTT	HbA1c<7%
Placebo	9	-0.46	-16.4	-8.4	-2351.7	-85.4	0%
GR 100mg	10	-1.37	-59.9*	-62.2**	-5793	167.8** A	40%
GR 200mg	8	-2.25&	-102&	-74.9**	-14010*	139.6*	63%**

*p<0.05; **p<0.01; &p<0.001; ANOVA=9.

110-LB

Efficacy and Safety of Once Weekly Dulaglutide vs. Once Daily Liraglutide in Type 2 Diabetes (AWARD-6)

KATHLEEN M. DUNGAN, SANTIAGO TOFÉ POVEDANO, THOMAS FORST, JOSÉ G. GONZÁLEZ, CHARLES ATISSO, WHITNEY SEALLS, JESSIE L. FAHRBACH, *Columbus, OH, Palma de Mallorca, Spain, Mainz, Germany, Monterrey, Mexico, Indianapolis, IN*

This Phase 3, randomized, open-label, parallel-arm 26-week (wk) study compared efficacy and safety of once weekly dulaglutide (DU) 1.5 mg, a long-acting GLP-1 receptor agonist, vs. once daily liraglutide (LIRA) 1.8 mg in metformin-treated (≥1500 mg) patients with type 2 diabetes. Patients (N=599) had a mean baseline age of 57 years; A1C of 8.1%; and weight of 94.1 kg. The primary objective was A1C change from baseline at 26 wks tested for noninferiority (margin 0.4%); DU 1.5 mg vs. LIRA 1.8 mg.

DU 1.5 mg was noninferior to LIRA 1.8 mg at 26 wks as measured by A1C change from baseline (between-group A1C change: -0.06; 95% CI [-0.19, 0.07]) (Table). While both groups experienced significant weight reduction, LIRA-treated patients demonstrated a 0.71 kg greater reduction than DU-treated patients (p=0.01). The most common treatment-emergent GI adverse events for DU 1.5 mg and LIRA 1.8 mg, respectively, were nausea (20.4%, 18.0%), diarrhea (12.0%, 12.0%), dyspepsia (8.0%, 6.0%), and vomiting (7.0%, 8.3%). Patients who discontinued study and/or study drug due to GI adverse events were similar (DU 1.5 mg [3.0%], LIRA 1.8 mg [4.3%]). Hypoglycemia rate was 0.34 (DU 1.5 mg) and 0.52 (LIRA 1.8 mg) events/pt/yr. No severe hypoglycemia was reported.

In conclusion, once weekly DU 1.5 mg demonstrated noninferior glycemic control compared to once daily LIRA 1.8 mg with a comparable safety and tolerability profile.

Efficacy Measures (26 wk, ITT)	DU 1.5 mg (N=299)	LIRA 1.8 mg (N=300)
A1C change, %, Least Square Mean (SE)[a]	-1.42 (0.05)‡	-1.36 (0.05)
% of patients with A1C <7.0%	68.3	67.9
Weight change, kg, Least Square Mean (SE)[b]	-2.90 (0.22)#	-3.61 (0.22)

‡ 1-sided p < 0.001 for noninferiority vs. LIRA for A1C change. # p = 0.01 vs. LIRA. [a]MMRM. [b]ANCOVA LOCF.

Supported By: Eli Lilly and Company

111-LB

Clinical Effects of Metreleptin in Partial vs. Generalized Lipodystrophy: The Role of Baseline Abnormalities

TALIA DIKER-COHEN, ELAINE K. COCHRAN, PHILLIP GORDEN, REBECCA J. BROWN, *Bethesda, MD*

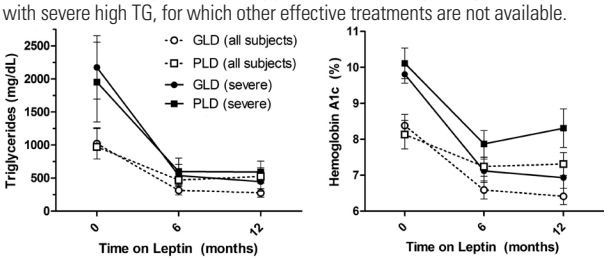
Lipodystrophies (LD) are rare diseases of subcutaneous fat loss, leptin deficiency, insulin resistance and high triglycerides (TG). Leptin replacement therapy has just been FDA-approved for generalized LD (GLD), but not for partial LD (PLD) due to uncertain benefit. We compared effects of metreleptin (ML, a recombinant leptin analog) on metabolic abnormalities in PLD vs. GLD, with subgroup analyses in patients with severe metabolic disease (A1c ≥8% or TG ≥500 mg/dL at baseline).

86 patients (31 PLD; 55 GLD) completed ≥6 months in an open-label trial of ML. Inclusion criteria were low leptin (<8 ng/mL in men; <12 in women) and ≥1

of: fasting TG >200 mg/dL, diabetes, or fasting insulin >30 uU/mL. A1c and TG were measured at baseline (N=86) and after 6 (N=74) and 12 (N=72) months.

There were no baseline differences for GLD vs. PLD. In the total cohort, A1c fell from 8.1 to 7.3 (PLD) and 8.4 to 6.4 (GLD). TG fell from 971 to 524 (PLD) and 1021 to 276 (GLD). In the severe subgroups, A1c fell from 10.1 to 8.3 (PLD, N=14) and 9.8 to 6.9 (GLD, N=34); TG fell from 1953 to 592 (PLD, N=13) and 2175 to 446 (GLD, N=22). (P<0.05 for all).

In LD patients selected for the presence of more severe metabolic disease, ML led to significant improvements in A1c and TG in both PLD and GLD, and should be considered as a potential therapy for PLD. This is especially true in patients with severe high TG, for which other effective treatments are not available.



112-LB

A Novel Dual Action GIP/GLP-1 Coagonist Peptide Shows Enhanced Activity on Weight Loss and Energy Utilization Whilst Maintaining Its Efficacy for Glycaemic Control

KRISTER BOKVIST, TAMER COSKUN, ROBERT CUMMINS, THOMAS B. FARB, JAMES V. FICORILLI, THOMAS FITCH, OLIVER GHOBRIAL, LILI GUO, JOHN P. MAYER, LIBBEY O'FARRELL, XIANBU PENG, JORGE ALSINA-FERNANDEZ, *Indianapolis, IN*

It is well known that the incretins GIP and GLP-1 released from the gut in response to food dramatically enhance glucose removal following a meal. Although both incretins have been studied in great detail individually it remains largely unknown if GIP and GLP-1 produce additional benefits when combined. Here we have characterized a novel balanced GIP and GLP-1 receptor coagonist (Cpd86) with regard to glycemic control, blood lipids, weight loss, body composition and energy utilization. Cpd86 was a balanced full dual agonist with binding K_i of 5.3 and 4.4 nM at GIPR and GLP1R, respectively and >1000x selective over GlucR. It enhanced insulin secretion from rat pancreatic islets with an EC50 of 5.4 nM. When given s.c. 16h prior to a glucose challenge Cpd86 enhanced insulin secretion in response to an i.v. bolus of glucose. The half-maximally efficacious dose was 2.5 nmol/kg. In a two-week weight loss study in DIO mice 10 nmol/kg of Cpd86 resulted in a 11% weight loss whereas vehicle was associated with a slight weight gain of +2.7%. As a comparison, in the same study, 10 nmol/kg of long-acting GLP-1 resulted in a 6.3% weight loss and combining the GLP-1 analogue with 100 nmol/kg long-acting GIP increased the weight loss seen to 11.3% suggesting that the added GIP pharmacology may enhance weight loss. The coagonist and the pure GLP-1 analogue both suppressed food intake to a similar extent, the inclusion of GIP pharmacology either in the form of a coagonist or as a combination treatment resulted in increased fat metabolism at rates that could explain the additional weight loss seen. Weight loss was predominantly fat mass (>80%), the remainder being water and lean mass. All compounds improved plasma lipids as well as glucose tolerance in an OGTT administered at the end of the 2-week study. In conclusion, our observations indicate that a GIP/GLP-1 coagonist may have additional benefits in treating diabetes compared to a pure GLP-1 analogue.

113-LB

Liraglutide Added to High-Dose Basal/Bolus Insulin in Type 2 Diabetes

WENDY S. LANE, STEPHEN WEINRIB, JONATHAN RAPPAPORT, *Asheville, NC*

Adding a GLP-1 receptor agonist to basal insulin is an effective treatment option in type 2 diabetes; the addition of GLP-1 to basal/bolus insulin therapy has not been studied. In this prospective trial 40 subjects with type 2 DM using >100 units per day of basal/bolus insulin therapy were randomized to receive liraglutide plus insulin (LIRA) or insulin only (control) for 6 months. Controls then crossed over to receive liraglutide plus insulin while the LIRA group remained on both agents for an additional 6 months. HbA1c, weight and total daily insulin dose (TDID) were measured at 3, 6, 9 and 12 months. Statistical comparisons within and between groups were made by analysis of variance (ANOVA) for repeated measures.

At 6 months, HbA1c improved from a baseline of 7.8% in both groups to 7.1% in the LIRA group (p =.002) and 7.4% in controls (p = .068). HbA1c in the LIRA group at 12 months was 7.1%. Adding liraglutide to insulin in controls further improved HbA1c from 7.4% at 6 months to 6.9% at 12 months (p= .019).

At 6 months the LIRA group experienced an average weight loss of 5.27 kg (p=.069) whereas controls had gained 0.37 kg (p=NS). By month 12, the LIRA group had regained 3.26 kg for a net loss of 2 kg (p=NS vs. baseline). Adding liraglutide from month 6 to 12 in controls resulted in weight loss of 9.78 kg (p= .001).

TDID was reduced by 34% in the LIRA group at 6 months from 200 to 132 U/d (p < .0001); controls had a small increase in TDID from 171 to 178 U/d (p=NS). From month 6 to 12, the LIRA group had a slight increase in insulin dose from 132 to 148 U/d (p=NS). Adding liraglutide to insulin in controls resulted in a 36% reduction in TDID from 178 U/d at 6 months to 114 U/d by 12 months (p < .0001).

Adding liraglutide to basal/bolus insulin therapy improved glycemic control over 12 months while lowering weight and TDID in patients with type 2 DM requiring > 100 units of insulin per day, but subjects regained some weight in the second 6 months of treatment. Additional weight loss and insulin-sparing treatments are needed in the management of this challenging population.

Supported By: Novo Nordisk, Inc.

114-LB

Efficacy and Tolerability of ITCA 650 (Continuous Subcutaneous Exenatide) in Poorly Controlled Type 2 Diabetes with Baseline A1C>10%

ROBERT R. HENRY, JULIO ROSENSTOCK, MICHELLE BARON, *San Diego, CA, Dallas, TX, Cambridge, MA*

ITCA 650, the injection-free GLP-1 receptor agonist that provides continuous SC exenatide for up to 12 months from a single sub-dermal placement, is undergoing extensive clinical evaluation in multiple Phase 3 double-blind studies. This report represents the first 6 month, open-label experience with ITCA 650 mini-pumps from an ongoing multicenter study in subjects with type 2 diabetes who did not meet enrollment criteria for the double-blind placebo controlled trial because of A1C >10%. Entrance criteria for this open-label trial were: A1C >10% to ≤12%, age 18-80 years, BMI 25-45 kg/m2, and on stable (≥3 months) diet and exercise and/or monotherapy or any combination of metformin, sulfonylurea, and thiazolidinedione. Treatment was initiated by placing a 3-month ITCA 650 mini-pump delivering 20 mcg/day, which was then replaced by a 6-month ITCA 650 mini-pump delivering 60 mcg/day for 26 weeks. Pre-study oral antidiabetic agents (OADs) were maintained unchanged for the 39 week of treatment. The primary endpoint was change in A1C from baseline to week 39. At the time of this initial interim analysis, 50, 39, and 25 of the 60 subjects enrolled had completed 13, 19, and 26 weeks of treatment; respectively. Mean baseline characteristics for the entire cohort (n=60) were A1C 10.7%, age 52.1 yrs, BMI 32.1 kg/m2, duration of diabetes 8.9 yrs, OADs use 69%. Mean reductions of A1C at Weeks 13 (n=50), 19 (n=39), and 26 (n=25) were -2.5%, -2.9%, and -3.2%, respectively. A1C reductions ≥2% were achieved by 78% of subjects who completed at least 13 weeks of treatment; 50% achieved >3% and 22% achieved ≥4% reductions. A1C targets of <7% were achieved in 22% of subjects who had completed at least 13 weeks of treatment. Adverse events were consistent with previous trials with ITCA 650. In conclusion, ITCA 650 has the potential to markedly improve glycemic control in patients with severe hyperglycemia and longstanding diabetes.

Supported By: Intarcia Therapeutics, Inc.

115-LB

Direct Vascular Protection against Glucose- and Lipid-induced Endothelial Dysfunction by Exenatide

JURAJ KOSKA, CAMELIA BURCIU, KAREN M. D'SOUZA, MICHELLE SANDS, SETH TRURAN, DANIEL A. FRANCO, RAYMOND MIGRINO, PETER D. REAVEN, *Phoenix, AZ*

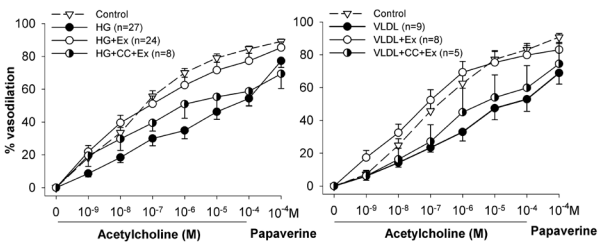
We previously showed that improvement of endothelial function by exenatide (Ex) *in vivo* was largely independent of metabolic action of Ex and involved activation of vascular GLP-1 receptors. In the present study we tested whether Ex prevents glucose and lipid induced endothelial dysfunction in human peripheral arterioles and assess which signaling pathways contribute to this vascular effect of Ex.

Vasodilation response of isolated subcutaneous adipose tissue arterioles to increasing dose of acetylcholine (Ach) and papaverine was measured before (control) and after exposure to high glucose (HG, 33 mM) or hydrolyzed VLDL (150 μM of fatty acids), with or without 10nM Ex. Phosphorylation of protein kinases (PK) A and B, and AMP-activated protein kinase (AMPK) by Ex was assessed by Western blot in human aortic endothelial cells (HAEC).

Ach vasodilation was attenuated with HG and VLDL (p<0.001 vs. control) and restored with Ex (p=1.0 vs. control, p<0.001 vs. HG or VLDL) (Figure).

In HAEC, Ex activated AMPK but not PKA or PKB. The AMPK inhibitor Compound C significantly attenuated Ex rescue of Ach vasodilation (p<0.001 vs. [HG or VLDL]+Ex; p>0.1 vs. HG or VLDL).

Our data indicate that Ex directly protects peripheral arterioles from glucose and lipid-induced endothelial dysfunction and that activation of the AMPK pathway appears to play a key role in preservation of vascular function by Ex.



Supported By: ADA (1-10-CT-31)

116-LB

Lipolytic and Insulinotropic Effects of HM12525A, a Novel Long-acting GLP-1/Glucagon Dual Agonist

YOUNG JIN PARK, SUNG-YOUB JUNG, JUNG KUK KIM, JONG SOO LEE, YOUNG-MI LEE, YOUNG HOON KIM, JAHOON KANG, MICHAEL TRAUTMANN, MARCUS HOMPESCH, SE CHANG KWON, *Hwaseong-si, Republic of Korea, Seoul, Republic of Korea, Hamburg, Germany, Chula Vista, CA*

Oxyntomodulin, an alternative cleavage product of proglucagon, is a gut hormone which can lead to enhanced body weight loss and improved glycemic control by activating GLP-1 (GLP-1R) and glucagon receptor (GCGR), respectively. However, its clinical application is limited due to low potency at the individual receptors and a short half-life. We developed a high potency GLP-1/glucagon dual agonist peptide and ultra-long acting dual agonist, HM12525A, by conjugating a novel GLP-1/glucagon dual agonist with the constant region of human immunoglobulin via a non-peptidyl linker. In a previous pre-clinical study, we demonstrated that once weekly administration of HM12525A exerted potent body weight loss and improved glycemic control in obese and/or diabetic animal models. The aim of this study was to investigate the molecular basis for the beneficial effects of HM12525A in adipocytes and pancreatic β-cells. Since HM12525A administration significantly reduced the fat mass in diet-induced obesity (DIO) mice, we firstly checked whether HM12525A has lipolytic effects in adipocytes. Interestingly, HM12525A dose-dependently inhibited the intracellular lipid droplet formation in 3T3-L1 adipocytes. In addition, phosphorylation of hormone-sensitive lipase (HSL), a key enzyme for lipolysis, and following glycerol release were significantly increased upon HM12525A treatment in 3T3-L1 adipocytes, suggesting stimulating effects of HM12525A on lipolysis. As to the effects in pancreatic β-cells, HM12525A increased insulin secretion in RINm5F cells. In line with this, HM12525A administration significantly increased insulin secretion as well as insulin sensitivity, thereby lowering glucose excursion during *ip*GTT in normal mice. Taken together, these results demonstrate that dual agonism of HM12525A mediates lipolytic and insulintropic effects in adipocytes and β-cells, conferring both anti-obesity and anti-diabetic potentials.

117-LB

Pramlintide-Insulin Fixed-Dose Combination: A Phase 1 Dose Ratio-Finding Study in Patients with Type 1 Diabetes Mellitus (T1DM)

KEVIN C.J. YUEN, MATTHEW C. RIDDLE, KATHRIN HERRMANN, TJERK DE BRUIN, PAULA MARTIN, ORVILLE G. KOLTERMAN, PETER ÖHMAN, *Portland, OR, San Diego, CA, Wilmington, DE, La Jolla, CA, Gaithersburg, MD*

Patients with T1DM lack secretion of both insulin and amylin, which are normally co-secreted by β-cells; thus, replacing both hormones may provide therapeutic advantages in optimizing glycemic control. In treating T1DM, fixed doses (eg, 60 µg) of pramlintide (an analog of human amylin) are administered adjunct to prandial insulin, irrespective of insulin dose. This phase 1 study adjusted pramlintide dose relative to insulin and examined the effects of 3 dose ratios on postprandial glucose and glucagon for 3 h after a standard breakfast (600 kcal, 55% carbohydrate, 15% protein, 30% fat). Subjects in this single-blinded, 4-way, crossover study received regular insulin (RI) + placebo (PBO), pramlintide 6 µg/U RI, 9 µg/U RI, and 12 µg/U RI in random order, using <10 U RI for breakfast and a 30% reduced dose of RI before test meal. AEs were based on non-directed questioning, lab, vital signs, and physical exam. Of 19 subjects randomized (mean [SD] age 46.2 [15.6] y, A1c 7.75 [0.58] %, weight 81.5 [11.1] kg, BMI 26.4 [2.6] kg/m^2), 17 completed all 4 treatments. Premeal FPG levels ranged from 138.4 (36.9) to 155.9 (35.5) mg/dL, and insulin doses from 5.1 (1.54) to 5.4 (1.28) U across groups. Mean (SE) postprandial incremental glucose $AUC_{0\text{-}3h}$ (mg/dL·h) for the pramlintide 6, 9, and 12 µg/U RI groups were 8226.3 (1849.9), 8588.9 (1864.7), and 5788.8 (1797.6), respectively, vs. 20584.9 (1796.3) for PBO. Postprandial incremental glucagon $AUC_{0\text{-}3h}$ (pg/mL·h) for the pramlintide 6, 9, and 12 µg/U RI groups were 649.4 (342.5), 614.9 (345.0), and 677.7 (333.8), respectively, vs. 1503.0 (334.2) for PBO. No treatment-related hypoglycemia was reported. One subject reported nausea in all 3 pramlintide dose ratios, and 1 reported abdominal pain and diarrhea. In summary, all 3 pramlintide dose ratios showed efficacy (58-72% and 55-59% lower incremental glucose and glucagon, respectively, for AUC vs. PBO) in lowering postprandial glucose and glucagon levels, and were generally well-tolerated.

Supported By: JDRF

118-LB

Effectiveness of Lixisenatide before Breakfast or the Main Meal Using CGM with AGP Analysis

ELLIE STROCK, ROGER MAZZE, MARGARET A. POWERS, ARLENE MONK, SARA RICHTER, RICHARD M. BERGENSTAL, ELISABETH SOUHAMI, NACIMA DEMIL, BO AHRÉN, *Minneapolis, MN, Paris, France, Lund, Sweden*

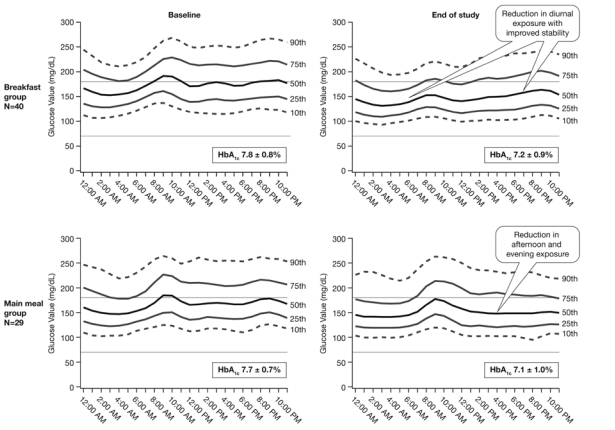
Blinded continuous glucose monitoring (CGM) was used 14 days before and during treatment of T2DM patients in a multicenter randomized trial of lixisenatide (LIXI) given before breakfast (BK) or the main meal (MM) (defined by the patient). Ambulatory glucose profile (AGP) analysis detected changes in diurnal glucose patterns (DGP). Sixty-nine patients completed (T2DM 7.8±4.9y; age 57.8±10.2y; 53.6% female). Table 1 summarizes CGM results. Figure 1 shows composite AGPs. LIXI significantly reduced 24hr and waking AUC in both groups. Sleeping AUC was significantly reduced in BK, but not MM. Less than 1% of time was spent in hypoglycemic range (<60mg/dL). HbA_{1C} reduction was similar in both groups. In summary, LIXI before MM appears to benefit afternoon and evening glucose exposure; LIXI before BK appears to have a sustained improvement in DGP.

Table 1. CGM endpoints using AGP analysis

	Breakfast group (N=40)			Main meal group (N=29)*		
CGM endpoint	Baseline	End	p-value	Baseline	End	p-value
Total glucose exposure AUC (mg/dL*24 hr)	4198.1 ± 652.3	3681.2± 699.6	<0.0001	4127.9 ± 876.8	3880.9 ± 1165.0	0.0224
Hourly waking AUC (mg/dL*hr)	181.1 ± 28.1	157.2 ± 29.5	<0.0001	177.9 ± 37.7	165.6 ± 48.2	0.0184
Hourly sleeping AUC (mg/dL*hr)	161.8 ± 28.0	144.6 ± 28.8	<0.0001	159.8 ± 36.4	153.4 ± 51.5	0.0942
Variability–IQR (mg/dL)	49.5 ± 14.8	45.9 ± 14.4	0.1109	48.8 ± 13.8	44.3 ± 11.3	0.0888
Stability – absolute hourly rate of change in median curve (mg/dL/hr)	8.6 ± 3.3	7.5 ± 2.1	0.0711	8.5 ± 2.5	8.7 ± 3.3	0.7513

*Lunch=14; dinner=13; breakfast=2

Figure 1. Composite AGPs for the BK and MM groups at baseline and study end. The AGP diurnal glucose profiles indicate that patients in the BK had improvements in sleeping, walking, post-meal glucose exposure and stability, whereas those in the MM group shows reductions in HbA_{1C}, primarily due to lowering of afternoon and evening exposure.



For author disclosure information, see page LB91.

119-LB

Effectiveness and Tolerability with Liraglutide among Patients with Type 2 Diabetes: Two-Year Data from EVIDENCE: A Prospective, Follow-up, Post-marketing Study

PIERRE GOURDY, ALFRED PENFORNIS, GUILLAUME CHARPENTIER, SULIYA MADANI, LUC MARTINEZ, EVELINE ESCHWÈGE, JEAN-FRANCOIS GAUTIER, *Toulouse, France, Besançon, France, Corbeil-Essonnes, France, Paris, France, Villejuif, France*

EVIDENCE is a 2-year multicenter, observational, post-marketing outpatient study requested by the French National Health Authority in order to evaluate the efficacy and safety of liraglutide in clinical practice. The primary objective is to determine the percentage of patients still taking liraglutide and at A1c target (<7%) after 2 years. Diabetologists and general practitioners in France recruited patients starting treatment with liraglutide. Patients and physicians completed questionnaires at study entry, 3 months and 6 months, then at 6-month intervals for a further 18 months. Baseline data (mean±SD) were collected from 3152 patients (53% male, age 59±11 years, BMI 34±7 kg/m^2, duration of diabetes 10±6 years, A1c 8.5±1.5%); 2029 patients (64.4%) remained at the end of the study. The majority of patients (n=2804, 90%) exceeded the ADA/EASD target with an A1c ≥7% at baseline. The proportion of patients with A1c <7% was significantly higher after 2 years' liraglutide treatment (n=759, 39.4%) vs. baseline (n=213, 11.0%; p<0.0001). Following 2 years of liraglutide treatment, significant reductions in A1c (-1.01±1.54%, p<0.0001), fasting plasma glucose (-0.32±0.63 g/L, p<0.0001) and body weight (-4.09±6.97 kg, p<0.0001) were observed from baseline. Gastrointestinal disorders (nausea, vomiting and diarrhea) were the most frequent adverse events, reported by 261 patients (8.7%) treated with liraglutide; they were also the most common reason for withdrawal. These results suggest that the effectiveness of liraglutide in real world clinical practice is similar to that observed in randomized clinical trials (RCTs) (up to -1.5% A1c reductions and -3.24 kg weight loss). The incidence of gastrointestinal events was lower than that reported in RCTs (up to 26.5%). In summary, 2-year results from the EVIDENCE study suggest that clinical trial data for liraglutide translate into therapeutic benefits in clinical practice.

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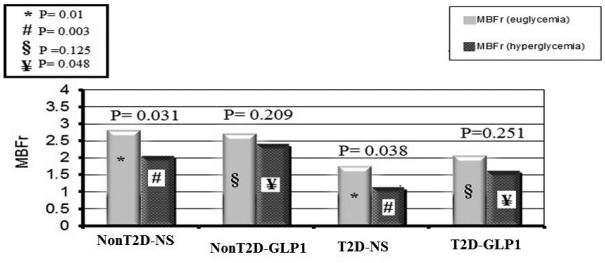
120-LB

Glucagon-like Peptide 1 Modulates Reductions in Myocardial Blood Flow Reserve during Euglycemia and Hyperglycemia in Both Type 2 Diabetics and Non-Diabetics

SAHAR S. ABDELMONEIM, LARA NHOLA, RUNGING HUANG, MARY E. HAGEN, EDWARD MENDRICK, BRENDA KIRBY, ANANDA BASU, SHARON L. MULVAGH, *Rochester, MN*

We evaluated the effect of Glucagon-like peptide-1 (GLP1) on myocardial blood flow reserve (MBFr) in subjects with & without type 2 diabetes (T2D & non-T2D) under eu- or hyperglycemia with somatostatin pancreatic clamp. 21 subjects [8 T2D&13 non-T2D] were enrolled. Both groups underwent 2 study visits each (GLP1: 1.2 pmol/kg/min GLP1 infusion; NS: Normal Saline infusion). During each visit, 2 stage pancreatic clamp [somatostatin, glucagon & insulin (0.75 mU/Kg /min)] was conducted. Glucose was infused to maintain euglycemia (5mM) followed by hyperglycemia (14 mM) (each 2 hr stages). Real time myocardial perfusion echocardiography (RT-MPE) was performed during each glycemic state using diluted Definity (200 ml/hr), at rest and during regadenoson stress (400 ug IV bolus). MBFr [stress/rest] was quantified. Non-T2D [85% female, age 48±6 yrs, BMI 25±3 kg/m^2, HbA1C 5.4 + .3 %] & T2D [75% male, age 54±6 yrs, BMI 32±4 kg/m^2, HbA1C 7.2± .7%]. Mean MBFr was reduced at hyper vs. euglycemia in T2D-NS (p=0.038) & non-T2D-NS (p=0.031); GLP1 infusion prevented this reduction, Figure. MBFr was lower in T2D-NS vs. non-T2D-NS (euglycemia: p=0.010; hyperglycemia: p = 0.003), but was not different in T2D-GLP1 vs. non-T2D-GLP1. GLP-1 modulates the magnitude of MBFr reduction in T2D, both during euglycemia and hyperglycemia, suggesting a protective cardiovascular effect.



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121-LB

Beneficial Effects of Liraglutide in Type 1 Diabetes

ANA CLAUDIA R. RAMALHO, JULIA JONES, LUCIANA LADEIRA, FABIO MOURA, EDUARDO NETTO, JOÃO GABRIEL J. PASSOS OLIVEIRA, *Salvador, Brazil, Recife, Brazil*

The diagnosis of Metabolic Syndrome has been frequntly done in type 1 diabetes, as found in 40-50% in U.S. Larkin et al found 30% of obesity in type 1. The need of a further terapy for metabolic syndrome and obesity in type 1, made liraglutide an option for these patients. This study aimed to evaluate the effect of liraglutide associated with insulin in body weight and metabolic control in type 1 diabetes. Materials and Methods: We evaluated 15 patients with type 1 diabetes before and after liraglutide with the following parameters: body mass index (BMI) hemoglobin glycated (A1c) and lipid profile. We also evaluate side effects. Results: The average age was 36,2 years and duration of diabetes of 19,1 years (3-33 years), the majority was female 12/3 (F/M). Forty percent was in insulin pump and 60% using analogs. Comparing before to after liraglutide 3-5 months, we note an improvement in A1C (7,9 x 7,0%) (p=0,02); a decrease in BMI (27,3 x 25,8) (p=0,02), decrease in LDL colesterol (110x102,5mg/dl) (p= 0,67) and an increase in HDL colesterol (58x62mg/dl) (p=0,73). The dose of liraglutide ranged between 0,6 à 1,8 mg. The side effects seen was: náusea, vomiting and the dose could not be increased in 3 patients. Discussion: We have scarce studies with liraglutide in type 1 diabetes. In our results, as in Varanasi et al and Kielgast et al, there was a decrease in BMI and an improvement in A1C. Conclusion: Treatment with Liraglutida in type 1 diabetes decrease A1C and BMI, improve colesterol and can be an aditional therapy in type 1 diabetes patients who gain weight with insulinization.

122-LB

Safe and Effective Use of the Single-Use Pen for Injection of Once-Weekly Dulaglutide in Injection-Naive Patients with Type 2 Diabetes

GLENN MATFIN, ALAN G. ZIMMERMANN, KATE VAN BRUNT, REBECCA THRELKELD, DEBRA A. IGNAUT, *Minneapolis, MN, Indianapolis, IN, Windlesham, United Kingdom*

Many patients with type 2 diabetes (T2D) fail to achieve adequate glycemic control with oral antihyperglycemic therapy alone, but patients and clinicians often avoid initiating injectable therapy-fearing pain and complexity. The single-use pen (SUP) device contains a pre-filled syringe and automates needle insertion and retraction, and drug delivery. It was designed for subcutaneous delivery of 0.5 ml of dulaglutide, a once weekly glucagon-like peptide-1 receptor agonist to treat T2D. The objective of this 4 week, Phase 3b, multicenter, open-label, single-arm, outpatient study was to demonstrate the safe and effective use of the SUP containing 0.5 ml of placebo in injection-naïve T2D patients as demonstrated by the final injection success rate (primary outcome) and the initial injection success rate following training (key secondary outcome). Patient-reported outcomes for pain, ease of use of the SUP, willingness to continue using the SUP, and fear of self-injecting were also reported. Mean baseline patient demographics (N=211) were: age 61 yr, duration of diabetes 7.7 yr, and BMI 31.7 kg/m^2. The primary objective was met, with a final injection success rate of 99.1% (95% CI: 96.6, 99.7). The initial injection success rate was 97.2% (95% CI: 93.9, 98.7), meeting the key secondary objective. On a scale of 0 (no pain) to 10, the mean (SD) of pain scores across injections was 1.0 (1.1). 99.0% of patients found the device easy to use and 96.7% of patients indicated they would be willing to continue to use the SUP after the study. There was a significant reduction (p<0.001) in patients' fear of self-injecting, as measured by the self-injecting subscale of the modified Diabetes Fear of Injecting and Self-Testing Questionnaire. The single-use pen was a safe and effective device for T2D patients who were injection naïve. Improvements in injection experience may be an important factor for some patients and providers when initiating injectable therapy.

Supported By: Eli Lilly and Company

123-LB

Effects of Allogeneic Mesenchymal Precursor Cells in Type 2 Diabetes: A Randomized, Placebo-Controlled Study

JAY S. SKYLER, VIVIAN FONSECA, JULIO ROSENSTOCK, MSB-DM003 INVESTIGATORS, *Miami, FL, New Orleans, LA, Dallas, TX*

Type 2 diabetes (T2D) is a chronic metabolic disease with inflammatory underpinnings that may be responsive to therapies which have anti-inflammatory attributes. This study assessed the safety and tolerability as well as exploratory metabolic effects of allogeneic, bone-marrow derived mesenchymal precursor cells (MPC) in T2D subjects insufficiently controlled on metformin +/- another oral antidiabetic agent. Subjects were enrolled in a dose-escalating randomized, placebo (PBO) controlled trial to receive a single intravenous (IV) infusion of 0.3 million (M) MPCs/kg (0.3M; n=15), 1.0 M MPCs/kg (1M; n=15), 2.0 M MPCs/kg (2M; n=15) or placebo (n=16). Study duration was 12 wk.

Sixty-one subjects (21 women, 40 men) with mean±SD baseline A1c 8.3±1.0%, BMI 33.5±5.5 kg/m2 and diabetes duration 10.1±6.0 years were

enrolled at 18 U.S. sites. No acute adverse events (AE) were associated with infusion. There were no serious AEs, serious hypoglycemia AEs, or discontinuations due to AEs over 12 wk. The rate and pattern of adverse events were comparable among groups. No AEs were deemed treatment-related. No subjects developed donor specific antibodies.

A single IV infusion significantly reduced A1c (%) from baseline at 8 wk in 2M MPC compared to PBO. The adjusted least squares mean (LSM) differences from PBO (95% confidence interval) at 8 wk were -0.2 (-0.6, 0.2), -0.1(-0.5, 0.3) and -0.4 (-0.9,-0.0) for 0.3M, 1M and 2M groups (p8% with MPC compared to placebo at 12 wk: -0.2 (-1.1, 0.6), -0.2 (-1.0, 0.6) and -0.5 (-1.4, 0.5) ±0.4 for 0.3M, 1M, and 2M (NS). Target A1c <7% was achieved by 5/15 2M vs. 0/15 PBO subjects (p<0.05).

In conclusion, infusion of MPCs showed no safety issues. Suggestive beneficial effects of 2M/kg MPC on glucose control need to be evaluated in a properly powered long-term controlled study.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—ORAL AGENTS

124-LB

A Novel Circadian Clock Modulator Improves Insulin Resistance in Diabetic Mice

ERIC MABERY, PAUL HUMPHRIES, JEFFREY JOHNSON, KERRYN MCCLUSKIE, TRAVIS RENNER, ERIK WILLIS, TIM RANTZ, ROSS BERSOT, TIM PARK, ERIN RIEGLER, NEERAJ TIRUNAGARI, TOD STEINFELD, *South San Francisco, CA*

Circadian rhythms are important for regulating physiology, and disruption of circadian rhythms has been associated with diverse changes in immune responses, behavior and metabolism. The bidirectional interaction between circadian rhythm and metabolism is well established, and metabolic diseases are associated with dysregulation of circadian rhythms.

Previous work by Hirota et al. (Science, 2012) resulted in the identification of compounds that interact with and stabilize Cryptochrome (Cry) proteins, which are key regulators of the intracellular circadian machinery. These compounds were found to modulate both core clock and metabolic gene transcription in vitro. We developed a series of Cry stabilizers with improved drug-like properties and tested them in two mouse models of diabetes: diet-induced obese (DIO) and db/db.

In vivo, Compound A alters expression of the core clock genes as determined by quantitative reverse transcription PCR (RT-PCR), reducing Period2 (Per2) gene expression and causing a phase delay in Bmal1 gene expression. After 7 days of oral QD dosing of Compound A, we found significant changes in glucose metabolism as measured by Fasting Blood Glucose (FBG) and Oral Glucose Tolerance Test (OGTT). These results were comparable to the efficacy of rosiglitazone and sitagliptin in these models, but were not associated with weight gain. Reductions in plasma insulin levels and increased insulin sensitivity were also observed in both models; Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values were significantly reduced, indicating re-sensitization. Compound A was also tested in the rat ZDF model of diabetes and significant changes were again found in glucose metabolism, comparable in efficacy to rosiglitazone.

Taken together, these data suggest that circadian rhythm modification represents a compelling new approach to treating type 2 diabetes and other metabolic disorders.

125-LB

Energy Balance Following Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibition

GIULIA FERRANNINI, THOMAS HACH, SUSANNE CROWE, ELE FERRANNINI, *Pisa, Italy, Ingelheim, Germany*

SGLT2 inhibitors lower glycemia by inducing urinary glucose excretion (UGE), with the attendant calorie loss. Evidence suggests that the resulting weight loss (WL) is less than expected from UGE. To quantify this phenomenon we analyzed data from 86 type 2 diabetic (T2D) patients (39 women, age = 58 ± 9 years, BMI = 29.8 ± 4.5 kg/m^2, HbA_{1c} = 7.8 ± 0.8%, FPG = 169 ± 41 mg/dL, eGFR = 89 ± 19 ml·min^{-1}·1.73m^2, μ ± SD), the per-protocol completers cohort of a clinical trial who received empagliflozin (25 mg/day) for 90 weeks with frequent (n=11) assessments of body weight, eGFR, and FPG. Time-dependent glucose filtration was calculated as the product of eGFR and FPG, time-dependent UGE was estimated by assuming - from previous direct measurements - a quasi-linear relationship between fractional UGE and glycemia. At week 90, WL averaged -3.2 ± 4.2 kg (range -17.0 to +5.5); over 90 weeks, UGE averaged 54 ± 15 g/day (fractional UGE = 45 ± 4%). The relation of calorie-to-weight changes was estimated using a mathematical model (http://bwsimulator.niddk.nih.gov) that simulates the time-course of WL for a given change in calorie balance. The observed WL corresponded to a calorie deficit of -78 ± 103 kcal/day. On the other hand, the observed calorie loss (-217 ± 59 kcal/day) predicted a WL of -8.7 ± 2.4 kg (range -4.0 to -15.3 kg) over 90 weeks. Thus, patients lost only 38 ± 53% of the WL predicted by their glycosuria. As previous studies showed that empagliflozin does not affect either resting or meal-induced energy expenditure, patients likely increased their energy intake (by an estimated +138 ± 116 kcal/day). This excess calorie intake was inversely related to baseline BMI (partial r=-0.33, p<0.01) and positively to baseline eGFR (partial r=0.30, p<0.01). In conclusion, chronic glycosuria elicits an adaptive increase in energy intake, particularly in leaner patients with preserved renal function. Combining SGLT2 inhibition with strategies to maintain energy intake or curb appetite is expected to be associated with major WL.

Supported By: Boehringer Ingelheim

126-LB

Factors Associated with Progression of Type 2 Diabetes and Impact of Treatment with Saxagliptin in the SAVOR-TIMI 53 Study

GIL LEIBOWITZ, OFRI MOSENZON, DEEPAK L. BHATT, BOAZ HIRSHBERG, CHERYL WEI, AVIVIT CAHN, GYÖRGY JERMENDY, WAYNE H-H SHUE, JOSE LOPEZ-SENDON, BENJAMIN M. SCIRICA, ITAMAR RAZ, *Jerusalem, Israel, Boston, MA, Wilmington, DE, Budapest, Hungary, Taichung, Taiwan, Madrid, Spain*

In T2D, glycemic control often deteriorates over time, requiring intensification of treatment. We aimed to identify factors associated with progression of diabetes and studied the impact of saxagliptin, a DPP-4 inhibitor, on diabetes progression. In addition, we evaluated the effect of saxagliptin on beta cell function as reflected by a decline in HOMA2-β.

We studied the association of clinical and biochemical parameters with diabetes progression in the SAVOR-TIMI 53 study, a randomized clinical trial of 16,492 patients with T2D treated with saxagliptin *vs.* placebo added to current anti-diabetic medications for a median of 2.1 years. Diabetes progression was defined by 1) HbA1C increase ≥0.5%, 2) initiation of new anti-diabetic medications, 3) increase in oral medication dose or 4) ≥25% increase in insulin dose for ≥3 months. HOMA2-β was measured at baseline and at year 2 in 4134 patients (25.1% of trial).

Progression of diabetes during the study occurred in 54.7% of all subjects. Compared with placebo, treatment with saxagliptin decreased the risk of diabetes progression (OR 0.60; 95% CI 0.57-0.65; p<0.001). The occurrence of an HbA1C increase of ≥0.5% was decreased by 30%; initiation of insulin was decreased by 30% and the increase in dose for an oral hypoglycemic medication or insulin by 19% in patients treated with saxagliptin compared with placebo. At 2 years, HOMA2-β was decreased by 7.6% with placebo, compared with 2.7% with saxagliptin (p=0.0004). A multivariate analysis that included baseline demographics, biochemical parameters, and medical treatments showed that older age, lower HDL, lower baseline HOMA2-β, and baseline sulfonylurea use were significantly associated with diabetes progression.

Saxagliptin decreased the progression of diabetes via improved glycemic indices and fewer concomitant anti-hyperglycemic agents compared with placebo, which may be related to reduced natural decline in β-cell function.

Supported By: AstraZeneca

127-LB

Dual Add-On Therapy in Poorly Controlled Type 2 Diabetes on Metformin: Randomized, Double-Blind Trial of Saxagliptin+Dapagliflozin vs. Saxagliptin and Dapagliflozin Alone

JULIO ROSENSTOCK, LARS HANSEN, PAMELA ZEE, YAN LI, WILLIAM COOK, BOAZ HIRSHBERG, NAYYAR IQBAL, *Dallas, TX, Princeton, NJ, Wilmington, DE*

SGLT2 and DPP-4 inhibitors have complementary mechanisms of action that can potentially improve glucose control with weight loss and low risk of hypoglycemia. We compared the efficacy and safety of dual add-on of saxagliptin (SAXA) and dapagliflozin (DAPA) to SAXA and DAPA alone. In this 24-week, multicenter, randomized, double-blind, active-controlled trial, adults with type 2 diabetes (T2D) and A1C ≥8.0% and ≤12.0%, received SAXA 5 mg and DAPA 10 mg once daily compared to SAXA and placebo (PBO) or DAPA and PBO on background of metformin XR ≥1500 mg/d. Primary end point was the change in A1C from baseline to week 24. Safety and tolerability assessments included adverse events (AEs) and hypoglycemia. 534 patients were randomized. Mean ± SD A1C at baseline in SAXA+DAPA, SAXA+PBO, and DAPA+PBO groups was 8.9 ± 1.2%, 9.0 ± 1.1%, and 8.9 ± 1.2%, respectively. Adjusted reduction from baseline in A1C was -1.47% in SAXA+DAPA compared to -0.88% in SAXA+PBO (difference –0.59%; 95% CI [-0.81, -0.37]; P<0.0001) and -1.20% in DAPA+PBO (difference –0.27%; 95% CI [-0.48, -0.05]; P<0.02). The adjusted proportion achieving A1C <7% was 41% in SAXA+DAPA compared to 18% in SAXA+PBO (difference of 23%; 95% CI [15, 32]) and 22%

in DAPA+PBO (difference of 19%; 95% CI [10, 28]). AEs occurred in 48.6%, 52.8% and 48.6% in SAXA+DAPA, SAXA+PBO and DAPA+PBO, respectively. Urinary and genital infections occurred with the expected frequency previously reported. Incidence of hypoglycemia was 1.1%, 0.6% and 1.1%, respectively with no episodes of major hypoglycemia. In conclusion, this first report of triple therapy adding a well-tolerated combination of DPP-4 and SGLT2 inhibitors to poorly controlled metformin-treated T2D demonstrated that the combination of SAXA and DAPA had greater improvements in glucose control than each component alone, bringing >40% of poorly controlled T2D to goal, with weight loss as DAPA alone and very low hypoglycemia risk.

Supported By: AstraZeneca/Bristol-Myers Squibb

128-LB

A Novel, Once-Weekly Oral DPP-4 Inhibitor Trelagliptin: A Phase 3, Double-Blind, Noninferiority Study in Japanese T2DM Patients

KOHEI KAKU, HITOSHI ONOUCHI, HIDEAKI MAEZAWA, SHINGO KURODA, NOBUYA INAGAKI, *Kurashiki, Japan, Osaka, Japan, Kyoto, Japan*

Trelagliptin is a novel dipeptidyl peptidase-4 (DPP-4) inhibitor, which is currently under development as a once-weekly oral anti-diabetic agent.

A phase 3, multicenter, randomized, double-blind, parallel-group, non-inferiority study was conducted to evaluate the efficacy and safety of once-weekly trelagliptin for 24 weeks with daily DPP-4 inhibitor (alogliptin) as a comparator in Japanese patients with type 2 diabetes mellitus (T2DM) with inadequate glycemic control despite diet and/or exercise therapy. A placebo group was also set as a reference group.

Patients were randomly assigned (allocation ratio 2:2:1) to receive either trelagliptin 100 mg once-weekly, alogliptin (Nesina) 25 mg daily or placebo (reference group).

A total of 243 patients were enrolled to either trelagliptin once-weekly group (n=101), alogliptin daily group (n=92) or placebo group (n=50). At baseline, patients had mean age (SD) of 58.9 (10.39) years, mean BMI of 24.96 (4.161) kg/m^2 and mean HbA1c of 7.78 (0.837)%. There was no major difference in baseline characteristics among the treatment groups.

As for efficacy, HbA1c was decreased significantly in trelagliptin group (-0.32%) and alogliptin group (-0.46%) compared to placebo group (0.24%) at the end of the treatment period (p<0.0001). The least square mean difference (trelagliptin - alogliptin) of change from baseline in HbA1c at the end of the treatment period was 0.11% (95% CI: -0.054 to 0.281). Non-inferiority of trelagliptin group to alogliptin group was demonstrated.

As for safety, the frequency of adverse events in trelagliptin group was similar to those in alogliptin group and in placebo group. No hypoglycemia was reported in trelagliptin group. In this study, trelagriptin was well tolerated and showed no major concern.

Once-weekly trelagliptin may provide a new treatment option for T2DM patients.

129-LB

Fixed Dose Combinations of Empagliflozin/Linagliptin for 24 Weeks in Drug-Naïve Patients with Type 2 Diabetes (T2DM)

ANDREW LEWIN, RALPH A. DEFRONZO, SANJAY PATEL, DACHENG LIU, RENEE KASTE, HANS J. WOERLE, ULI C. BROEDL, *Los Angeles, CA, San Antonio, TX, Bracknell, United Kingdom, Ridgefield, CT, Ingelheim, Germany*

A 52-week Phase III study evaluated the efficacy and safety of fixed dose combinations (FDCs) of empagliflozin/linagliptin (EMPA/LINA). Drug-naïve subjects with T2DM were randomized to EMPA 25 mg/LINA 5 mg (n=137), EMPA 10 mg/LINA 5 mg (n=136), EMPA 25 mg (n=135), EMPA 10 mg (n=134), or LINA 5 mg (n=135). Primary endpoint was change from baseline in HbA1c at week 24. Key secondary endpoints were changes from baseline in fasting plasma glucose (FPG) and weight, and percentage of subjects with baseline HbA1c ≥7% who had HbA1c <7% at week 24. Efficacy was evaluated in 667 subjects (mean [SD] age 54.6 [10.2] years; BMI 31.6 [5.6] kg/m^2).

At week 24, FDCs of EMPA/LINA reduced HbA1c, FPG and weight vs. LINA 5 mg. EMPA 10 mg/LINA 5 mg reduced HbA1c vs. EMPA 10 mg (table). Adverse events (AEs) were reported in 58.8%, 63.2%, 57.8%, 62.2% and 64.4% of subjects on EMPA 25 mg/LINA 5 mg, EMPA 10 mg/LINA 5 mg, EMPA 25 mg, EMPA 10 mg and LINA 5 mg, respectively, over 24 weeks. Confirmed hypoglycemic AEs (glucose ≤70 mg/dL and/or requiring assistance) were reported in 2 subjects on EMPA 25 mg and 1 each on EMPA 10 mg and LINA 5 mg; none required assistance.

In subjects with T2DM, FDCs of EMPA 25 mg or 10 mg/LINA 5 mg for 24 weeks significantly reduced HbA1c, FPG and weight vs. LINA 5 mg. HbA1c reductions were greater with EMPA 10 mg/LINA 5 mg than EMPA 10 mg, but similar with EMPA 25 mg/LINA 5 mg and EMPA 25 mg. All treatments were well tolerated.

	EMPA 25 mg/ LINA 5 mg (n=134)	EMPA 10 mg/ LINA 5 mg (n=135)	EMPA 25 mg (n=133)	EMPA 10 mg (n=132)	LINA 5 mg (n=133)
HbA1c (%)					
Baseline	7.99 (0.08)	8.04 (0.08)	7.99 (0.08)	8.05 (0.09)	8.05 (0.08)
Change from baseline at week 24	-1.08 (0.07)	-1.24 (0.07)	-0.95 (0.07)	-0.83 (0.07)	-0.67 (0.07)
Difference vs. EMPA 25 mg (95% CI)	-0.14 (-0.33, 0.06)	–	–	–	–
Difference vs. EMPA 10 mg (95% CI)	–	-0.41 (-0.61, -0.21)***	–	–	–
Difference vs. LINA 5 mg (95% CI)	-0.41 (-0.61, -0.22)***	-0.57 (-0.76, -0.37)***	–	–	–
Subjects with HbA1c ≥7% at baseline† who had HbA1c <7% at week 24, n (%)	67 (55.4)	76 (62.3)	49 (41.5)	47 (38.8)	41 (32.3)
Odds ratio vs. EMPA 25 mg (95% CI)	1.89 (1.1, 3.3)*	–	–	–	–
Odds ratio vs. EMPA 10 mg (95% CI)	–	2.96 (1.7, 5.2)***	–	–	–
Odds ratio vs. LINA 5 mg (95% CI)	3.1 (1.8, 5.3)***	4.3 (2.5, 7.5)***	–	–	–
FPG (mg/dL)					
Baseline	156.1 (3.1)	157.2 (3.1)	152.8 (3.4)	160.3 (3.6)	156.0 (3.2)
Change from baseline at week 24	-29.6 (2.7)	-28.2 (2.7)	-24.2 (2.7)	-22.4 (2.7)	-5.9 (2.7)
Difference vs. EMPA 25 mg (95% CI)	-5.3 (-12.7, 2.1)	–	–	–	–
Difference vs. EMPA 10 mg (95% CI)	–	-5.8 (-13.3, 1.6)	–	–	–
Difference vs. LINA 5 mg (95% CI)	-23.6 (-31.1, -16.2)***	-22.3 (-29.7, -14.9)***	–	–	–
Body weight (kg)					
Baseline	87.9 (1.6)	87.3 (1.6)	86.7 (1.7)	87.8 (2.1)	89.5 (1.7)
Change from baseline at week 24	-2.0 (0.4)	-2.7 (0.4)	-2.1 (0.4)	-2.3 (0.4)	-0.8 (0.4)
Difference vs. EMPA 25 mg (95% CI)	0.1 (-0.9, 1.1)	–	–	–	–
Difference vs. EMPA 10 mg (95% CI)	–	-0.5 (-1.5, 0.5)	–	–	–
Difference vs. LINA 5 mg (95% CI)	-1.2 (-2.2, -0.2)*	-2.0 (-3.0, -1.0)***	–	–	–

Baseline values are mean (SE). Changes are adjusted mean (SE) based on ANCOVA in subjects treated with ≥1 dose of trial medication who had a baseline HbA1c and on-treatment HbA1c value, with last observation carried forward imputation. Differences vs. EMPA in changes in body weight were exploratory analyses. Data at week 24 were analyzed before study completion.

†n=121 for EMPA 25 mg/LINA 5 mg, n=122 for EMPA 10 mg/LINA 5 mg, n=118 for EMPA 25 mg, n=121 for EMPA 10 mg, n=127 for LINA 5 mg. *p<0.05; **p<0.01; ***p<0.001.

Supported By: Boehringer Ingelheim/Eli Lilly and Company

130-LB

Fixed-Dose Combinations of Empagliflozin/Linagliptin for 24 Weeks as Add-On to Metformin in Patients with Type 2 Diabetes (T2DM)

RALPH A. DEFRONZO, ANDREW LEWIN, SANJAY PATEL, DACHENG LIU, RENEE KASTE, HANS J. WOERLE, ULI C. BROEDL, *San Antonio, TX, Los Angeles, CA, Bracknell, United Kingdom, Ridgefield, CT, Ingelheim, Germany*

A 52-week Phase III study evaluated the efficacy and safety of fixed dose combinations (FDCs) of empagliflozin/linagliptin (EMPA/LINA) as add-on to stable-dose metformin in subjects with T2DM. Subjects were randomized to EMPA 25 mg/LINA 5 mg (n=137), EMPA 10 mg/LINA 5 mg (n=136), EMPA 25 mg (n=141), EMPA 10 mg (n=140), or LINA 5 mg (n=132). Primary endpoint was change from baseline in HbA1c at week 24. Key secondary endpoints were changes from baseline in fasting plasma glucose (FPG) and weight, and percentage of subjects with baseline HbA1c ≥7% who had HbA1c <7% at week 24.

In 674 subjects (mean [SD] age 56.2 [10.2] years; BMI 31.0 [5.5] kg/m^2), FDCs of EMPA/LINA reduced HbA1c and FPG vs. the respective monotherapies (table). Adverse events (AEs) were reported in 54.7%, 54.4%, 63.1%, 57.1% and 54.5% of subjects on EMPA 25 mg/LINA 5 mg, EMPA 10 mg/LINA 5 mg, EMPA 25 mg, EMPA 10 mg and LINA 5 mg, respectively, over 24 weeks. Confirmed hypoglycemic AEs (glucose ≤70 mg/dL and/or requiring assistance) were reported in 2 subjects each on EMPA 25 mg/LINA 5 mg, EMPA 10 mg/LINA 5 mg, EMPA 10 mg and LINA 5 mg, and 4 on EMPA 25 mg; none required assistance.

As add-on to metformin in subjects with T2DM, FDCs of EMPA 25 mg/LINA 5 mg and EMPA 10 mg/LINA 5 mg for 24 weeks significantly reduced HbA1c and

FPG versus LINA 5 mg and vs. respective EMPA monotherapies, and reduced weight vs. LINA 5 mg. All treatments were well tolerated.

	EMPA 25 mg/ LINA 5 mg (n=134)	EMPA 10 mg/ LINA 5 mg (n=135)	EMPA 25 mg (n=140)	EMPA 10 mg (n=137)	LINA 5 mg (n=128)
HbA1c (%)					
Baseline	7.90 (0.07)	7.95 (0.07)	8.02 (0.07)	8.00 (0.08)	8.02 (0.08)
Change from baseline at week 24	-1.19 (0.06)	-1.08 (0.06)	-0.62 (0.06)	-0.66 (0.06)	-0.70 (0.06)
Difference vs. EMPA 25 mg (95% CI)	-0.58 (-0.75, -0.41)***	–	–	–	–
Difference vs. EMPA 10 mg (95% CI)	-	-0.42 (-0.59, -0.25)***	–	–	–
Difference vs. LINA 5 mg (95% CI)	-0.50 (-0.67, -0.32)***	-0.39 (-0.56, -0.21)***	–	–	–
Subjects with HbA1c ≥7% at baseline† who had HbA1c	76 (61.8)	74 (57.8)	43 (32.6)	35 (28.0)	43 (36.1)
Odds ratio vs. EMPA 25 mg (95% CI)	4.19 (2.32, 7.57)***	–	–	–	–
Odds ratio vs. EMPA 10 mg (95% CI)	–	4.50 (2.47, 8.18)***	–	–	–
Odds ratio vs. LINA 5 mg (95% CI)	3.50 (1.92, 6.36)***	2.80 (1.56, 5.00)***	–	–	–
FPG (mg/dL)					
Baseline	154.6 (2.9)	156.7 (3.0)	159.9 (3.2)	161.6 (3.0)	156.4 (2.7)
Change from baseline at week 24	-35.3 (2.5)	-32.2 (2.5)	-18.8 (2.5)	-20.8 (2.5)	-13.1 (2.6)
Difference vs. EMPA 25 mg (95% CI)	-16.4 (-23.4, -9.5)***	–	–	–	–
Difference vs. EMPA 10 mg (95% CI)	–	-11.3 (-18.3, -4.4)**	–	–	–
Difference vs. LINA 5 mg (95% CI)	-22.2 (-29.3, -15.1)***	-19.1 (-26.2, -12.0)***	–	–	–
Body weight (kg)					
Baseline	85.5 (1.8)	86.6 (1.6)	87.7 (1.5)	86.1 (1.6)	85.0 (1.6)
Change from baseline at week 24	-3.0 (0.3)	-2.6 (0.3)	-3.2 (0.3)	-2.5 (0.3)	-0.7 (0.3)
Difference vs. EMPA 25 mg (95% CI)	0.2 (-0.7, 1.0)	–	–	–	–
Difference vs. EMPA 10 mg (95% CI)	–	-0.1 (-0.9, 0.8)	–	–	–
Difference vs. LINA 5 mg (95% CI)	-2.3 (-3.2, -1.4)***	-1.9 (-2.8, -1.1)***	–	–	–

Baseline values are mean (SE). Changes are adjusted mean (SE) based on ANCOVA in subjects treated with ≥1 dose of trial medication who had a baseline HbA1c and on-treatment HbA1c value, with last observation carried forward imputation. Differences vs. EMPA in changes in body weight were exploratory analyses. Data at week 24 were analyzed before study completion.

†n=123 for EMPA 25 mg/LINA 5 mg, n=128 for EMPA 10 mg/LINA 5 mg, n=132 for EMPA 25 mg, n=125 for EMPA 10 mg, n=119 for LINA 5 mg. *p<0.001.

Supported By: Boehringer Ingelheim/Eli Lilly and Company

131-LB

Saxagliptin Effect on Urinary Albumin/Creatinine Ratio (ACR) and eGFR: Analysis of Pooled Phase 3 Studies

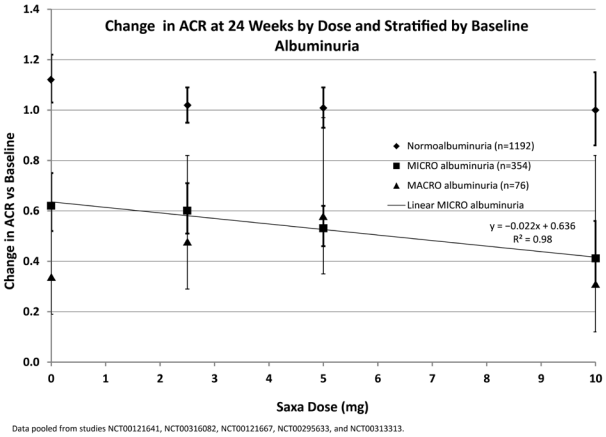
ROBERT FREDERICH, NAYYAR IQBAL, MIKAELA SJÖSTRAND, WILLIAM COOK, BOAZ HIRSHBERG, *Princeton, NJ, Wilmington, DE*

Saxagliptin (SAXA) significantly reduced the proportion with micro- (ACR 30-300 mg/g) and macro- (>300 mg/g) albuminuria in the SAVOR outcome study. This prompted a *post-hoc* pooled analysis of 5 phase 3, double-blind, placebo (PBO) controlled studies (2 drug-näive, plus add-on to metformin, SU, and TZD).

At 24 weeks there was a net shift in the size of the population with albuminuria (-4.6%, -6.9%, -15.0%, -28.9% for PBO, 2.5, 5, & 10 mg SAXA respectively). Further analysis revealed (Figure):

1. Normoalbuminuria (geometric mean ACR = 8-9 mg/g across arms): All SAXA doses prevented the rise in ACR vs. baseline (BL) seen with PBO.
2. Microalbuminuria (ACR = 61-76 mg/g): There was a dose linear reduction in ACR vs. BL.
3. Macroalbuminuria (ACR = 823-1054 mg/g): All 4 arms had a reduction in ACR vs. BL. The wide 95% CI (excluding 1) prevented seeing a clear pattern.
4. eGFR in the full study pool: From BL (108-115 ml/min), there was a small mean reduction in eGFR for PBO (-1.8), 2.5 mg (-2.3) and 5 mg SAXA (-3.0), with 95% CI excluding zero, and a small increase in eGFR for 10 mg SAXA (2.0 [0.1, 4.0]).

In summary, as observed in SAVOR, SAXA reduced the proportion with albuminuria. Though limited by the size of the albuminuria subpopulations, the data suggest: 1) in those without albuminuria SAXA prevents the upward drift observed with PBO and 2) in those with microalbuminuria SAXA treatment reduces albuminuria dose proportionately.



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132-LB

LX4211, a Dual Inhibitor of SGLT1/SGLT2, Reduces Postprandial Glucose in Patients with Type 2 Diabetes Mellitus and Moderate to Severe Renal Impairment

PABLO LAPUERTA, ARTHUR SANDS, IKE OGBAA, PAUL STRUMPH, DAVID R. POWELL, PHILLIP BANKS, BRIAN ZAMBROWICZ, *The Woodlands, TX*

The prevalence of renal impairment (RI) in type 2 diabetes mellitus (T2DM) is ≥20%. Since selective sodium-glucose co-transporter 2 (SGLT2) inhibitors target only the kidney, they have reduced efficacy in T2DM patients with RI. Because LX4211 blocks both SGLT2-mediated renal glucose reabsorption and SGLT1-mediated gastrointestinal glucose absorption, it should benefit patients with T2DM and RI by significantly reducing postprandial glucose (PPG) levels.

The primary objective was to evaluate the effect of LX4211 on 4-hour PPG AUC change from baseline to Day 7 in patients with T2DM and baseline renal function (eGFR) ≥15 and ≤59 mL/min/1.73 m^2 (calculated by MDRD). Patients (N=31) were randomly assigned to receive LX4211 (400 mg, n=16) or placebo (n=15) 15 minutes before a standard breakfast on 7 consecutive days. Glucose and GLP-1 were measured 15 minutes prior to breakfast and 1, 2, 2.5, 3, and 4 hours post breakfast at baseline and on Day 7.

LX4211 significantly reduced mean PPG $AUC_{(-15min\ -\ 4hr)}$ by 169.3 mg·hr/dL compared to placebo in all treated patients, p=0.003. In patients with baseline eGFR values <45 mL/min/1.73 m^2, the LX4211-treated patients (N=5) had a 259.6 mg·hr/dL mean PPG reduction compared to the placebo patients (N=9), p=0.002. Compared to placebo, LX4211 also showed significant elevations in the mean change in incremental AUC between baseline and Day 7 for total GLP-1 of 9.7 pmol·hr/L (p=0.017) and for active GLP-1 of 4.7 pmol·hr/L (p=0.042) in all patients. There were no serious adverse events (SAEs) and no discontinuations due to AEs. There were 3 mild cases of hypoglycemia reported as treatment-emergent adverse events during the trial: 1 in the LX4211-treated patients and 2 in placebo patients.

These results indicate that LX4211 may enhance glycemic control in patients with moderate to severe RI.

133-LB

Effect of Empagliflozin (EMPA) Monotherapy on Postprandial Glucose (PPG) and 24-h Glucose Variability Using Continuous Glucose Monitoring (CGM) in Japanese Patients with Type 2 Diabetes (T2DM)

RIMEI NISHIMURA, YUKO TANAKA, KAZUKI KOIWAI, KOHEI INOUE, THOMAS HACH, AFSHIN SALSALI, SØREN S. LUND, ULI C. BROEDL, *Tokyo, Japan, Ingelheim, Germany, Ridgefield, CT*

A Phase IIIb randomized study evaluated the effect of EMPA on PPG and 24-h glucose variability in Japanese patients with T2DM.

Patients (N=60; baseline mean [SD] HbA1c 7.91 [0.80]%; age 62.7 [8.5] years; BMI 24.3 [3.2] kg/m^2) were randomized to EMPA 10 mg (n=20), EMPA 25 mg

For author disclosure information, see page LB91.

(n=19) or placebo (PBO; n=21) qd double-blind as monotherapy for 28 days. A meal tolerance test and blinded CGM for 24 h were performed at baseline and on days 1 and 28. Primary endpoint was change from baseline in area under the glucose concentration-time curve 3 h after breakfast (AUC_{1-4h} for PPG) at day 28. CGM endpoints included changes from baseline in mean 24-h glucose and AUC for glucose ≥180 mg/dL within 3 h of each meal at days 1 and 28.

EMPA 10 mg and 25 mg significantly reduced AUC_{1-4h} for PPG, mean 24-h glucose vs. PBO at days 1 and 28 (Table). EMPA reduced AUC (≥180 mg/dL) within 3 h of breakfast (Table), lunch and dinner vs. PBO at days 1 and 28. Adverse events (AEs) were reported in 15.0%, 15.8% and 9.5% of patients on EMPA 10 mg, EMPA 25 mg and PBO, respectively. No confirmed hypoglycemic AEs (plasma glucose ≤70 mg/dL and/or requiring assistance) were reported.

To conclude, EMPA 10 mg or 25 mg for 28 days significantly reduced PPG, mean 24-h glucose and AUC (≥180 mg/dL) within 3 h of each meal vs. PBO from the first dose in Japanese patients with T2DM. EMPA was well tolerated.

	Placebo (n=20)	Empagliflozin 10 mg (n=20)	Empagliflozin 25 mg (n=19)
AUC_{1-4h} for PPG (mg·h/dL)			
Baseline†	672.6 (18.0)	680.4 (20.6)	658.1 (26.7)
Change from baseline at day 1	7.9 (9.9)	-89.2 (10.4)	-83.7 (10.5)
Difference vs. placebo (95% CI)		-97.1 (-126.5, -67.8)***	-91.6 (-120.4, -62.8)***
Change from baseline at day 28	-18.1 (13.9)	-103.6 (14.2)	-122.9 (14.4)
Difference vs. placebo (95% CI)		-85.5 (-126.0,-45.0)***	-104.9 (-144.8,-65.0)***
24-h mean glucose (mg/dL)			
Baseline†	181.4 (6.4)	181.3 (5.8)	178.4 (7.7)
Change from baseline at day 1	0.3 (2.1)	-20.5 (2.2)	-23.6 (2.2)
Difference vs. placebo (95% CI)		-20.8 (-27.0, -14.7)***	-23.9 (-30.0, -17.9)***
Change from baseline at day 28	-5.8 (3.7)	-30.3 (3.8)	-37.6 (3.9)
Difference vs. placebo (95% CI)		-24.5 (-35.4,-13.6)***	-31.7 (-42.5,-20.9)***
AUC (≥180 mg/dL) within 3 h of breakfast (mg·h/dL)			
Baseline†	107.5 (21.5)	108.6 (17.5)	103.4 (23.7)
Change from baseline at day 1	41.2 (9.8)	-31.9 (10.3)	-44.7 (10.4)
Difference vs. placebo (95% CI)		-73.1 (-102.2, -44.0)***	-85.9 (-114.5, -57.4)***
Change from baseline at day 28	-8.1 (10.8)	-62.9 (11.1)	-71.7 (11.3)
Difference vs. placebo (95% CI)		-54.8 (-86.4, -23.2)**	-63.6 (-94.8, -32.3)***

Baseline values are mean (SE), change from baseline values are adjusted mean (SE) based on ANCOVA.

†For day 1 analyses, n=21 for placebo (mean [SE] baseline of AUC_{1-4h} for PPG: 682.8 [19.9] mg·h/dL; mean [SE] baseline of 24-h mean glucose: 184.1 [6.7] mg/dL; mean [SE] baseline of AUC (≥180 mg/dL) within 3 h of breakfast: 119.2 [23.5] mg·h/dL).

**p<0.001.

Supported By: Boehringer Ingelheim/Eli Lilly and Company

134-LB

Validating the Dual Modes of Action of HMS5552, a Novel Pancreatic- and Hepatic-Targeting Glucokinase Activator

LI CHEN, YING LENG, XIAOWEI JIN, YONGGUO LI, XUENING LI, YI ZHANG, *Shanghai, China*

HMS5552 is a novel allosteric glucokinase (GK) activator targeting both pancreatic and liver GK that enhances glucose stimulated insulin release (GSIR) and suppresses hepatic glucose production. Here, we present preclinical and clinical Phase 1a data to demonstrate this dual-targeting mode of action.

In vitro, HMS5552 enhanced GSIR in rodent pancreatic islets and increased glucose uptake in cultured rodent primary hepatocytes. In vivo at low doses in rodents (3 mg/kg), HMS5552 reduced fasting glucose (24.9%) with no increase in fasting insulin secretion, in contrast to significantly reducing post-meal glucose (48.2%) while increasing post-meal insulin. At higher 10 and 30 mg/kg dose groups, HMS5552 showed insulin secretion at both fasting and post-meal states, accompanied by glucose lowering in both states.

Sixty Chinese healthy volunteers orally received either placebo or single dose of HMS5552 under fasting conditions in 6 dose cohorts (5, 10, 15, 25, 35 and 50mg). HMS5552 was safe and well tolerated, showed dose proportional increase in plasma exposure and had good PK properties supporting BID therapeutic dosing. HMS555s demonstrated dose-dependent reductions in fasting glucose levels (average change from baseline of -11% at 5mg to -31% at 50mg) without significant increases in fasting insulin which is consistent with reductions in hepatic glucose production. In contrast, significant dose-dependent increases in post-meal insulin (average difference from post-meal placebo AUC of 2% at 5mg to 131% at 50mg) were consistent with GK pancreatic β cell activation.

In conclusion, the significant increase in insulin after meals but not during fasting periods in both preclinical and the Phase 1a clinical studies supports the dual-target mode of action of GK in mediating both pancreatic GSIR and lowering fasting glucose by reduction of hepatic glucose production.

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135-LB

Risk of New Onset Heart Failure in Patients Using Sitagliptin

DEAN T. EURICH, DANIALA L. WEIR, SCOT H. SIMPSON, AMBIKAIPAKAN SENTHILSELVAN, FINLAY A. MCALISTER, *Edmonton, AB, Canada*

Recent randomized controlled trials have suggested that DPP-4 inhibitors may be associated with an increased risk of incident heart failure (HF); although results are inconsistent. Thus, we examined whether patients using sitagliptin, the most widely prescribed DPP-4 inhibitor in the U.S., at the time of acute coronary syndrome (ACS) are at greater risk for incident heart failure (HF) than those not exposed.

Using a large commercially insured U.S. claims database, diabetes subjects without a history of HF in the 3 years prior to admission to hospital for an ACS event were identified based on ICD-9 CM codes between 2004 to 2010. We used a nested case control design whereby cases were patients who developed incident HF within 30 days of admission to hospital for ACS and matched (using risk set sampling) by age and sex with up to 10 controls with no HF prior to the index date for their given case. Subjects exposed or not exposed to sitagliptin in the 90 days prior to ACS admission were compared using conditional logistic regression after adjustment for demographics, clinical & laboratory data, pharmacy claims, health care utilization and propensity scores (conditional probability of being treated with metformin or sulfonylurea or insulin or sitagliptin).

In total, 457 HF cases were matched to 4,570 controls. Average age of subjects was 55 years, 65% were male, 71% had a history of dyslipidemia and 81% had a history of hypertension. Overall, 11 of 147 sitagliptin users (7%) developed HF compared to 446 of 4,880 non-users (9%) (adjusted odds ratio [aOR]: 0.75, 95% CI: 0.38 – 1.46; p=0.40). Similarly, sitagliptin use pre-ACS was not associated with an increased risk of death or HF combined (7% vs. 9%, aOR: 0.66, 95% CI: 0.34-1.28).

In our large population based cohort, sitagliptin use was not associated with an increased risk of HF following admission to hospital for ACS, raising doubts around the hypothesis that DPP-4 inhibitors have adverse cardiovascular effects in patients with type 2 diabetes.

136-LB

Treatment Maintenance Duration of Dual Therapy with Metformin and Sitagliptin in Type 2 Diabetes: The Odyssee Observational Study

PAUL VALENSI, GERARD DE POUVOURVILLE, NATHALIE BENARD, CELINE CHANUT-VOGEL, CHRISTINE MOISAN, CHRISTIAN KEMPF, JEAN DALLONGEVILLE, *Bondy, France, Paris, France, Courbevoie, France, Lille, France*

Sulfonylurea and DPP4 inhibitors are usually prescribed for T2DM patients in combination with metformin. Odyssée, a prospective, real-world, observational study conducted in France in primary care practices, compared the duration of maintenance of treatment without modification (withdrawal, substitution or add-on therapy) in T2DM patients in whom dual therapy with metformin + sitagliptin (MetSita) or metformin + sulfonylurea (MetSu) was initiated, based on physician choice. Patients were not randomized and were followed for a period of up to three years.

At baseline, differences between the two arms (MetSita [n = 1874] and MetSu [n = 733]) were modest (mean age: 62.4 vs. 64.2 years, BMI: 30.3 vs. 29.6 kg/m^2, diabetes duration: 6.4 vs. 7 years, respectively). HbA1c levels were similar (7.5 vs. 7.6%).

The median treatment duration for patients in the MetSita group was longer than the MetSu group (median treatment duration 43.2 vs. 20.2 months, respectively, between-group difference 23 months, log-rank p <0.0001).This difference persisted after adjustment for baseline differences with propensity score and *application of maximum bias* hypothesis for missing data (42.4 vs. 20.2 months). A similar reduction in HbA1c was noted in both arms (- 0.6%) and the incidence of hypoglycemia (prior to treatment modification) was lower in the MetSita arm (9.7% vs. 21.0%).

Conducted in real-life conditions, the Odyssée study shows that combined therapy MetSita is maintained without treatment modification longer than combined therapy MetSu. In addition, the study confirms that glycemic efficacy is similar, with a lower incidence of symptomatic hypoglycemia with MetSita compared to MetSu.

Supported By: MSD

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—PHARMACOLOGIC TREATMENT OF COMPLICATIONS

137-LB

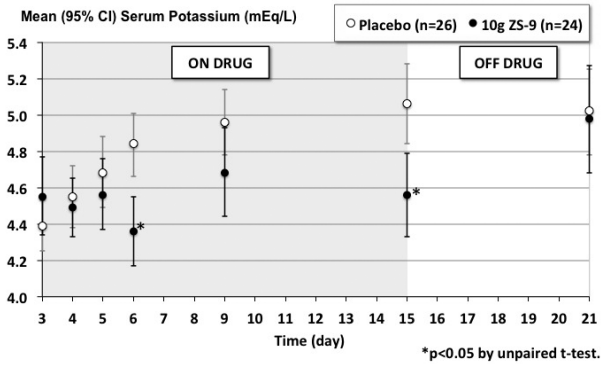
ZS-9 Achieves and Maintains Normal K+ in Hyperkalemic Patients with Diabetes on RAASi

DAVID K. PACKHAM, WAJEH Y. QUNIBI, PHILIP T. LAVIN, ALEX YANG, HENRIK S. RASMUSSEN, *Melbourne, Australia, San Antonio, TX, Framingham, MA, Belmont, CA, Coppell, TX*

Hyperkalemia (HK) is a serious finding in patients (pts) with diabetes mellitus (DM) and limits use of renin-angiotensin-aldosterone system inhibitors (RAASi). ZS-9 is a cation exchanger designed to entrap potassium (K^+) in the gut. We present efficacy and tolerability in a subset of DM pts on RAASi treated with 10g ZS-9 or placebo (PBO) from a Phase 3 randomized double-blind, controlled trial of ZS-9 in pts with HK. In the acute phase, pts with serum K^+ 5.0-6.5 mEq/L randomized (1:1) to 10g ZS-9 or PBO orally 3X daily (TID; 30g total daily) were treated for 48 hr. For the extended phase, pts in the 10g TID group who achieved normokalemia acutely (K^+ 3.5-5.0 mEq/L) were re-randomized 1:1 to 10g ZS-9 or PBO but given once daily (QD; 10g total daily) for Day 3-15. RAASi were kept constant. In the acute phase, 56 pts randomized to 10g ZS-9 TID and 66 to PBO had DM and were on RAASi (baseline mean K^+, 5.3 mEq/L). At 48 hr, K^+ decreased by -0.74 mEq/L with 10g ZS-9 TID (vs. -0.26 mEq/L for PBO; p<0.001). Of 50 pts on 10g ZS-9 TID acutely who entered the extended phase, the 24 pts treated with 10g ZS-9 QD maintained normokalemia during Days 3-15 whereas K^+ levels increased in 26 pts switched to PBO (Figure).

The AE incidence was comparable between groups in both phases (p=ns). 10g ZS-9 was effective in achieving and maintaining serum K^+ <5.0 mEq/L in DM pts on RAASi, with comparable AEs to placebo, indicating that ZS-9 might enable continuation of RAASi in DM pts with HK.

Extended Treatment Mean Serum K^+ for 10g ZS-9 vs Placebo in Patients with DM on RAASi



Supported By: ZS Pharma, Inc.

138-LB

Risk of Hypoglycemia in People Receiving Linagliptin: Pooled Data from 1,489 Adults Aged = 65 Years with Type 2 Diabetes Mellitus (T2DM)

KAMLESH KHUNTI, MICHAEL NAUCK, ATSUSHI ARAKI, SUSANNE CROWE, YAN GONG, DOUGLAS CLARK, MAXIMILIAN VON EYNATTEN, HANS-JUERGEN WOERLE, *Leicester, United Kingdom, Bad Lauterberg im Harz, Germany, Tokyo, Japan, Ingelheim, Germany, Ridgefield, CT*

Risk of hypoglycemia (HYPO) in elderly patients with T2DM is a major concern, especially when drug regimens include either insulin (INS) or secretagogues (SECR). We pooled data from a global clinical trials program to further assess the safety, focusing on HYPO, of the DPP-4 inhibitor linagliptin (LINA). Adults with T2DM aged ≥65 years who participated in 11 randomized, placebo (PBO)-controlled, Phase III trials were included. Efficacy was assessed by change in HbA1c from baseline to Week 24 using the full analysis set (FAS). Incidence of confirmed HYPO (plasma glucose ≤70 mg/dL) or severe HYPO (requiring third-party assistance) was assessed in the treated set (TS) with consideration for background therapy: regimens including INS but no SECR, SECR but no INS, or neither therapy. Overall, 1489 patients were treated (TS: LINA, n=948; PBO, n=541). Mean ± SD age was 70.9 ± 4.6 y (range, 65-91). In both treatment groups (FAS: LINA, n=936; PBO, n=530), mean baseline HbA1c was 8.1 ± 0.8%. Linagliptin significantly decreased HbA1c at Week 24 by a PBO-adjusted mean (95% CI) of –0.60% (–0.69, –0.51; p <0.0001). Incidence of confirmed HYPO was 26.3% in the LINA group and 34.0% in the PBO group (RR: 0.77 [95% CI: 0.66, 0.91; p <0.05]). In the subgroup of patients receiving INS but no SECR (LINA, n=247; PBO, n=256), incidence was 53.4% vs. 55.9%, respectively (RR: 0.96 [CI: 0.82, 1.12; p ≥0.05]). In the subgroup receiving a SECR but no INS (LINA, n=309; PBO, n=126), incidence was 32.0% vs. 25.4% (RR: 1.26 [CI: 0.90, 1.77; p ≥0.05]). Finally, in those whose regimens included neither SECR nor INS (LINA, n=371; PBO, n=152), incidence was 1.3% vs. 3.3% (RR: 0.41 [CI: 0.12, 1.39; p ≥0.05]). Overall, incidence of severe HYPO was low in both groups (LINA, 0.8%; PBO, 1.3%). In an elderly population, overall risk of HYPO was not increased when LINA was added to improve hyperglycemia, with lower incidence rates compared to PBO when LINA was given with background INS but higher rates with background SECR.

Supported By: Boehringer Ingelheim Pharma GmbH & Co. KG

139-LB

Metformin Action Prevents Sedentariness-induced Damages in Mice

LIVIO LUZI, ILEANA TERRUZZI, PAMELA SENESI, ANNA MONTESANO, ROBERTO CODELLA, STEFANO BENEDINI, *Milan, Italy*

Metformin (Metf), a widely prescribed drug to treat type 2 diabetes, is being increasingly considered for treatment and prevention of sedentariness damages, insulin resistance and obesity, as well as for the extension of healthy lifespan. Recent data demonstrate that long-term treatment with Metf in middle-aged male mice extends healthy lifespan in male mice. In order to determine if Metf action was limited to middle age condition, our group studied Metf effects on sedentary adult young mice. To achieve this aim, C57BL/6 mice male at 12 weeks of age was treated with Metf (250 mg/kg per day, in drinking water) for 3 months. Control mice group drank water only. A muscular performance, evaluated by a submaximal running test prior and upon completion of the study, revealed that Metf treated mice exhibit an enhanced performance respect to the control mice. To assess how Metf enhanced physical performance and healthy lifespan of the sedentary animals, we analyzed the principal target tissues of insulin resistance: skeletal muscle, liver and visceral adipose tissues. Western Blot results revealed that Metf activated AMPK in these tissues, suggesting how this drug could prevent dysregulation of glucose and lipid metabolism. In liver, Metf decreased the levels of the principal kinases involved in hepatic stress conditions, ERKs. In skeletal muscle, Metf increased the activation of AKT, a central kinase involved not only in insulin signaling but also in cellular mechanisms of skeletal muscle function maintenance. Moreover, we would clarified this Metf molecular role on skeletal muscle using an immortalized model of satellite cells, C2C12 cells line. Immunofluorescence and Western Blot analysis revealed that Metf did not modify the C2C12 proliferation capacity, while positively influenced the differentiation process and the myotube maturation. Together, our novel results suggest that Metf may have a positive action not only on the promotion of healthy aging but also on the prevention of sedentariness damages.

HEALTH CARE DELIVERY—ECONOMICS

140-LB

Hospitalization Costs, Resource Utilization, and Clinical Outcome in Patients Undergoing CABG Receiving Intensive vs. Conservative Glucose Control

DAWN SMILEY, SAUMETH CARDONA, JEFF WEAVER, KENYON REGISTER, LIMIN PENG, FRANCISCO PASQUEL, GUILLERMO E. UMPIERREZ, *Atlanta, GA*

The GLUCO-CABG trial reported that intensive control (IC) targeting a BG of 100-140 mg/dl in the ICU vs. conservative control (CC) targeting BG of 141-180 mg/dl did not reduce a composite of hospital complications including wound infection, pneumonia, acute respiratory or renal failure, major cardiovascular events, bacteremia and death (42% vs. 52%, p=0.08) in hyperglycemic patients undergoing CABG surgery. The financial impact of this intervention, however, is unknown. Accordingly, we conducted a post-hoc, cost analysis to compare hospitalization costs using 2011-2013 cost-charge ratios from Centers for Medicare & Medicaid Services, as well as resource utilization and hospital complications in CABG patients receiving IC vs. CC. A total of 288 of 302 patients (IC: 144, CC: 144) had financial data for analysis. The mean age was 64.2±9.5 with 50% prevalence of diabetes in each group.

Median total hospitalization costs in the IC group were lower at $39.4K compared to $42.2K in the CC group (p=0.043), with a median cost savings of $2,699 (95% CI: $557-6,750). Median resource utilization, expressed as instances, was higher in the CC group for radiology (20 vs. 15, p=0.001), laboratory (248 vs. 213, p=0.018), consult service (14 vs. 9, p=0.017), and ICU use (3 vs. 2, p=0.013) which resulted in higher median total resource costs compared to the IC group ($16.3K vs. $14.2K, p=0.006). The CC group had more complications (52% vs. 42%, p=0.076) compared to the IC group. A multivariate analysis adjusted for

treatment group, DM status and complications suggested that the observed cost benefit of IC is primarily due to the reduced complication rate.

In summary, intensive glucose control compared to conservative control in ICU patients that have undergone CABG procedures is associated with fewer complications and this in turn results in significantly lower hospitalization costs and resource utilization.

Supported By: ADA (7-07-CR-56); Sanofi; Glytec, LLC.

141-LB

Comparative Effectiveness of Patient Participation Training vs. Diabetes Education in Low Socioeconomic Status Patients with Type 2 Diabetes: A Pragmatic Randomized Trial of Coached Care

SHELDON GREENFIELD, JOHN BILLIMEK, DARA H. SORKIN, SHERRIE H. KAPLAN, *Irvine, CA*

We compared the impact on glycemic control of two community health worker (CHW) interventions: Coached Care, where the CHW teaches patients skills to participate more actively in their care, versus Diabetes Education, where the CHW presents information about diabetes but no training on participation skills.

An ethnically diverse, low-income sample of type 2 diabetes patients with HbA1c >7.5% was recruited. Participants (N=545) were randomized to either Coached Care or Diabetes Education. In both arms, the CHW met the patients at the clinic before every diabetes-related medical visit during the study period to conduct a 20-minute session. Change in HbA1c from baseline to one-year follow-up was estimated using a linear mixed model adjusting for age, sex, race and education.

Reduction in HbA1c was greater in patients randomized to Coached Care (-0.43% 95% CI -0.59, -0.26; p<0.0001) versus Diabetes Education (-0.10% 95% CI: -0.28, 0.08; p=0.27), in spite of similar intensity of medication therapy.

CHWs teaching patient participation skills improved glycemic control in this diverse, low-income sample.

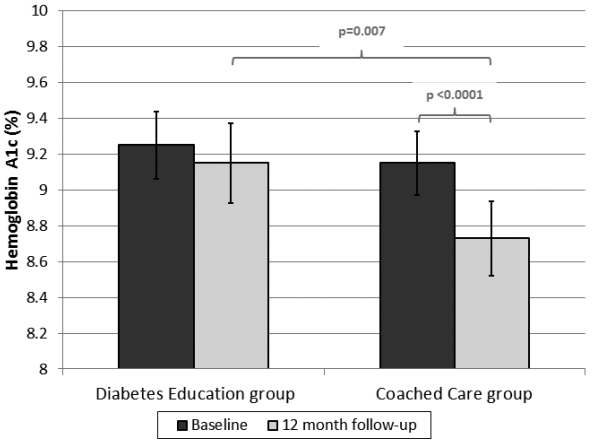


Figure 1. Reduction in hemoglobin A1c from baseline to one year follow-up. Results are estimated means (error bars represent 95% confidence intervals from linear mixed-effects models, adjusted for age, sex, race/ethnicity and education. Test for condition by time interaction shows that the size of the change in HbA1c from baseline to follow-up differs between the Diabetes Education and Coached Care groups (p=0.009).

142-LB

Costs of Diabetes in the U.S.: 1996-2030

HONGYU CHEN, MANU V. VENKAT, LISA S. ROTENSTEIN, JESSICA P. DONG, NINA RAN, MARK YARCHOAN, RICHARD KAHN, KELLY L. CLOSE, *San Francisco, CA, Boston, MA, Philadelphia, PA*

Diabetes is responsible for substantial healthcare expenditure in the U.S., and prevalence continues to rise. More robust data on the past and future costs of diabetes are needed to inform public health policy and influence cost management strategies.

The purpose of this study was to assess U.S. healthcare costs directly attributable to diabetes from 1996 to 2010, and to forecast future cost trends through 2030. Expanding upon the strong methodology of the ADA's five-year cost-of-illness studies, we calculated more granular cost data for every year from 1996 through 2010, drawing from the most robust longitudinal data sources available. We used this data to forecast future costs of diabetes through 2030.

Our analysis showed that the total annual healthcare costs directly attributable to diabetes in the U.S. rose from $64 billion in 1996 to $167 billion in 2010; we project costs to reach $494 billion by 2030. Broken down by components, we found that inpatient hospitalization declined from 58% of all costs in 1996 to 46% in 2010; we project a further decrease to 36% in 2030. The fastest growing cost segments were non-insulin prescription medications (7% in 1996, 16% in 2010, and a projected 26% in 2030) and diabetes supplies (3% in 1996, 10% in 2010, and a projected 12% in 2030). To explore the effects of diabetes prevention, we modeled the impact of a 1%, 5%, and 10% reduction in annual diabetes incidence from 2010 through 2030. Such reductions would save a cumulative projected total of $87 billion, $427 billion, and $798 billion, respectively, during that time period.

We conclude that, based on historical trends, the future costs attributable to diabetes in the U.S. will climb significantly, to levels greater than those projected by existing literature. Stemming this rise will likely require more successful diabetes prevention, as the total costs of diabetes are proportional to the size of the affected population. The dataset developed in this analysis opens exciting opportunities to study costs segmented by population demographics, complications, and care setting.

143-LB

The Synergy to Control Emergency Department Hyperglycemia in Type 2 Diabetes Project: STEP-Diabetes

MICHELLE F. MAGEE, CARINE M. NASSAR, MIHRIYE METE, JEFFREY S. DUBIN, *Washington, DC*

We assessed the impact of an intervention focused on glycemic management for adults with type 2 diabetes (T2DM) presenting to the emergency department (ED) with uncontrolled hyperglycemia.

A 4 week randomized controlled trial provided algorithm-based antihyperglycemic medications management; survival skills diabetes self-management education (DSME); and navigation to primary care for adults presenting to the ED with BG≥200mg/dL. Medications were titrated and DSME content delivered by endocrinologist-supervised certified diabetes educators at each visit. Controls received standard ED care.

One hundred and one patients were consented (96%, Black, 62.3% Medicaid and/or Medicare insurance, and no prior DSME (55.4%)). Seventy-eight (77.2%) completed the week 4 visit.

In both the intervention (INT) and control (CON) groups mean BG decreased (403±132 to 192± 93 mg/dL and 412 ±120 to 259±124mg/dL, respectively), p< 0.001. Post-BG was significantly lower for the INT, p<0.01. A1C went down within each group, (11.8± 2.4 to 10.5±1.9%, p < 0.001 for INT, and 11.5±2.0 to 11.1±2.1%, p=0.012 for CON). Absolute reduction in A1C was 0.9% greater in the INT than the CON group (p=0.01). The BG level of <180 mg/dl was reached by 65% of INT and 29% of CON subjects, p=0.002. Hypoglycemia rates between groups did not differ and no severe hypoglycemia was reported.

Modified Morisky Medication Adherence Scale© total scores decreased from 3.2 ±2.0 (low adherence) pre- to 1.4 ±1.4 (medium adherence) at 4 weeks (p<0.001) for the intervention and were sustained to 12 weeks. Improvement was greater for the intervention (-2.0 ±2.5 vs.- 0.3±2.43), p=0.001.

The STEP-Diabetes study results demonstrate that ED visits made by adults with uncontrolled T2DM can be used to initiate a focused intervention providing timely titration of antihyperglycemic medications and survival skills DSME to improve medication adherence and short-term glycemic outcomes, without increasing risk for hypoglycemia.

Supported By: ADA (7-11-CT-23)

144-LB

WITHDRAWN

145-LB

Bridging Income Generation through Provision of Incentives for Care (BIGPIC)

SONAK PASTAKIA, SIMON MANYARA, JEMIMA H. KAMANO, DIANA MENYA, BENJAMIN ANDAMA, JEREMIAH LAKTABAI, *Eldoret, Kenya, Webuye, Kenya*

In resource-constrained settings, chronic diseases have been neglected leaving patients with limited prospects for a healthy life. Through the BIGPIC program we have piloted a holistic approach which directly addresses socioeconomic barriers while encouraging positive health seeking behaviours.

This pilot project will establish whether the provision of group based healthcare combined with microfinance leads to improved chronic disease control and access for resource-constrained patients in rural western Kenya. Screen positive patients form community based microfinance groups where they receive portable care and are trained on various aspects of diabetes and hypertension self-care. Patients are required to pay subsidized user fees for all services and medications. The distinct groups are then assessed and incentivized based on their utilization of services and clinical outcomes.

917 individuals were screened for diabetes and hypertension of which 170 (18.5%) were screen positive with 147 for hypertension and 23 with diabetes and/or hypertension. 112 (65.9%) returned for confirmatory diagnosis, with 85 (81%) of those patients being confirmed positive and subsequently forming microfinance groups. After six months, 69 (65.7%) of the patients were retained in care with the overall group demonstrating a 12mmHg decline in systolic blood pressure and patients with diabetes having a 1 point reduction in HbA1C. Through the groups' microfinance activities, they were able to generate a cumulative savings of $3,690 with an accrued interest of $1065 after six months. This approach demonstrated statistically improved linkage (65.9% compared to 20%, P<0.01) and retention (65.7% compared to 21%, P<0.01) compared to the standard of care in the public sector of Kenya.

By linking provision of health to microfinancing groups, we have been able to sustainably improve traditional elements of health and assist the population with economic opportunities to break the poverty cycle.

Supported By: Purdue University

PEDIATRICS—OBESITY AND TYPE 2 DIABETES

146-LB

Metabolic Changes in Severely Obese Adolescents Eight Years after Gastric Bypass

THOMAS INGE, TODD JENKINS, TAWNY W. BOYCE, SHELLEY KIRK, JESSICA WOO, ROBERT SIEGEL, STAVRA XANTHAKOS, MICHAEL HELMRATH, LAWRENCE M. DOLAN, *Cincinnati, OH*

Background: Severe adolescent obesity is associated with marked metabolic dysfunction. Little is known about long-term metabolic outcomes after roux en Y gastric bypass (RYGB) performed for adolescent severe obesity. The Follow-up of Adolescent Bariatric Surgery-5+ (FABS-5+) assessed BMI and metabolic variables >5 yrs postoperatively.

Methods: Adolescents and young adults who underwent laparoscopic RYGB from 2001-2007 were targeted for follow-up between 2011-2013. Baseline (pre-surgery) data were abstracted from charts. Patients were re-located to participate in a standardized research visit including a fasting blood draw. Body mass index (BMI) and biochemical changes were evaluated using Wilcoxon signed rank sum tests, McNemar's test and Bowker's test of symmetry.

Results: 80% of all subjects eligible for FABS-5+ were enrolled. The cohort (n=46) for this analysis included 32 females (70%), 39 Caucasians (85%) and 1 Hispanic (2%). Mean interval from surgery was 7.9 yrs. BMI declined by 33%, plasma insulin by 83%, and fasting glucose (FG) by 18% (all p<0.01; Table). The proportion with normal FG (<100mg/dL) increased significantly from 59% at baseline to 93%. Diabetes remitted in 7 of 8 subjects with no incident cases.

Conclusion: In severely obese adolescents with metabolic dysfunction, these data strongly suggest that RYGB is associated with major, sustained weight loss and marked improvement in glucose homeostasis.

Baseline and Follow-up Metabolic Characteristics.

	Baseline	n	Follow-Up	n	Paired p-value	Paired n
Mean Age ± SD (range), yrs	17.3 ± 1.7 (14.0, 21.4)	46	25.2 ± 2.4 (20.7, 29.9)	46	—	—
Median BMI (IQR), kg/m2	57.2 (50.4, 63.7)	46	38.3 (31.3, 50.5)	46	<0.01	46
Median Insulin (IQR), uIU/mL	34.4 (26.2, 48.4)	41	5.7 (4.3, 8.3)	42	<0.01	37
Median Glucose (IQR), mg/dL	97.0 (90.0, 102.0)	39	80.0 (75.0, 90.0)	43	<0.01	36
Median HOMA-IR* (IQR)	7.6 (5.9, 11.3)	36	1.3 (0.8, 1.9)	42	<0.01	32
Diabetes†, n (%)	8 (17%)	46	1 (2%)	46	<0.01	46
Fasting Glucose 1) 2) 100-125 mg/dL, n(%) 3) ≥ 126 mg/dL, n(%)	 1) 23 (59%) 2) 13 (33%) 3) 3 (8%)	39	 1) 40 (93%) 2) 2 (5%) 3) 1 (2%)	43	<0.01	36

*HOMA-IR = fasting insulin × fasting glucose / 405.

† Provider Dx or (HgbA1c ≥ 6.5 or Fasting Glucose ≥ 126mg/dL) or Meds for Diabetes.

Supported By: Ethicon Endo-Surgery, Inc.

147-LB

Examining Family Planning Vigilant Behavior in Adolescent Females with Type 2 Diabetes

JESSICA J. CHOI, NEIL H. WHITE, SUSAN SEREIKA, PATRICIA SCHMITT, DENISE C. CHARRON-PROCHOWNIK, *Pittsburgh, PA, St. Louis, MO*

Unplanned pregnancies in teenagers, especially with diabetes, could cause severe maternal and fetal complications. Preconception Counseling (PC) provides family planning information to prevent unplanned pregnancies. ADA recommends PC beginning at puberty. Adolescent females with type 2 diabetes (T2D) avoiding pregnancies should be vigilant in using effective family planning. This study reports levels of vigilance with family planning behaviors [e.g., consistent use of birth control (BC), abstinence, and seeking family planning advice/information from health care professionals (HCP)] in adolescent females with T2D. A subsample of 112 female subjects from the TODAY Study cohort completed a reproductive health questionnaire. The questionnaire measured reproductive health and diabetes knowledge, intentions, and behaviors. At baseline (of the TODAY Study), subjects had a mean age of 14.0±2.0 yrs and only 19.6% were non-Hispanic white. During the study, 62% had ever been sexually active, with a mean age of sexual debut of 16.5 yrs (range 12-22 yrs). Of these, 97% had used some form of BC, but only 31% were vigilant about using BC every time they had sex while they were not planning a pregnancy. Only 21% intended to be abstinent in the future. Although 74% of the teens reported having gotten information from their HCP about the importance of planning a pregnancy with diabetes, only 39% intended to get preconception counseling for planning future pregnancies, and only 29% ever actually discussed diabetes and birth control with their HCP. With regards to knowledge of family planning vigilance, 23% did not know that a condom is a form of BC, and 22% believed that women with diabetes have very limited choices of BC. Deficiencies were noted in family planning vigilant behaviors; these deficiencies could lead to unplanned pregnancies. Adolescents with diabetes could benefit from PC starting at puberty and booster sessions at routine diabetes clinic visits.

Supported By: NIH

148-LB

Obese Adolescents with T2DM Have a More Atherogenic Lipoprotein Pattern at a Given Insulin Sensitivity Compared to Those with Insulin Resistance or Prediabetes

SHEELA N. MAGGE, RAY C. BOSTON, JUSTINE SHULTS, NICOLAS STETTLER, LORRAINE KATZ, DANIEL J. RADER, *Philadelphia, PA, Falls Church, VA*

Obesity and T2DM are risk factors for metabolic dyslipidemia, but it is unknown if T2DM increases dyslipidemia risk beyond obesity and IR.

We compared 5 pubertal adolescent groups: lean controls n=42, and obese insulin sensitive (OIS) n=44, insulin resistant (OIR= fasting insulin>20uM/mL) n=36, pre-diabetic (OPreT2 by OGTT) n=23, diabetic (OT2) n=11. NMR lipoproteins and FSIVGTT (in obese) were measured. Linear regression measured associations between Si (Minmod) and lipoproteins, with further inclusion of group by lipoprotein interactions. Lincom in Stata identified associations differing between OT2, and OIR or OPreT2.

For author disclosure information, see page LB91.

Si was associated lnHDL-C (β 1.6 p<0.0001), lnTG (β -0.9 p<0.0001), lnLDL-C (p=0.007), small LDL-P (p<0.0001), LDL-P size (p=0.006) and HDL-P size (p<0.0001). Interaction terms (OT2 status by Si) were significant for lnHDL-C, lnTG, lnLDL-C, lnNon-HDL-C, small LDL-P, LDL-P size, HDL-P size, with OIS as reference group (Figure 1). Similar findings observed using OIR as reference for lnHDL-C, lnTG, lnLDL-C, lnNon-HDL-C, HDL-P size, and using OPreT2 as reference for lnTG and lnNon-HDL-C.

We demonstrate for the first time that T2DM is associated with a more atherogenic lipoprotein pattern for a given Si compared to OIS, OIR, and OPreT2, suggesting worsening of metabolic dyslipidemia with progressive dysglycemia, beyond IR.

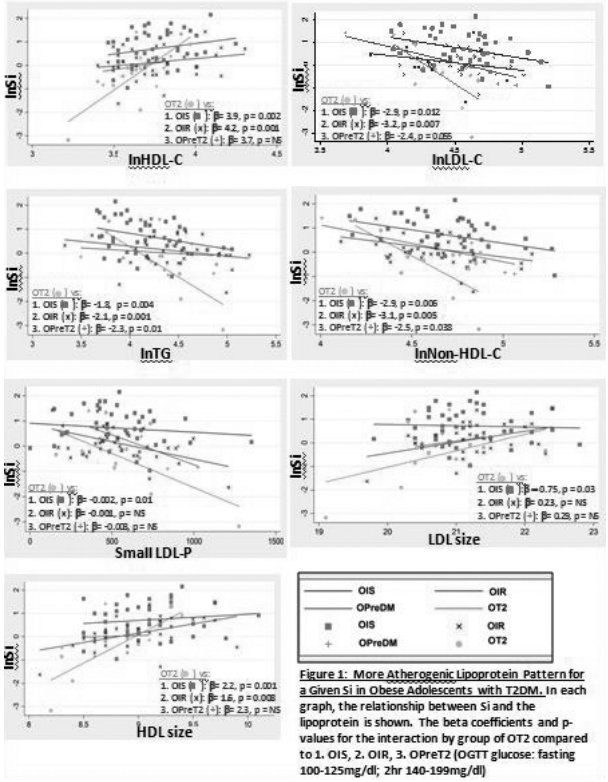


Figure 1: More Atherogenic Lipoprotein Pattern for a Given Si in Obese Adolescents with T2DM. In each graph, the relationship between Si and the lipoprotein is shown. The beta coefficients and p-values for the interaction by group of OT2 compared to 1. OIS, 2. OIR, 3. OPreT2 (OGTT glucose: fasting 100-125mg/dl; 2hr 140-199mg/dl)

Supported By: NIH (K23PA05143, UL1RR024134)

PEDIATRICS—TYPE 1 DIABETES

149-LB

The Proinsulin/C-peptide Ratio and HSP90: Potential Biomarkers for Early Detection of Type 1 Diabetes

ZUNAIRA Z. CHAUDHRY, RENECIA A. WATKINS, CRAIG BEAM, LYNETTE GUINDON, RAGHAVENDRA G. MIRMIRA, JANICE BLUM, LINDA A. DIMEGLIO, CARMELLA EVANS-MOLINA, TYPE 1 DIABETES TRIALNET STUDY GROUP, *Indianapolis, IN, Kalamazoo, MI*

Type 1 diabetes (T1D) has been classically attributed to autoimmune-mediated β cell destruction. Recent data suggest that stress pathways, such as endoplasmic reticulum (ER) and/or oxidative stress, are triggered early in disease evolution and may precede autoimmune-mediated β cell destruction. We hypothesized that earlier clinical identification of intrinsic β cell stress pathways may allow for more effectively timed therapeutic interventions. In Type 2 diabetes, serum proinsulin is increased relative to mature and fully processed insulin (assessed by measuring C-peptide) and is indicative of β cell ER stress, while heat shock protein 90 (HSP90) is a protein chaperone upregulated in β cell during inflammatory stress. To test the utility of the proinsulin/C-peptide (PI/C) ratio and HSP90 as candidate biomarkers of β cell stress and evolving preclinical T1D, banked serum samples were obtained from the TrialNet Pathway to Prevention cohort, which is a longitudinal study of non-diabetic first, second, or third degree relatives of individuals with T1D who are positive for at least one β cell autoantibody. Samples were obtained from T1D progressors 10-14 months prior to disease onset (n=38; 43.5% male; avg age 20.06 ± 2.26 yrs; n=24 ≤18 yrs) and compared to age, gender, and BMI-matched nonprogressors who remained normoglycemic (n=38; 43% male; avg age 20.14 ± 2.212; n=24 ≤18 yrs) and had been followed in the study for a comparable time period. HSP90 levels were not different between the progressors and nonprogressors. However, the PI/C ratio was 1.57-fold higher in T1D progressors compared to nonprogressors (p=0.012; 95% CI 1.11-2.23). In addition, there was a significant positive correlation between PI/C and body mass index (p=0.034) and a significant negative correlation between the PI/C ratio and age (p=0.003). These data suggest that elevations in the serum PI/C ratio may help predict the onset of T1D at a time prior to the development of clinically apparent hyperglycemia.

150-LB

Higher Skin Autofluorescence in Youth with Type 1 Diabetic Retinopathy

YOON HI CHO, MARIA E. CRAIG, ANDRZEJ S. JANUSZEWSKI, STEPHEN HING, ALICIA J. JENKINS, KIM C. DONAGHUE, *Westmead, Australia, Sydney, Australia*

Skin autofluorescence (AF) provides a non-invasive measure of accumulation of advanced glycation end-products (AGEs) in skin collagen. Skin AF is associated with vascular complications in older adults with diabetes, independent of HbA1c.

Our aims were: (1) to compare accumulation of skin AGEs, as measured by skin AF, in young people with type 1 diabetes (T1D) vs. controls, and (2) the association between skin AF and retinopathy in T1D.

Skin AF was measured as a mean of 6 readings at the forearm using the DiagnOptics AGE-Reader in 78 youth with T1D (mean age 17.4 yrs ±3.8, duration 10.1 yrs ± 4.0, HbA1c 8.8% ±1.6; 73mmol/L) and 70 age-matched controls (mean 17.6 yrs ±6.0). Retinopathy was assessed using 7-field stereoscopic fundal photography and graded using Modified Airlie House Criteria, defined as ≥21 in any eye.

Age-adjusted mean skin AF was higher in diabetes vs. controls (1.43 ±0.04 vs. 1.22 ±0.04, p<0.001). Retinopathy was seen in 22% of diabetic patients. Age-adjusted mean skin AF was higher in retinopathy-free diabetes vs. controls (p<0.05) and tended to be higher in diabetes with retinopathy vs. retinopathy-free (p=0.08). ROC analysis showed skin AF as a strong screening tool for presence of retinopathy (AUC 0.78, p=0.001). Skin AF was associated with older age (β= 0.06, 95% CI 0.04-0.08; p<0.001) and higher HbA1c (0.1, 0.04-0.15; p=0.001), or longer duration (0.04, 0.02-0.06; p=0.002) and higher HbA1c (0.1, 0.04-0.16; p=0.002). Highest quartile skin AF (≥1.62) was associated with retinopathy (6.3, 1.9-20.5, p=0.003), which remained significant after adjusting for HbA1c (4.3, 1.2-15.3; p=0.03).

Accumulation of skin AGEs in youth with diabetes is associated with retinopathy in cross sectional analysis. Longitudinal studies will determine the utility of skin AF as a non-invasive screening tool to predict future retinopathy risk and potentially provide a measure of "metabolic memory" in diabetes complications, which cannot be accurately measured by serial HbA1c alone.

151-LB

Phenotype of Insulin Resistance in Type 1 Diabetes Differs from the Typical Metabolic Syndrome Pattern

MEGAN M. KELSEY, JERI FORSTER, MELANIE CREE-GREEN, AMY WEST, JANE E.B. REUSCH, KRISTEN J. NADEAU, *Aurora, CO*

The contribution of insulin resistance to the development of type 2 diabetes (T2D) is well described, whereas type 1 diabetes (T1D) is typically considered primarily a disease of β-cell failure. However, evidence also exists for insulin resistance in youth with T1D. Moreover, youth with T1D are at increased risk for developing cardiovascular disease (CVD). However, little is known about whether insulin resistant T1D and T2D youth have the same CVD risk pattern. The goal of this study was to compare insulin resistance and CVD risk profile in youth with T1 and T2D and lean controls. The study included 151 youth aged 12-19 years (75 T1D, 47 T2D, 29 lean controls). Insulin resistance was measured by hyperinsulinemic euglycemic clamp, reported as glucose disposal rate (GDR). Group means were compared for GDR and HbA1c, as well as for CVD risk markers, including waist circumference (WC), body mass index (BMI), fasting lipids, liver transaminases, and inflammatory markers. Groups were similar for age, sex, and pubertal stage. Controls and T1D youth were lean (BMI z-score [BMIz]=0.19±0.77 and 0.44±0.96, respectively), whereas youth with T2D were obese (BMIz=2.1±0.47). GDR was greatest in lean controls (14.3±4.0), least in T2D youth (4.2±2.4), and intermediate for T1D youth (8.4±3.3 $mg/m^{2*}min^{-1}$, all p<0.0001). Lean and T1D youth were similar for all CVD risk markers, whereas T2D youth had lower HDL and adiponectin, and higher triglycerides, blood pressure, WC , ALT, CRP, and % body fat (all statistically significant). In conclusion, despite being significantly more insulin resistant than lean, healthy youth, youth with T1D do not show a similar high-risk metabolic profile as youth with T2D. Further research is needed to better understand the underlying pathophysiology of insulin resistance in youth with T1D. Furthermore, because insulin resistant youth with T1D do not display a typical metabolic syndrome phenotype, long term studies are needed to further characterize CVD risk markers in T1D.

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152-LB

Protective Effect of Sulforaphane on Type 1 Diabetes-induced Testicular Apoptosis Is Associated with Upregulation of Nrf2 Expression and Function

JIANG XIN, YANG BAI, YING XIN, LU CAI, *Changchun, China, Louisville, KY*

Infertility is a common complication in diabetic men, mainly due to the loss of germ cells by apoptotic cell death. Diabetes-induced testicular apoptosis is predominantly due to increased oxidative stress. The nuclear factor-erythroid 2-related factor 2 (Nrf2), as a master transcription factor in controlling anti-oxidative systems, is able to be induced by sulforaphane (SFN). To examine whether SFN could prevent testicular apoptosis through up-regulation of Nrf2, type 1 diabetic mouse model was set up with multiple intraperitoneal injections of low-dose streptozotocin. Diabetic and age-matched control mice were treated with or without SFN at 0.5 mg/kg daily in five day of each week for 3 months and then kept until 6 months. At 3 and 6 months of diabetes, testicular apoptosis, fibrosis, inflammation, and oxidative damage were assessed by Western blot, real-time qPCR, and histopathological examination. Diabetes significantly induced testicular apoptosis that was associated with ER-stress and mitochondrial cell death pathways, shown by increased expression of CHOP, cleaved caspase-12, Bax to Bcl2 ratio and cleaved caspase-3. Diabetes also significantly increased testicular oxidative damage (3-NT and 4-HNE), inflammation (ICAM and PAI-1) and fibrosis (TGF-β1 and CTGF), as well as decreased the germ cell proliferation (PCNA). All these diabetes-induced testicular damages were significantly prevented by 3-month SFN treatment that up-regulated Nrf2 function, reflected by increased Nrf2 phosphorylation and its downstream antioxidants (Catalase, HO-1 and NQO1) at mRNA and protein level. These results suggest that SFN is able to prevent testicular oxidative damage and apoptosis in type 1 diabetes, which was associated with the up-regulated Nrf2 expression and transcription function.

Supported By: ADA (1-11-BS-17); NSFC (81201218)

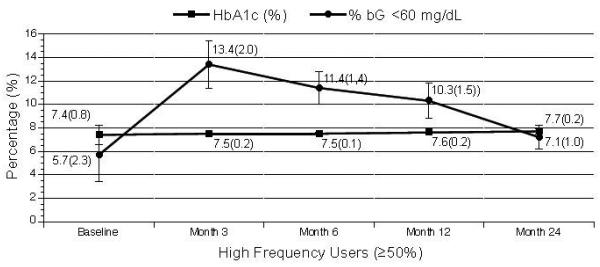
153-LB

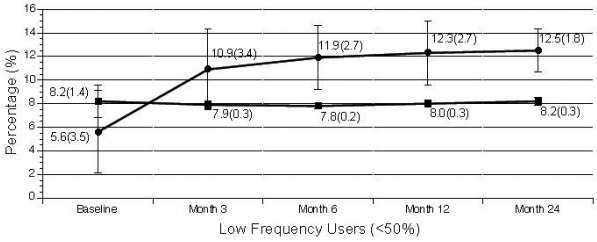
Does Frequent, Extended Use of an Automated Bolus Advisor Reduce Hypoglycemia in Pediatric Patients Treated with Insulin Pump Therapy? First Results of the BABE Study

RALPH ZIEGLER, CHRISTEN REES, NEHLE JACOBS, CHRISTOPHER PARKIN, MAUREEN R. LYDEN, BETTINA PETERSEN, ROBIN S. WAGNER, *Münster, Germany, Indianapolis, IN, Boulder City, NV, Tampa, FL, Mannheim, Germany*

The Bolus Advisor Benefit Evaluation (BABE) study was a single-center, retrospective cohort study that assessed the impact of frequent use of the Accu-Chek Aviva Combo system bolus advisor (BA) feature on glycemic control among 104 pediatric type 1 diabetes patients on insulin pumps treated at a pediatric diabetology clinic in Germany. At 6 months, frequent use of an automated bolus advisor was associated with significant improvements in glycemic control with no increase in hypoglycemia. We further assessed the impact of frequent BA use at 12 and 24 months in a consistent cohort of 40 study patients (mean (SD) baseline: HbA1c 7.6 (1.0)%, age 13.4 (4.3) years, diabetes duration 47.2 (40.4) months, and 57.5% female): 28 high frequency (HF) users (≥50%); 12 low frequency (LF) users (<50%). ANCOVA controlled for baseline differences in HbA1c, diabetes duration and age. Clinically significant between-group differences in HbA1c persisted to 24 months but without statistical significance in this small study group. Percentage of blood glucose (bG) values <60 mg/dL in both HF and LF users increased at month 3 but decreased over time and was significantly lower in HF users at 24 months: 7.1(1.0) vs. 12.5(1.8), p=0.0253. (Figure) Frequent, persistent BA use is associated with improved glycemic control over time in pediatric type 1 diabetes patients.

Figure. HbA1c and % bG values <60 mg/dL over 24 months





154-LB

Correlation of Continuous Glucose Monitoring Profiles with Pregnancy Outcomes in Non-Diabetic Women

JOYCE SUNG, ELIZABETH KOGUT, HENRY LEE, KASRA NAVABI, MARK TASLIMI, YASSER EL-SAYED, *Aurora, CO, Stanford, CA, Albuquerque, NM*

We wished to determine whether hyperglycemic excursions detected by continuous glucose monitoring (CGM) correlate with birth weight percentile and other pregnancy outcomes, and whether CGM correlates better with these outcomes than a single glucose value from a 1-hour glucose challenge test (GCT).

This was a prospective observational study of 55 pregnant patients without pre-existing diabetes, who wore a CGM device for up to 7 days, between 24-28 weeks' gestation. The area under the curve (AUC) of hyperglycemic excursions above various thresholds (110, 120, 130, 140, and 180 mg/dl) was calculated. These AUC values, and results from a standard 50-g glucose challenge test, were correlated with our primary outcome of birth weight percentile, and secondary outcomes of unplanned operative delivery, pregnancy complications, delivery complications, fetal complications, and neonatal complications.

A consistent correlation was seen between all AUC thresholds and birth weight percentile (r=0.29, p<0.05 for AUC-110, -120, -130, and -140; r=0.25, p=0.07 for AUC-180). This correlation was stronger than that of 1-hour oral GCT (r=-0.02, p=0.88). There was no association between AUC values and other outcomes.

In conclusion, among non-diabetic pregnant patients, hyperglycemic excursions detected by CGM show a stronger correlation to birth weight percentile than blood glucose values obtained 1-hour after a 50-g oral GCT.

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155-LB

WITHDRAWN

EPIDEMIOLOGY—CLINICAL—DIAGNOSIS AND SCREENING

156-LB

Identifying Japanese Americans at Risk for Prevalent or Incident Type 2 Diabetes by BMI, Waist, or Intra-Abdominal Fat

YUKIKO ONISHI, TOMOSHIGE HAYASHI, KYOKO K. SATO, MARGUERITE J. MCNEELY, DONNA L. LEONETTI, STEVEN E. KAHN, EDWARD J. BOYKO, WILFRED Y. FUJIMOTO, *Tokyo, Japan, Osaka, Japan, Seattle, WA*

To determine the optimal approach using body anthropometrics to identify Japanese Americans at risk for prevalent or incident type 2 diabetes (T2D), we performed receiver operating characteristic (ROC) curve analysis using BMI, waist circumference (WC) and intra-abdominal fat area (IAFA) by computed tomography. Of 658 Japanese Americans, 139 had prevalent T2D. Of those without T2D at baseline, 100 out of 426 followed for 10-11 years developed T2D, diagnosed from a 75-g oral glucose tolerance test (1997 ADA criteria). For prevalent T2D, area under the ROC curve (AUROC) was: IAFA 0.745 (95% CI 0.699-0.790) [men (m) 0.689 (0.626-0.752), women (w) 0.798 (0.726-0.869)]; WC 0.668 (0.618-0.717) [m 0.626 (0.555-0.697), w 0.711 (0.641-0.782)]; and BMI 0.644 (0.594-0.694) [m 0.618 (0.550-0.686), w 0.658 (0.580-0.736)]. For incident T2D, AUROC was: IAFA 0.706 (0.648-0.763) [m 0.698 (0.618-0.779), w 0.724 (0.639-0.808)]; WC 0.655 (0.594-0.715) [m 0.651 (0.564-0.738), w 0.673 (0.591-0.755)]; and BMI 0.625 (0.560-0.690) [m 0.666 (0.577-0.755), w 0.600

For author disclosure information, see page LB91.

(0.507-0.693)]. WC and IAFA were better but BMI is more useful clinically. Optimal BMI cut-offs to identify those with or at risk for T2D was ascertained by Youden's Index [maximum (J = Sensitivity + Specificity -1)] (BMI 1) or BMI where sensitivity was nearly equal to specificity (BMI 2). For prevalent T2D, BMI 1 was 24.8 kg/m^2 (m), 23.5 (w); BMI 2 was 25.5 (m), 23.5 (w). For incident T2D, BMI 1 was 26.9 (m), 22.9 (w); BMI 2 was 25.5 (m), 22.8 (w). At 80%, 70%, and 60% sensitivity, BMI to detect prevalent T2D was 23.8, 24.8, 25.4 (m) and 21.9, 22.7, 23.5 (w); BMI to identify those at risk for incident T2D was 23.4, 25.1, 25.6 (m) and 21.2, 21.6, 22.9 (w). To minimize missing at-risk Japanese Americans, BMI cut-offs at 80% sensitivity may be appropriate, especially since the diagnostic test for T2D is inexpensive, confirming that the BMI cut-off should be lower than 25 for identifying Japanese Americans at risk for prevalent and incident T2D.

157-LB

Evaluation of FPG, 2h-PPG, and HbA1c Measurements in Screening Diabetes and Prediabetes in a Chinese Population: A Cross-Sectional Study

XIANCHAO XIAO, CHENGLIN SUN, YUJIA LIU, SUYAN TIAN, ZHONGHUA SUN, YING GAO, YAZHEN LI, JIE CHENG, YOU LV, MEI LI, ZHUO LI, YUMIN ZHANG, GANG WANG, YANG LIU, YUAN GAO, LIWEN ZHU, YAN LIU, GUIXIA WANG, *Changchun, China*

Objective: To evaluate the sensitivity and specificity of fasting plasma glucose (FPG), 2-h post-load plasma glucose (2h-PPG), and glycosylated hemoglobin (HbA1c) measurements in the screening of diabetes and prediabetes in a Chinese population, and to determine the cutoff point of HbA1c in the diagnosis of diabetes and prediabetes in a Chinese population. Research Design and Methods: A total of 7, 611 individuals aged over 40 years old who did not have a prior history of diabetes were randomly selected in the Changchun area. For each subject, a questionnaire was completed and a physical examination and an oral glucose tolerance test were performed. For data analysis, FPG, 2h-PPG, and HbA1c values were compared by area under the receiver operating characteristic (ROC) curves. The sensitivity, specificity, and Youden index for different measurements were also compared by statistical analysis. Results: The prevalence of newly diagnosed diabetes and prediabetes was 12.71% and 29.39%, respectively. For subjects with newly diagnosed diabetes, the area under the ROC curve was 0.8368 for FPG, 0.9330 for 2h-PPG, and 0.8064 for HbA1c; whereas for prediabetes, these values were 0.8022, 0.9288, and 0.6895, respectively. The sensitivity and specificity for 2h-PPG were the highest among all three indices. Conclusions: As a screening tool for diabetes and prediabetes, the 2h-PPG measurement demonstrated the highest sensitivity and specificity; thus, it is the optimal method for a Chinese population. In addition, HbA1c ≥ 6.3% (45 mmol/mol) and 5.8-6.2% (40-44 mmol/mol) were the optimal cutoffs for the diagnosis of diabetes and prediabetes, respectively.

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158-LB

A Novel Testing Model for Screening of Prediabetes and Diabetes among U.S. Adults

LIWEI CHEN, YURONG ZHANG, LU ZHANG, RACHEL MAYO, GANG HU, *Clemson, SC, Xi'an, China, Metairie, LA, Baton Rouge, LA*

Historically, routine screening for diabetes in primary practice is challenging, largely for cost and time-consuming considerations. Hemoglobin A1c (HbA1c) is an attractive diagnostic test for diabetes because it is quick and does not require fasting. However, the sensitivity of using HbA1c alone is unacceptably low. The objective of this study was to evaluate whether a new model combining a diabetes risk score and HbA1c would be an acceptable tool in screening prediabetes and undiagnosed diabetes in general populations. This cross-sectional analysis included 3,886 adults (age ≥ 20 years) from the 2005-2010 U.S. National Health and Nutrition Examination Survey who attended the morning sessions and had an OGTT. The Finnish Diabetes Risk Score (FINDRISC) was selected because it is simple, non-invasive, and has been validated in the U.S. population in our previous study. The FINDRISC score was developed based on 8 variables (age, BMI, waist circumference, use of antihypertensive drug, history high blood glucose, family history of diabetes, daily physical activity and fruit & vegetable intake). The crude prevalence was 7.0% for undiagnosed diabetes and 43.1% for prediabetes (27.7% for isolated impaired fasting glucose (IFG), isolated 5.1% for impaired glucose tolerance (IGT), and 10.3% for having both IFG and IGT). The sensitivity and specificity of using the HbA1c alone was 24.2% and 99.6% for diabetes (cutoff: ≥6.5%), and 35.2% and 86.4% for prediabetes (cutoff: ≥5.7%). The sensitivity and specificity of using the FINDRISC alone (cutoff: ≥9) was 79.1% and 48.6% for diabetes and 60.2% and 61.4% for prediabetes. Using the simultaneous testing model with a combination of FINDRISC and HbA1c improved the sensitivity to 88.2% for diabetes and 74.2% for prediabetes. This simultaneous testing model is a practical and valid tool in diabetes screening in the general U.S. population and further study is warranted to evaluate the cost effectiveness of this screening model in primary practice.

159-LB

Increased Hemoglobin Concentration Is Associated with Future Development of Diabetes: The Insulin Resistance Atherosclerosis Study (IRAS)

CARLOS LORENZO, ANTHONY J. HANLEY, STEVEN M. HAFFNER, *San Antonio, TX, Toronto, ON, Canada*

For each chronic kidney disease stage, diabetes is associated with a 1 g/dl decrease in hemoglobin (Hb) concentration. Since Hb concentration tends to be lower in inflammatory conditions, we hypothesized that lower Hb concentration may precede the development of diabetes. We examined this issue in 868 non-diabetic participants in the IRAS. We assessed diabetes status by oral glucose tolerance test at baseline and after a 5-year follow-up period, and insulin sensitivity (S_I) and acute insulin response (AIR) by the frequently sampled intravenous glucose tolerance test. After controlling for age, sex, ethnicity, and clinic, Hb concentration was inversely related to log-transformed S_I (r = - 0.11, p = 0.002), but was not related to S_I-adjusted log-transformed AIR (r = 0.02, p = 0.622). Participants in the upper tertile of Hb concentration had greater odds of developing diabetes than those in the lower tertile (Table). Sex did not have an interaction effect on the relationship between Hb concentration and incident diabetes. In summary, higher rather than lower Hb concentration is associated with more insulin resistance. Higher Hb concentration may also precede the development of diabetes.

Table. Odds of Developing Incident Diabetes by Hb Tertiles.

Participants	Adjustment model	1st tertile	2nd tertile	3rd tertile	sex × Hb interaction
		6 – 13.5 mg/dl	13.6 – 14.9 mg/dl	15 – 19.1 mg/dl	*p* value
In men	Age, ethnicity, clinic, and IGT	1.00	1.12 (0.33 – 3.86)	2.58 (0.78 – 8.55)	—
In women	Age, ethnicity, clinic, and IGT	1.00	0.81 (0.41 – 1.62)	1.97 (0.76 – 5.07)	—
All	Age, sex, ethnicity, clinic, and IGT	1.00	1.01 (0.58 – 1.76)	2.64 (1.36 – 5.12)	0.739
All	+ BMI	1.00	1.06 (0.61 – 1.86)	2.78 (1.42 – 5.46)	0.619
All	+ log S_I and log AIR	1.00	1.04 (0.57 – 1.91)	2.71 (1.30 – 5.66)	0.875

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160-LB

Discontinuation of Oral Antihyperglycemic Agents among Diabetes Patients

KRISTI REYNOLDS, JAEJIN AN, TERESA N. HARRISON, RONG WEI, JUN WU, CATHERINE S. WLODARCZYK, JOHN MARTIN, SWAPNIL N. RAJPATHAK, *Pasadena, CA, Downey, CA, Whitehouse Station, NJ, Los Angeles, CA*

Oral antihyperglycemic agents (OHAs) are commonly prescribed in the treatment for type 2 diabetes mellitus. Many studies have examined medication adherence to OHA therapy, but few studies have examined OHA discontinuation rates in clinical practice. Using electronic health record data from a large, integrated healthcare delivery system in the U.S., we estimated rates of OHA discontinuation and examined factors associated with OHA discontinuation among patients with diabetes on dual therapy. We identified adult patients aged ≥ 18 years with a diagnosis of type 2 diabetes who initiated dual therapy (dispensed 2 different classes of OHAs) between 1/1/2005 and 6/30/2010. The index date was defined as the date of initiation of the second OHA. Patients using insulin, those on 3 or more classes of OHAs, and those who died or left the health plan during a 3 year follow-up were excluded. Discontinuation was defined as a gap of >1.5 times the last days' supply without subsequent reinitiation during follow-up. Multivariable log-binomial regression models were used to investigate factors associated with OHA discontinuation. Among 28,458 eligible patients with diabetes (mean ± SD age: 58±12 years; 44% female; 34% white, 36% Hispanic, 12% black; 12% Asian/Pacific Islander; 6% other), 38.7% discontinued one (26.4%) or both (12.3%) of their OHAs. The mean ± SD time to discontinuation was 573.8±368.5 days (median time, 625 days). Patients who discontinued their OHA were more likely to be female, younger, black or of Hispanic ethnicity, have a higher Charlson co-morbidity index, higher medication co-pays, fewer concomitant medications, more likely to have started both OHAs at the same time, and to have higher health care utilization in the year before the index date. Discontinuation of OHAs is common among patients with diabetes and is associated with several patient factors. Future research should further examine the reasons for OHA discontinuation and evaluate the impact of discontinuation on health outcomes.

161-LB

Optimum BMI Cut-Points to Screen Asian Americans for Type 2 Diabetes

MARIA ROSARIO G. ARANETA, ALKA KANAYA, WILFRED FUJIMOTO, WILLIAM C. HSU, HEALANI CHANG, ANDREW GRANDINETTI, EDWARD J. BOYKO, TOMOSHIGE HAYASHI, STEVEN E. KAHN, DONNA L. LEONETTI, MARGUERITE J. MCNEELY, YUKIKO ONISHI, KYOKO K. SATO, *La Jolla, CA, San Francisco, CA, Seattle, WA, Boston, MA, Honolulu, HI, Osaka, Japan, Tokyo, Japan*

Lower BMI cutpoints have been suggested to identify Asian Americans (AA) for diabetes (DM) screening but few studies have evaluated BMI cut-points using sensitivity, specificity, and receiver operating characteristic (ROC) curve analysis. We used data from 1663 asymptomatic AA, ages ≥45 years, without a prior DM diagnosis. Participants were of South Asian, Filipino, Japanese, Chinese, Korean, or mixed Asian ancestry, without non-Asian admixture from the MASALA, UCSD Filipino, North Kohala and Seattle JACDS studies. Clinical measures included a 2-h 75g oral glucose tolerance test, BMI and HbA1C (except in Seattle). Mean age was 60 years, mean BMI was 25.4 kg/m2, 58% were women, and the prevalence of undiagnosed DM (by ADA criteria) was 16.4%. At BMI≥25, sensitivity (63.7%) and specificity (52.8%) were most similar and area under the ROC curve was 0.583 (Table), but limiting screening at this BMI cut-point would miss 36.3% of AA with DM. For screening purposes, higher sensitivity is desirable to minimize missing cases, especially if the diagnostic test is relatively simple and inexpensive. The BMI≥23 kg/m2 cut-point had a high sensitivity (84.7%) and would fail to identify only 15.3% of AAs with DM. Results were similar at age >=35 (n=2042) or >=40 years (n=1899). We conclude from these findings that the BMI cut-point for identifying AA who should be screened for undiagnosed DM should be lower than 25 and ≥23 may be the most practical.

BMI (kg/m2)	Diabetes (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Area under the ROC curve
>=22	255 (15.3)	90.8	18.4	15.3	0.546
>=23	238 (14.3)	84.7	28.8	19.5	0.567
>=24	208 (12.5)	74.0	40.7	20.3	0.574
>=25	179 (10.8)	63.7	52.8	21.5	0.583
>=26	145 (8.7)	51.6	65.3	23.2	0.584
>=27	122 (7.3)	43.4	73.6	25.1	0.585
>=27.5	102 (6.1)	36.3	77.8	24.9	0.570

162-LB

WITHDRAWN

EPIDEMIOLOGY—DIABETES COMPLICATIONS

163-LB

Physical Activity, Sedentary Behavior, and All-Cause Mortality among Blacks and Whites with Diabetes

KIMBERLY R. GLENN, LOREN LIPWORTH, *Nashville, TN*

Previous studies of the relationship between physical activity (PA) and all-cause mortality (ACM) among individuals with diabetes were conducted primarily in white male populations.

We examined the association between PA and sedentary behavior and ACM risk in a racially diverse population of 15,645 low-income black and white men and women with diabetes from the Southern Community Cohort Study. Self-reported total PA and sedentary time (ST) were classified as metabolic equivalent tasks hours per day and total hours per day, respectively. Hazard ratios (HR) and 95% confidence intervals (95% CI) for ACM risk associated with total PA and total ST were estimated from multivariate Cox proportional hazards models. During follow-up (median 6.2 years), 2,370 participants died. Overall, the multivariate ACM risk was 37% lower among participants in the highest quartile of PA compared to those in the lowest (HR 0.63 [95% CI 0.56-0.71]). ACM was significantly increased for participants in the highest quartile of ST compared to those in the lowest after adjusting for PA (HR 1.18 [95% CI 1.05-1.32]). Significant trends of decreasing ACM with rising PA and increasing ACM with rising ST were observed among both blacks and whites.

While causal inferences cannot be made from these observational data, the findings suggest that increasing PA and decreasing ST may extend survival among patients with diabetes regardless of race.

HRs (95% CIs) for the Association between Quartiles of Total PA, Total ST, and ACM Risk among SCCS Participants with Diabetes, 2002-2009

	Person-Years	*# Events*	*HR (95% CI)[a]*
TOTAL PA (MET-h/d)			
Black (n = 11,137)			
- **< 6.9**	16,085	601	Reference
- **6.9-13.9**	17,314	422	0.80 (0.70 – 0.91)
- **14.0-23.7**	18,073	337	0.67 (0.58 – 0.77)
- **≥ 24.0**	18,402	325	0.68 (0.59 – 0.79)
p-for trend			< 0.0001
White (n = 4,508)			
- **< 6.9**	6,339	286	Reference
- **6.9-13.9**	6,371	162	0.65 (0.54 – 0.81)
- **14.0-23.7**	6,175	135	0.62 (0.50 – 0.77)
- **≥ 24.0**	5,890	102	0.53 (0.42 – 0.67)
p-for trend			< 0.0001
TOTAL ST (h/d)			
Black (n = 11,137)			
- **< 6**	20,969	514	Reference
- **6 – 8.4**	14,757	350	0.98 (0.86 – 1.13)
- **8.5 – 11.9**	17,265	426	1.12 (0.98 – 1.27)
- **≥ 12**	16,883	395	1.14 (1.00 – 1.31)
p-for trend			0.04
White (n = 4,508)			
- **< 6**	6,954	191	Reference
- **6 – 8.4**	5,533	136	0.90 (0.72 – 1.12)
- **8.5 – 11.9**	6,565	177	1.02 (0.83 – 1.26)
- **≥ 12**	5,723	181	1.23 (0.99 – 1.52)
p-for trend			0.02

[a]Adjusted for age, sex, BMI, income, education, hypertension, high cholesterol, myocardial infarction, stroke, insulin use, duration of diabetes, and total PA or ST

164-LB

Effect of Randomisation to Intensive Multifactorial Cardiovascular Treatment on Serum Methylglyoxal Levels: The Addition Trial

TROELS M. JENSEN, DANIEL R. WITTE, DORTE VISTISEN, THOMAS H. FLEMING, PETER P. NAWROTH, ANNELLI SANDBAEK, TORSTEN LAURITZEN, MARIT E. JØRGENSEN, *Gentofte, Denmark, Strassen, Luxembourg, Heidelberg, Germany, Aarhus, Denmark*

Elevated methylglyoxal (MG) has been implicated in the development of micro- and macrovascular diabetic complications, but it remains unclear how current treatments for type 2 diabetes affect its circulating levels. In a secondary analysis of the Danish arm of the ADDITION trial, we examined the effect of intensive multifactorial treatment of people with screen-detected type 2 diabetes on serum levels of MG, compared to routine care. Serum MG was measured in baseline (n=1304) and 6-year followup (n=1153) samples. We observed a significant decrease in MG in both treatment arms, with no effect of allocation to intensive treatment. At baseline MG was associated with current smoking and fasting glucose levels. In observational analyses of all patients adjusting for treatment allocation, a 1 mmol/l higher LDL cholesterol level at followup was associated with a 5.8% lower MG level (95%CI: -11.3;-1.0, p=0.03). No associations were observed between baseline risk factors and 6-year change in MG or between 6-year change in risk factors and change in MG. Patients receiving lipid lowering treatment at follow up had higher MG, and those who initiated lipid lowering treatment during the trial period experienced a larger increase in MG (Table 1). No other treatment effects were observed. Our results suggest a potential interplay between MG, LDL cholesterol and lipid-lowering treatment.

Table 1. Treatment Status vs. Log-Methylglyoxal.

	% difference	95% CI	P
Any lipid-lowering treatment at baseline (n=165) vs. no treatment at baseline (n=1144)	3.0	[-8.4 to 16.1]	0.61
Any lipid-lowering treatment at followup (n=946) vs. no treatment at followup (n=233)	28.4	[13.7 to 45.0]	<0.0001
Change in lipid-lowering treatment vs. change in MG during followup (reference group n=217)			
Treatment initiated (n=766)	15.8	[2.7 to 30.5]	0.02
Treatment continued (n=142)	9.6	[-6.4 to 28.3]	0.25
Change in glucose-lowering treatment vs. change in MG during followup (reference group n=496)			
Treatment initiated (n=625) [All analyses adjusted for age, sex, cluster randomisation, randomisation arm and treatment target]	-0.2	[-8.8 to 9.2]	0.96

For author disclosure information, see page LB91.

165-LB

Trends in Emergency Department Visit Rates for Hypoglycemia and Hyperglycemic Crisis among Adults with Diabetes, United States, 2006-2011

JING WANG, LINDA S. GEISS, DESMOND WILLIAMS, EDWARD W. GREGG, *Atlanta, GA*

Recent studies raised concern about the frequency of hypoglycemia in the diabetic population and the morbidity that may result. We examined the trends in emergency department (ED) visit rates for hypoglycemia and hyperglycemic crisis among adults with diabetes in United States from 2006 to 2011. Using the Nationwide Emergency Department Sample, visits for hyperglycemic crisis were determined by ICD-9-CM 250.1 or 250.2 and visits for hypoglycemia were determined via a validated algorithm among visits with diabetes identified by ICD-9- CM 250. We estimated the number of diabetic adults from the National Health Interview Survey. In 2011, ED visits for hypoglycemia and hyperglycemic crisis together comprised 3.6% of all visits by diabetic adults, declining from 4.7% in 2006.

Rates for hypoglycemia displayed a J-shape curve across age with the highest rates in persons aged ≥75 years (2.4 per 100 persons) while rates for hyperglycemic crisis presented an L shape with the highest rates among persons aged 18-44 years (3.7 per 100 persons). Overall rates for hypoglycemia declined by 24% from 1.8 (95% CI 1.7-1.9) per 100 persons in 2006 to 1.4 (95% CI 1.3-1.5) per 100 persons in 2011 ($p<0.01$). The rates decreased 33%, 22%, and 22% for persons aged 65-74 years, 75+ years, and 45-64 years respectively (all $p<0.05$) but were unchanged for persons 18-44 years ($p=0.2$).

In contrast to hypoglycemia, rates of hyperglycemic crisis remained stable overall and across all age groups ($p>0.05$ for all) with the exception of persons aged 65-74 years for whom rates increased 17% (from 0.18 (95% CI 0.16-0.19) per 100 persons in 2006). In recent years, ED visit rates for hypoglycemia declined particularly among older adults while rates for hyperglycemic crisis were stable. Continued surveillance is important for examining the benefits and harm of glycemic control on acute complications.

EPIDEMIOLOGY—NUTRITION

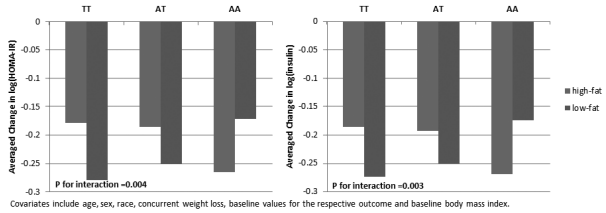
166-LB

Dietary Fat Modifies the Effects of FTO Genotype on Changes in Insulin Sensitivity: The POUNDS Lost Trial

YAN ZHENG, TAO HUANG, GEORGE A. BRAY, FRANK M. SACKS, LU QI, *Boston, MA, Baton Rouge, LA*

The common variants in the fat mass and obesity-associated (FTO) gene have been associated with obesity and insulin sensitivity. Recently emerging data also linked FTO variants with macronutrient intakes. We investigated whether diet interventions varying in macronutrients modified the effects of FTO genotypes on changes of insulin sensitivity in a randomized weight-loss dietary intervention trial. We genotyped FTO rs1558902 and rs9939609 in 743 overweight or obese adults (aged 30-70 years, 60% females) and measured insulin sensitivity in fasting plasma samples at baseline, 6-month and 2-year visits in the Preventing Overweight Using Novel Dietary Strategies (POUNDS Lost) trial. We found significant interactions between rs1558902 and diet fat on plasma HOMA-IR and insulin (P values < 0.01, Fig). Each risk allele (A) of rs1558902 was related with 0.05-unit smaller averaged reduction in both log (insulin) and log (HOMA-IR) among the participants assigned to low-fat diets, but related with 0.04-unit larger such reduction among those assigned to high-fat diets, during the 2-year period of intervention. Our data showed that the association between rs9939609 and changes in insulin sensitivity was not modified by diet macronutrient intakes. Our data suggest that carriers of the risk alleles of rs1558902 might benefit more in improving insulin sensitivity by taking high-fat diets than low-fat diets.

Fig. Averaged change in insulin and insulin resistance by rs1558902 genotype and diet fat groups



Covariates include age, sex, race, concurrent weight loss, baseline values for the respective outcome and baseline body mass index.

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167-LB

Dietary Lipophilic Load and Lipophilic Index with Risk of Type 2 Diabetes in U.S. Men and Women

HONGYU WU, QI SUN, FRANK B. HU, ERIC L. DING, *Boston, MA*

Background: Fatty acid lipophilicity is suggested to be associated with risk factors of diabetes, such as insulin resistance and inflammation. However, conventional fat classifications might not adequately capture the lipophilic properties. We investigated a novel set of lipophilic indices of dietary fatty acid in relation to risk of type 2 diabetes (T2DM).

Methods: We prospectively followed 75089 women and 42239 men from the Nurses' Health Study (1984-2008) and the Health Professionals Follow-up Study (1986-2008), who were free of chronic diseases at baseline. Dietary Lipophilic Load (DLL) was computed by summing the products of intakes of fatty acids (g/d) and melting points of each fatty acid (°C). Dietary Lipophilic Index (DLI) was calculated as DLL divided by total fatty acid intake. Intakes of dietary fatty acids were derived from repeated food frequency questionnaire. Incident T2DM was updated every two years. The relative risks (RRs) of incident T2DM were estimated by Cox proportional hazards regression.

Results: During 2,521,669 person-years of follow-up, we identified 10909 incident T2DM. A higher DLL was significantly associated with increased risk of T2DM (pooled multivariate adjusted RR = 1.22, 95% CI: 1.13-1.31). After further adjustment for BMI, the associations between DLL and diabetes were attenuated but remained significant (pooled RR = 1.15, 1.05-1.25) in 5th quintile of DLL. DLI was also significantly associated with an increased risk of T2DM (pooled RR comparing extreme DLI quintiles = 1.07, 1.00-1.14; P=0.03 for trend) after multivariate adjustment including BMI. Although the associations for DLI were attenuated after further adjustment for dietary polyunsaturated to saturated fat ratio (P:S), the association for DLL remained robust after further adjustment for P:S and other risk factors.

Conclusions: Our findings suggest that a higher dietary Lipophilic Load is associated with an increased risk of T2DM, which is independent of other traditional risk factors.

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168-LB

Consumption of Soy Foods and Isoflavones and Risk of Type 2 Diabetes: A Pooled Analysis of Three U.S. Cohorts

MING DING, AN PAN, VASANTI MALIK, QI SUN, FRANK B. HU, *Boston, MA, Singapore, Singapore*

Background: The association between consumption of soy foods and risk of type 2 diabetes (T2D) is unclear.

Objective: We evaluated the association between soy foods consumption and risk of T2D in U.S. adults.

Design: We followed 73,221 women in the Nurses' Health Study (1984-2008), 91,654 women in the Nurses' Health Study II (1991-2010), and 41,227 men in the Health Professionals Follow-Up Study (1986-2010). Diet was assessed by validated food-frequency questionnaire, and was updated every 4 y. Incident T2D was confirmed by a validated supplementary questionnaire.

Results: The percentage of participants who reported consumption of soy products (tofu or soy milk) was 12% in NHS, 20% in NHS II, and 25% in HPFS. During 1,513,340 person-years of follow-up, 10,346 T2D cases were documented. In the multivariate model, consumption of soy food was weakly inversely associated with risk of T2D (comparing the highest with the lowest tertile: pooled hazard ratio (HR) = 0.88; 95% CI: 0.76-1.00). Consumption of total isoflavones was also inversely associated with risk of T2D. Soy foods consumption was inversely associated with risk of T2D in postmenopausal women without hormone replacement therapy (HRT), but not in premenopausal women or postmenopausal women with HRT (P for interaction = 0.038).

Conclusion: A weak inverse association between intakes of soy food and risk of T2D was found in the pooled cohorts of U.S. adults, especially in postmenopausal women. Further studies are needed to examine these associations in other populations.

EPIDEMIOLOGY—OTHER

169-LB

Assessing Time to Insulin Use among Type 2 Diabetes Patients Treated with Sitagliptin or Sulfonylurea-Plus-Metformin Dual Therapy

LAWRENCE BLONDE, YING QIU, SWAPNIL RAJPATHAK, KIMBERLY G. BRODOVICZ, SAMUEL S. ENGEL, PANAGIOTIS MAVROS, LARRY RADICAN, PHILIPPE BRUDI, KAAN TUNCELI, CHUN-PO S. FAN, ZHIYI LI, JACKSON TANG, SILVIO E. INZUCCHI, *New Orleans, LA, Whitehouse Station, NJ, North Wales, PA, Rahway, NJ, New York, NY, New Haven, CT*

In type 2 diabetes mellitus (T2DM), decline of β-cell function over time leads to the need for treatment intensification and eventually initiation of insulin

therapy in many patients (pts). Sitagliptin (SITA) and sulfonylureas (SU) are commonly prescribed after metformin as dual therapy in T2DM. This study assessed the time to insulin initiation among pts treated with MET+SITA vs. MET+SU.

This retrospective cohort study used a sample from the GE Centricity database. Included were pts with T2DM, ≥18 years (yrs), with continuous medical records. Index was the date of the 1st prescription of SITA or SU used as dual therapy with metformin for ≥90 days in 2006-13. SITA and SU users were matched 1:1 using propensity score (PSM). Differences in time to insulin use (from index date) between SITA and SU users were assessed using Kaplan-Meier (KM) curves and Cox regression. Conditional logistic regression (CLR) examined the likelihood of insulin use in each of yrs 1-5 post index. Baseline characteristics were adjusted. Subgroup analyses for baseline A1C< 9% or ≥9% were then conducted.

PSM produced 3,862 matched pairs. The percent of pts progressing to insulin by yrs 1-6 were 3.6, 8.4, 12.9, 17.7, 22.4, 26.6 for SITA and 4.1, 9.4, 14.6, 21.0, 27.1, 34.1 for SU users, respectively. KM curves were significantly different (p=0.0034) indicating that SITA users progressed more slowly to insulin initiation than SU users. This remained significant after adjusting for baseline characteristics (HR=0.76, 95% CI: [0.464, 0.897]). CLR analyses confirmed the robustness of the results (ORs: 0.77; 0.79; 0.81; 0.57; 0.29; for yrs 1-5 respectively, p<.05 for Yr 4 and Yr 5). The SITA vs. SU comparison in pts with baseline A1C <9% and ≥9% produced hazard ratios of: 0.77 [0.621, 0.945], and 0.75 [0.490, 1.145], respectively.

In this matched cohort study, pts with T2DM who started with MET+SITA dual therapy progressed to insulin therapy at a slower rate than those who started with MET+SU dual therapy.

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170-LB

Statins and Finasteride Use Differentially Modifies the Impact of Metformin on Prostate Cancer Incidence in Men with Type 2 Diabetes Who Remain Insulin Naive

CHEN-PIN WANG, JOHN R. DOWNS, CARLOS LORENZO, JAVIER HERNANDEZ, DONNA M. LEHMAN, *San Antonio, TX*

This study assessed if concurrent use of statins or finasteride modified the impact of metformin on prostate cancer risk in men with type 2 diabetes who were insulin naive.

The study cohort consisted of 77,951 men with type 2 diabetes seen in the Veteran Administration Health Care System, without prior cancer or liver diseases, nor prescription of thiazolidinediones or insulin between FY2003-FY2013. Cox proportional hazard analyses were conducted to compare the hazard ratio (HR) of PCa associated with metformin use between statins or finasteride users and none users, where covariates and propensity scores of metformin use were adjusted for.

Mean follow-up was 6.4±2.8 years; 5.2% (N= 4070) of the cohort subsequently received a PCa diagnosis. Both statins and finasteride significantly modified the impact of metformin on PCa incidence (p-value<.001): the impact of metformin on decreased PCa incidence (HR=0.88, p-value<.001) was greater among statin users (HR=0.73, p-value<.001), while this impact was altered among finasteride users HR=1.31, p-value<.001). Compared to non-users, metformin alone (HR=0.88), statin alone (HR=0.75), finasteride alone (HR=0.50), or the combination of statin+metformin (HR=0.55), metformin+finasteride (HR=0.66), statin+finasteride (HR=0.41), or statin+metformin+finasteride (HR=0.61) were all associated with reduced PCa incidence.

Metformin was associated with reduced PCa risk in insulin naïve men with type 2 diabetes. The beneficial impact of metformin was enhanced by statin use but attenuated by finasteride use. Metformin, statins, and finasteride use alone or in combination were associated with decreased PCa risk. The interaction of metformin with finasteride and statins on PCa risk needs to be confirmed in other cohorts of men with type 2 diabetes.

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171-LB

Ambient Air and Traffic Pollutants Have Adverse Effects on Insulin and Glucose Homeostasis in Mexican Americans

ZHANGHUA CHEN, RICHARD M. WATANABE, ANNY H. XIANG, THOMAS A. BUCHANAN, MUHAMMAD T. SALAM, CLAUDIA M. TOLEDO-CORRAL, ENRIQUE TRIGO, FREDERICK W. LURMANN, FRANK D. GILLILAND, *Los Angeles, CA, Pasadena, CA, Petaluma, CA*

Ambient air pollution (AP) exposures have been shown positively associated with insulin resistance measured by HOMA-IR, yet no studies have addressed the relationship of both ambient and traffic AP with direct measures of insulin sensitivity and secretion. We hypothesized that 1- and 12-month AP exposures are associated with insulin resistance and poor insulin secretion. Data were from the BetaGene study which included Mexican American adults (n=1176, mean age 34±8 years, mean BMI 29.7 kg/m^2, 72% female) with measurements from DXA, oGTT, FSIGT, lipid panel, and self-reported dietary and physical activity (PA). Ambient AP exposure metrics were estimated using data from air quality monitors. Traffic-related exposures were assessed by residential distance from nearest freeway and estimated nitric oxides (NOx) as predicted by a dispersion model. Individual and multiple APs ($PM_{2.5}$, O_3, and NO_2) were analyzed for their associations with metabolic outcomes using variance components models. After adjustment for age, sex, percent body fat, and seasons, one standard deviation increase of 1-month average ambient air $PM_{2.5}$ was associated with 4.9% decrease of insulin sensitivity (S_I) measured by FSIGT (p=0.001). Higher 1- and 12-month average $PM_{2.5}$ were also associated with higher fasting glucose and insulin, HOMA-IR, LDL, and lower HDL (all $p \leq 0.01$). Higher freeway-related NOx was associated with higher fasting glucose and insulin, and lower acute insulin response (p=0.001, 0.001, and 0.043, respectively). Adjustment for each other in the joint model including both ambient air $PM_{2.5}$ and freeway-related NOx did not change the conclusion. Results were robust to further adjustment for weekly PA minutes and daily calorie intakes. We concluded that ambient air and traffic-related pollutants may adversely impact insulin and glucose homeostasis, and lipid profiles. Our findings suggest that ambient air and traffic pollution may play a role in T2D pathophysiology.

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172-LB

Development of Diabetes According to the Body Phenotype in Korean Adults: The Korean Genome and Epidemiology Study

JI HEE YU, SUN HWA KIM, JA YOUNG RYU, JAE HEE AHN, NAM HOON KIM, HO CHEOL HONG, HYE JIN YOO, JI A. SEO, SIN GON KIM, KYUNG MOOK CHOI, SEI HYUN BAIK, DONG SEOP CHOI, CHOL SHIN, NAM HAN CHO, NAN HEE KIM, *Seoul, Republic of Korea, Suwon, Republic of Korea*

Introduction: Longitudinal studies evaluating the relevance of metabolically healthy obese (MHO) or metabolically obese but normal weight (MONW) phenotype at risk for diabetes are few and results are contradictory. We aimed to investigate associations between combinations of body mass index (BMI) categories and metabolic syndrome and risk of the development of diabetes in Korean adults.

Methods: We studied 3,723 participants without diabetes, aged 40-69 years at baseline from the Korean Genome and Epidemiology Study. Participants were divided into four groups based on the BMI and metabolic syndrome: metabolically healthy normal weight (MHNW), MONW, MHO, and metabolically abnormal obese (MAO) subjects. Diabetes was diagnosed by 75g oral glucose tolerance test and medication history. The incidence of diabetes was identified by biennial health examinations during the 8-years of follow-up.

Results: The proportion of MHNW, MONW, MHO, and MAO subjects were 36.2, 19.7, 17.8, 26.4% of the baseline population. After 8 years, those were changed into 28.4, 29.0, 10.2 and 32.4%, respectively. The cumulative incidence of diabetes was 7.8%, 23.3%, 10.6%, and 29.0% in MHNW, MONW, MHO, and MAO subjects. In age- and sex-adjusted time-dependent Cox proportional hazards models, the risk for diabetes was increased in MONW (hazard ratio 2.88 [95% confidence interval: 2.29-3.63]) and MAO (3.78 [3.05-4.69]), while it was not increased in MHO (1.37 [0.99-1.90]), compared with the MHNW subjects. In this population, the risk factors for the development of diabetes were systolic blood pressure (1.01 [1.00-1.01]), triglyceride (1.88 [1.57-2.26]), and fasting glucose levels (1.06 [1.05-1.07]), but not BMI.

Conclusion: Metabolically unhealthy phenotypes were increased during the 8-years of follow-up, and those were more important risk factors for diabetes than obesity itself in Korea.

173-LB

A Systematic Review and Meta-analysis of the Association between Hyperglycemia and Surgical Site Infections

EMILY T. MARTIN, HUONG NGUYEN, MARESSA SANTAROSSA, CAITLIN KNOTT, ELIZABETH A. CONGER, KEITH KAYE, LINDA A. JABER, *Detroit, MI*

Hyperglycemia is frequently hypothesized to be a risk factor for surgical site infection (SSI) in adults; however the magnitude of this effect is difficult to discern with an adequate sample size. Our objective was to conduct a systematic review and meta-analysis of the association between hyperglycemia and SSI. We conducted a systematic literature search of relevant articles published from December 1985 through April 2013. Articles were reviewed for eligibility and the most-adjusted estimate was abstracted. Only studies which assessed a threshold definition for hyperglycemia were included in the analysis. Summary estimates and predictive intervals were calculated by random-effects meta-analysis. Our initial search terms yielded 2,371 articles. All abstracts were screened per inclusion criteria and 96 articles were reviewed in depth. Twelve articles were eligible for analysis, encompassing 30,199 patients.

Study-specific definitions for hyperglycemia ranged from > 100 to ≥ 200 mg/dL with 7 studies using a threshold of ≥ 200 mg/dL. Six studies provided estimates for the effect of preoperative hyperglycemia (Pooled OR: 1.69 (95% Confidence Interval 1.24, 2.32)). Nine studies provided estimates for the effect of postoperative hyperglycemia (Pooled OR: 1.37 (95% Confidence Interval 1.16, 1.60)). Our meta-analysis demonstrated similar increases in surgical site infections among patients with preoperative or postoperative hyperglycemia. These increases were small in magnitude, highlighting the need for future trials of glucose control protocols to use large cohorts with adequate power.

EPIDEMIOLOGY—TYPE 1 DIABETES

174-LB

Cancer among T1D Patients: 8,800 Cases in 3.7 Million Person—Years of Follow-up in Four Countries

BENDIX CARSTENSEN, SØREN FRIIS, JESSICA HARDING, DIANNA J. MAGLIANO, REIJO SUND, ILMO KESKIMÄKI, RICKARD LJUNG, ANN-MARIE SVENSSON, SARAH WILD, SOFFIA GUDBJÖRNSDOTTIR, *Gentofte, Denmark, Copenhagen, Denmark, Melbourne, Australia, Helsinki, Finland, Stockholm, Sweden, Gothenburg, Sweden, Edinburgh, United Kingdom*

Diabetes (DM) patients carry an excess risk of cancer in the order of 20-25%; this is mainly derived from follow-up of type 2 patients (T2D). The excess risk of cancer among type 1 (T1D) patients is described here as it is anticipated to be different from T2D patients. T1D patients from four countries with nation-wide diabetes registers: Australia (1997-2008), Denmark (1995{-2009), Finland (1972-2010), and Sweden (1987-2011) were followed for cancer occurrence. T1D was defined by diagnosis of DM before age 30. Cancer incidence rates were compared to population cancer incidence rates from national cancer registries. We used Poisson-models for rates, adjusting for age and date of follow-up, and date of birth. We estimated the overall rate ratio (RR) for all T1D patients and the effect of time since DM diagnosis. There were a total of 8,807 cancers among T1D patients during 3.7 million person-years of follow-up with median age at cancer diagnosis 51.1 (IQR: 43.5,59.5). Overall, we found an RR of any type of cancer of 1.00 (95% CI: 0.97-1.03) among men and 1.05 (95% CI: 1.02-1.08) among women. The highest RRs were found for colorectal cancer, (RR=1.13 (M), 1.14 (F)), liver cancer (RR=2.14 (M), 1.50 (F)), pancreas cancer (RR=1.74 (M), 1.31 (F)), endometrial cancer (RR=1.4 kidney cancer (RR=1.28 (M), 1.44 (F)), and thyroid cancer (RR=1.29 (M), 1.46 (F)), all significant. We found a strong effect of diabetes duration, with an RR of 2.5 during the first year, decreasing to 1.2 (M) and 1.1 (F), after 2-5 years. Some of the observed excess risk may be explained by risk factors for cancer being more frequent in T1D patients (obesity), however this effect is presumably smaller than in T2D patients, and hence consistent with the smaller excess risk. The long-term RR (>5 years of DM) is less than 1.2, which means that some small effect of exogenous insulin cannot be excluded, but the study is also consistent with an assumption of no such effect.

Supported By: EFSD

175-LB

Change in A1c One Year after Continuous Subcutaneous Insulin Infusion (CSII) Initiation in Adults with Type 1 Diabetes (T1D): The Joslin (JDC) and Steno (SDC) Experiences

SANJEEV N. MEHTA, MARTIN J. ABRAHAMSON, HOWARD A. WOLPERT, HENRIK ULLITS ANDERSEN, EVA E. HOMMEL, WILLIAM MCMULLEN, MARTIN RIDDER-STRÅLE, *Boston, MA, Gentofte, Denmark*

Adults with T1D often consider CSII to improve glycemic control. We performed a retrospective analysis of adults ≥18 years with T1D seen at 2 diabetes centers since 2002 to assess change in A1c (ΔA1c) 1 year after CSII start. All JDC and SDC patients were analyzed for age, T1D duration, weight (kg), and A1c (%) before and 1 year after CSII initiation to identify independent variables explaining ΔA1c at 1 year. Data were available for 871 patients (271 JDC, 49% male; 600 SDC, 38% male). Mean age and T1D duration at CSII initiation were 46±15 years and 19±13 years (JDC) and 40±14 years and 22±13 years (SDC). Baseline A1c was 7.8±1.1% (JDC) and 8.4±1.6% (SDC). Overall, ΔA1c was -0.2% (JDC) and -0.6% (SDC). The table shows ΔA1c and weight change (ΔWt) according to baseline A1c. ΔA1c was inversely correlated with ΔWt at SDC (r=-0.12, p<.05), but not JDC. At JDC, higher baseline A1c (p<.05) was the only independent predictor of ΔA1c at 1 year. At SDC, higher baseline A1c, older age, and female sex were independent predictors (p<.05 for all) of ΔA1c at 1 year. Both models explained 26% of the variability of ΔA1c. CSII initiation resulted in lower A1c, most notably in those with the highest baseline A1c; greater A1c reduction at SDC may reflect the higher baseline A1c observed in this group. Modest weight gain was observed in adults with A1c≥9% prior to CSII initiation.

Change in A1c, Weight in Adults with T1D 1 Year after CSII Initiation.

Baseline A1c (%)	n, JDC/SDC	Baseline A1c (JDC)	Baseline A1c (SDC)	ΔA1c (JDC)	ΔA1c (SDC)	ΔWt (JDC)	ΔWt (SDC)
<7.0	50/41	6.4±0.4	6.5±0.9	0.2	0.0	0.6	0.3
7.0-7.9	107/183	7.5±0.3	7.5±0.4	0.0	-0.3*	-0.4	0.0
8.0-8.9	70/205	8.4±0.3	8.4±0.4	-0.3†	-0.7*	0.8	0.0
≥9.0	44/171	9.6±0.5	9.8±1.1	-1.0*	-1.1*	1.7‡	1.1*

*p<.0001, †p<.005,‡p.

176-LB

Glycemic Control in Patients with Type 1 Diabetes: The Role of Insulin Pump

NOEMI GONZALEZ, LUCRECIA HERRANZ, ROSALIA SANCHEZ, CRISTINA GRANDE, NATALIA HILLMAN, BEATRIZ BARQUIEL, FELIPE PALLARDO, *Madrid, Spain*

To assess glycemic control in type 1 patients at a Diabetes Unit, evaluate the effectiveness of CSII, and examine the relationship of A1c to long-term diabetes.

A1c and clinical data from patients in 2012 were collected from clinical reports. Adequate control was defined as A1c <7% and long-term diabetes > 10 years. Pump/non pump users were compared by Student's t test and $\chi 2$ test. Predictive factors of adequate A1c were assessed by multiple logistic regression. Patients were further stratified according to diabetes duration.

833 patients were included. Clinical characteristics are shown in table 1.

	total DM-1 (833)	non pump users (676)	pump users (157)	p
age (years)	42 (13)	42 (13)	39 (10)	<0.001
female gender	55.8%	53%	68.2%	0.001
Dm1 duration (years)	17 (10-26)	17 (8-26)	19 (13-25)	0.285
A1c (%)	7.4 (1.1)	7.4 (1.1)	7.1 (0,8)	<0.001
A1c <7%	41.8%	38.9%	54.1%	0.001
Retinopathy	24.6%	24.4%	25.5%	0.779
Nefropathy	9.6%	9.8%	8.9%	0.746
Hypertension	17.1%	18.2%	12.2%	0.072
Hypercholesterolemia	59.4%	61.7%	49.7%	0.006

Data are expressed as percentage, median (SD) or median (RIQ).

Pump users had better glycemic control. Adjusting for gender, age and hypercholesterolemia the OR for A1c<7% in this group was 1.77 (1.24-2.53), p=0.002. If diabetes duration was <10y no A1c differences were found (7.4 vs. 7.3; p=0.614). If long-term diabetes, A1c was lower in pump users (7.0 ± 0.7 vs. 7.5±1.0; p<0.001). They were younger (40±9 vs. 46±13y; p<0.001), had less hypertension (13.5 vs. 23%; p=0.018) and hypercholesterolemia (50.4 vs. 70.9%; p<0.001). The adjusted OR for A1c<7% was 2.17 (1.45-3.26); p<0.001.

Globally, pump users have better glycemic control. However, when stratified for diabetes duration, pump benefit is only for patients with long-term diabetes, when difficulty in maintaining glycemic control may be related to loss of pancreatic reserve.

GENETICS—TYPE 2 DIABETES

177-LB

Differential Transcriptome Analysis of Diabetes Resistant and Sensitive Mouse Islets Reveals Significant Overlap with Human Diabetes Susceptibility Genes

DANIELA MATZKE, OLIVER KLUTH, ANNE KAMITZ, GUNNAR SCHULZE, MARKUS JÄHNERT, HANS-GEORG JOOST, ANNETTE SCHÜRMANN, *Potsdam, Germany, Nuthetal, Germany*

Type 2 diabetes in humans and in obese mice is polygenic. However, the majority of genetic markers discovered in recent genome-wide association studies (GWAS) explain only a small fraction of the genetic impact to the disease. New Zealand Obese (NZO) mice are diabetes susceptible and show beta-cell failure, whereas obese mice on C57BL/6-background (B6-ob/ob) do not develop diabetes, because they are able to compensate by enhancing beta-cell proliferation. Our aim was to identify responsible genes mediating beta-cell failure in NZO mice and to validate human diabetes genes, which have been identified in GWAS. RNA-sequencing based transcriptome analysis of islets from NZO and B6-ob/ob mice that received a short glucose challenge identified 2416 differentially expressed genes. Pathway enrichment studies indicate major differences in cell cycle regulation (G1 to S transition), cell adhesion, cytoskeleton remodeling, and glutathione metabolism between NZO

and B6-ob/ob islets. Projection of differentially expressed genes to QTL of a F2 (NZOxC57BL/6) population depicted 5 genes hypomorphic in B6 and 9 genes hypomorphic in NZO on Chr. 1,12,13 and 19. One gene exclusively expressed in NZO, the Interferon-activated gene 202b (Ifi202b), is located within the diabesity QTL Nob3 on Chr.1. Overexpression of Ifi202b significantly inhibited cell proliferation in MIN6 cells indicating that it participates in disability of NZO islets to compensate. Alignment of the differentially expressed mouse genes to 106 human diabetes candidate genes revealed an overlap of 20 genes, including TCFL2, IGFBP2, CDKN2A, CDKN2B, GRB10 and PRC1, that can be linked to the regulation of the cell cycle. Our data provide a functional validation of human diabetes candidate genes including those involved in regulating islet cell recovery and proliferation and furthermore deliver additional candidates that might be involved in human beta-cell failure.

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178-LB

Meta-analysis of Birth Weight Genome-Wide Association Studies Identifies Two Novel Loci Extending Links between Early Growth and Adult Metabolic Diseases

MOMOKO HORIKOSHI, MARJOLEIN N. KOOIJMAN, JONATHAN P. BRADFIELD, LISBETH CARSTENSEN, DAVID STRACHAN, NATÀLIA V. TEJEDOR, MARCELLA MARINELLI, RICO RUEEDI, NIINA PITKÄNEN, ESKIL KREINER-MØLLER, ELISABETH THIERING, WEI ANG, CAROL WANG, PETER K. JOSHI, EILEEN T.H. BOH, IOANNA NTALLA, ELISABETH M. VAN LEEUWEN, VIRPI LINDI, DIANA L. COUSMINER, YING WU, TARUNVEER S. AHLUWALIA, NIELS GRARUP, STRUAN F.A. GRANT, MARK I. MCCARTHY, RACHEL M. FREATHY, INGA PROKOPENKO, ANDREW P. MORRIS, EGG CONSORTIUM, *Oxford, United Kingdom, Rotterdam, Netherlands, Philadelphia, PA, Copenhagen, Denmark, London, United Kingdom, Barcelona, Spain, Lausanne, Switzerland, Turku, Finland, Munich, Germany, Perth, Australia, Edinburgh, United Kingdom, Singapore, Singapore, Leicester, United Kingdom, Kuopio, Finland, Helsinki, Finland, Chapel Hill, NC, Exeter, United Kingdom*

Lower birth weight (BW) is associated with increased risk of future type 2 diabetes (T2D) and cardiovascular diseases. Based on HapMap 2 imputation, we previously reported 7 loci associated with BW, of which two (*ADCY5*, *CDKAL1*) have been implicated in T2D and one (*ADRB1*) in hypertension. Here we report reanalysis based on an increased sample size and imputation up to 20.8M SNPs from the more dense 1000 Genomes Project reference panels. Our aims were to: discover novel loci; detect BW associations involving low-frequency (LF) variants (MAF<5%) of larger effect sizes; and fine-map established and novel loci to identify potential causal variants by constructing credible sets of variants with 99% overall posterior probability of being causal.

For analysis, we considered 41,551 European singletons (17 studies) born at ≥37 weeks' gestation with genome-wide association (GWA) and imputation data. Standardized sex-specific Z-scores of BW were tested for association with each SNP assuming an additive genetic model. Association summary statistics were combined across studies using inverse-variance fixed-effects meta-analysis.

We detected two novel common variant loci at genome-wide significance: near *MAFB* ($p=3.1x10^{-8}$) and *SREBF2* ($p=3.9x10^{-9}$). *MAFB* has been implicated in hyperlipidemia and *SREBF2* is involved in cholesterol biosynthesis. There was no evidence for causal LF variants explaining common GWA study signals. The 99% credible sets defined by fine-mapping at known GWA study signals included fewer than 20 SNPs at 4 loci. At *ADRB1*, the credible set included just 5 variants, including G389R.

Collectively, 4 of the 9 known and novel loci provide genetic links between BW and T2D, hypertension and hyperlipidemia, highlighting complex non-linear relationships between genetic variation, early growth and later metabolic disease including T2D.

179-LB

Regulators of Mendelian Disease Genes Are Enriched among T2D-associated Variants

JASON M. TORRES, KAANAN SHAH, NANCY J. COX, *Chicago, IL*

Thousands of associations between Mendelian and complex diseases have been recently detected through extensive data mining of medical records from more than 110 million patients and constitute a "non-degenerate Mendelian code" (Blair et al., *Cell* 2013). Given that common variants within Mendelian disease (MD) genes implicated by this code were found to be significantly associated with common diseases (Blair et al. 2013), we hypothesized that regulators of MD gene expression would be overrepresented among top signals from GWAS on T2D. We evaluated single nucleotide polymorphisms associated with gene expression (eSNPs) mapped in human adipose, skeletal muscle, lymphoblastoid cell lines (LCLs) and nine additional tissues mapped by the GTEX Consortium for enrichment among T2D-associated variants in the Wellcome Trust Case Control Consortium T2D GWAS dataset. We excluded eSNPs for genes underlying monogenic forms of diabetes to ensure that any observed enrichment would not be attributable to effects from established diabetes genes. The proportion of eSNPs for MD genes with false discovery rate (FDR) q-values ≤ 5% is $2x10^{-4}$ whereas the proportion for all GWAS-interrogated SNPs is $3x10^{-5}$. The MD eSNPs most associated with T2D correspond with myeloid differentiation primary response gene (*MyD88*). MyD88 deficiency caused by loss of function mutations has been observed in patients with increased susceptibility to pyogenic bacterial infections. Moreover, the L265P mutation is common in patients diagnosed with Waldenstrom macroglobulinemia. Interestingly, we did not observe an enrichment of eSNPs for MD genes previously associated with T2D. The narrow-sense heritability explained by eSNPs of MD genes is disproportionate relative to the proportion of all SNPs in this set by a factor of 2.18. Taken together, these results support an important yet complex role for genetic regulators of MD genes in T2D susceptibility.

180-LB

Analysis of a Cardiovascular Disease Genetic Risk Score in the Diabetes Heart Study

LAURA M. RAFFIELD, AMANDA J. COX, JEFFREY CARR, BARRY I. FREEDMAN, FANG-CHI HSU, CARL D. LANGEFELD, DONALD W. BOWDEN, *Winston-Salem, NC, Nashville, TN*

Recent studies have examined genetic risk scores of single nucleotide polymorphisms (SNPs) identified by genome-wide association studies (GWAS) for their cumulative impact on cardiovascular disease (CVD) related traits. Most analyses have used SNPs associated with a single trait; in this analysis, we instead examined a more comprehensive risk score of SNPs associated with blood pressure, arterial calcification, C-reactive protein, body mass index, electrocardiogram traits, stroke, coronary heart disease, fasting plasma glucose, glomerular filtration rate, lipids (triglycerides, low-density and high-density lipoprotein, or total cholesterol), and type 2 diabetes (T2D). This risk score was analyzed for potential associations with subclinical CVD, prior CVD events, and mortality in 1175 individuals of European descent from 467 families in the Diabetes Heart Study (DHS), a T2D- enriched cohort at elevated risk of CVD. 83.7% of participants were affected by T2D, with average diabetes duration of 10.5 ± 7.2 years. Genetic scores were derived by adding the number of risk alleles across 215 SNPs; scores ranged from 186 to 245 (212.9 ± 8.6, mean ± SD). Associations were examined using marginal models with generalized estimating equations for subclinical CVD and prior CVD events and Cox proportional hazards models with sandwich-based variance estimation for mortality in SAS 9.3. Analyses were adjusted for age, sex, and T2D affected status. An increase in genetic risk score was modestly associated with increased coronary artery calcification (p=0.0044), with a trend for association with increased carotid artery calcification (p=0.11). No significant associations with aortic calcification, prior CVD events, or all-cause or CVD mortality were observed. These results indicate that a comprehensive genetic risk score for CVD related traits does not have compelling predictive power for CVD in the DHS, highlighting the limits of current knowledge of the genetics of CVD in individuals affected by T2D.

181-LB

Quantitative Glycemic Trait Genetic Loci Are More Enriched for Common Variants with Regulatory Potential Compared with Type 2 Diabetes Risk Loci

SRIDHARAN RAGHAVAN, AARON S. LEONG, MARCO DAURIZ, CHING-TI LIU, JOSÉE DUPUIS, JOSE C. FLOREZ, JAMES B. MEIGS, *Boston, MA, Verona, Italy*

Background: Many common single nucleotide polymorphisms (SNPs) identified through genome-wide association studies, including for glycemic quantitative traits (QTs, fasting glucose (FG), fasting insulin (FI)) and type 2 diabetes (T2D), are neither protein coding nor in linkage disequilibrium (LD) with coding variants, suggesting that regulatory variation plays a prominent role in the genetic basis of common diseases. Here, we examined regulatory variation at or around SNPs associated with FG, FI, and T2D.

Methods: We used RegulomeDB to classify SNPs at 108 QT- or T2D-associated loci as having strong evidence for regulatory function (RegulomeDB score 1-3) or weak/no evidence for regulatory function (RegulomeDB score 4-7). We excluded loci at which QT and T2D SNPs were in strong LD ($r^2 \geq 0.8$) with non-synonymous SNPs where coding variation could explain the associations. For remaining loci, we counted the number of SNPs with strong or weak evidence for regulatory potential in strong LD with the lead SNPs, and compared the proportion of SNPs with strong regulatory potential at QT, T2D and overlapping loci.

Results: After excluding 16 loci harboring coding variants (6 QT, 7 T2D, and 3 overlapping), 92 loci (30 QT, 46 T2D, and 16 overlapping) were examined for regulatory variation. Of these, 19 QT, 17 T2D, and 7 overlapping loci had ≥1 SNP

with RegulomeDB scores 1-3. QT loci had a greater proportion of SNPs with RegulomeDB scores 1-3 (54 of 553 SNPs; 9.8%) than T2D (34 of 878 SNPs; 3.9%) and overlapping (11 of 304 SNPs; 3.6%) loci. The lower RegulomeDB scores at QT loci compared to T2D loci appear driven by enrichment for transcription factor binding sites (16.5% vs. 10.8%) and eQTLs (2.7% vs. 0.1%).

Conclusions: Glycemic QT and T2D loci harbor regulatory variation with QT loci associated with a greater proportion of predicted regulatory SNPs based on current annotation of the genome.

182-LB

Integration of Genomic and Expression Data Confirms 40 Known Loci to Be Cosmopolitan Disease Susceptibility Loci for Type 2 Diabetes in Both European and African American Populations

TOBY ANDREW, WINSTON LAU, NIKOLAS MANIATIS, *London, United Kingdom*

We aim to assess if the established 65 disease susceptibility loci for type 2 diabetes (T2D) identified in Europeans are also risk loci for African Americans. We conducted a genome-wide association study using fine-scale population-specific genetic maps derived from HapMap Phase II data, applied to 1) genomic array data for Type 2 diabetes (T2D) cases and controls for European (WTCCC1 and WTCCC2) and African-American T2D (NIDDK) and 2) fine map genomic and adipose and skin expression data for healthy European samples with T2D cases excluded (EBI, E-TABM-1140).

The method utilises a powerful multi-marker test of association based upon the Malécot model to assess approximately 5000 analytic windows across the human genome, each of equal genetic size. The same analytic window co-ordinates were used for both disease and cis-eQTL expression mapping to provide commensurability between populations and to assess evidence that identified disease loci are eQTLs and hence confer risk by regulating gene expression. For each window, a test statistic is obtained along with a genomic location estimate and 95% confidence intervals for the location of the putative functional variant.

We have been able to establish: 1) that the same loci for over 50% of the 65 loci in Europeans are also disease susceptibility loci for African-African samples; 2) more refined functional variant location estimates and 3) based upon the adipose expression data (and depending upon threshold criteria used), we estimate approximately 25% of all the identified susceptibility loci are themselves expression quantitative trait loci (eQTLs). We conclude that there are still likely to be many common genomic disease susceptibility variants that can be usefully characterized and that integrative genomic methods have the potential to provide important mechanistic clues about gene function and disease susceptibility.

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183-LB

Functional Connectivity and Annotation on Fasting Plasma Glucose Risk-associated Variants in East Asians

JOO-YEON HWANG, MIN JIN GO, BOK-GHEE HAN, BONG-JO KIM, *Chung-buk, Republic of Korea*

Fasting plasma glucose (FPG) has been recognized as an important indicator for the overall glycemic state preceding the onset of metabolic diseases. However, previous GWAS results have fundamentally limited by functional consequences. Our combined meta-analysis identified three new FPG loci reaching genome-wide significance in East Asians. To investigate functional connectivity, we performed the Gene Relationships Across Implicated Loci (GRAIL) literature-based annotation analysis. The strongest connections were observed in biological pathways (insulin secretion, circadian rhythm, and carbohydrate digestion) with the most frequently connecting terms including insulin, glucose, circadian and growth. The results highlighted biological functions of newly identified loci in the regulation of glucose metabolism. We also observed an additional aspect of three-dimensional chromatin interaction as well as regulatory functional annotations from the ENCODE project. Our results could provide additional insight into the genetic variation implicated in fasting glucose regulation.

184-LB

Metabochip Genotyping in a Mexican Case-Control Study Identified New Loci Associated with Type 2 Diabetes

MARIA AURORA MEJIA BENITEZ, AMÉLIE BONNEFOND, LOIC YENGO, STEPHANE LOBBENS, ADAN VALLADARES SALGADO, JESUS PERALTA, JAIME GARCIA MENA, MIGUEL CRUZ LOPEZ, PHILIPPE FROGUEL, *Distrito Federal, Mexico, Lille, France*

The prevalence of type 2 diabetes (T2D) is very high in Mexico (14%). Performing genetic studies in Mexicans could identify risk alleles that are common in this population but rare in others, towards new pathways involved into T2D pathophysiology. Here, we analyzed 196,725 single nucleotide polymorphisms (SNPs) in a Mexican case-control study.

We genotyped DNA from 988 cases and 987 controls using Metabochip arrays. The association between SNPs and T2D was assessed via logistic regressions adjusted for age, sex, body mass index and principal components for population stratification, under an additive model.

We found significant associations between T2D and several SNPs (not in linkage disequilibrium) in or close to *GLIS3*, *JAZF1*, *FGD6*, *ARRP21* and *CYBRD1* (Table). When analyzing a genetic risk score from 69 T2D-associated SNPs in Europeans, we found a strong association of this score with T2D (effect size by risk-allele of 0.065; P=3.92×10^{-8}).

The involvement of *GLIS3* or *JAZF1* into T2D has been already reported in other populations. The association between *CYBRD1* rs13392902 and T2D was only suggested. However, the contributions of *FGD6* rs6538592 and *ARRP21* rs7613472 to T2D risk are novel. Both SNPs were present in the array because of their suggested association with cardiovascular disease or related traits.

Gene	SNP	AA***	Population	*N*	AAF*** (%)	AAF (%) Europe	Odds Ratio	*P-value*
*GLIS3**	rs12335418	A	Control	987	40.1	71.4	—	—
			Diabetic	988	38.2		0.67	3.16×10^{-7}
*GLIS3**	rs12350696	A	Control	987	56.1	69.0	—	—
			Diabetic	988	52.0		0.68	1.15×10^{-6}
*GLIS3**	rs12000159	T	Control	987	48.2	69.2	—	—
			Diabetic	988	42.1		0.70	3.39×10^{-6}
*GLIS3**	rs7849638	A	Control	987	51.3	65.5	—	—
			Diabetic	988	50.1		0.69	1.95×10^{-6}
*GLIS3**	rs17717221	G	Control	987	58.4	96.7	—	—
			Diabetic	988	58.6		1.49	6.45×10^{-6}
*GLIS3**	rs73382379	G	Control	987	91	97.5	—	—
			Diabetic	988	93.5		1.48	9.75×10^{-6}
*GLIS3**	rs17212955	A	Control	988	40.0	34.2	—	—
			Diabetic	987	46.3		1.42	6.99×10^{-6}
*FGD6**	rs6538592	G	Control	988	44.1	50.0	—	—
			Diabetic	987	42.6		0.67	4.13×10^{-6}
*ARRP21**	rs7613472	A	Control	988	77.3	70.4	—	—
			Diabetic	987	70.0		0.62	1.84×10^{-6}
*JAZF1**	rs849142	A	Control	988	34.1	48.3	—	—
			Diabetic	987	33.2		0.68	5.74×10^{-6}
*JAZF1**	rs12531540	C	Control	988	62.0	50.8	—	—
			Diabetic	987	60.1		0.68	5.81×10^{-6}
*JAZF1**	rs849138	G	Control	988	46.2	70.2	—	—
			Diabetic	987	46.0		0.68	8.39×10^{-6}
*JAZF1**	rs702814	A	Control	988	32.1	49.2	—	—
			Diabetic	987	30.0		0.60	8.97×10^{-6}
*JAZF1**	rs864745	A	Control	988	36.1	50.8	—	—
			Diabetic	987	32.1		0.69	9.85×10^{-6}
*CYBRD1***	rs13392902	A	Control	988	91.0	90.8	—	—
			Diabetic	987	90.2		0.47	9.50×10^{-6}

*Adjusted for age, sex and BMI. **Adjusted for age and sex only. ***__AA__: Ancestral Allele / __AAF__: AA frequency.

IMMUNOLOGY

185-LB

Transcriptional Profiling of Polarized Macrophages Using RNA Sequencing

SRIKANTH KANAMENI, KRANTI KONGANTI, WEI YING, CHENG AN-CHANG, HUI SONG, FANG YANG, HAIQING WANG, PATALI S. CHERUKU, BEIYAN ZHOU, *College Station, TX, Wuhan, China*

Macrophages display remarkable plasticity and can display an array of activation states in response to environmental cues. Macrophages (M0) are polarized to classical pro-inflammatory (M1) or alternative anti-inflammatory (M2). The adipose tissue macrophages (ATMs) of obese individuals are major inflammatory mediators in white adipose tissue and crucial contributors to of adipose tissue inflammation and insulin resistance. However, modulatory networks governing ATMs polarization have been investigated but the full picture remains vague.

To explore genome wide signaling network in controlling ATM polarization, we generated transcriptome profiles from macrophages with various activation status - M0, M1 and M2. After analysis with multiple algorithms, we identified 13400 aligned unique loci in the mm10 database. Expression of 1803 transcripts are induced at least 2 fold during M1 and 765 during M2 activation, whereas 1612 are downregulated upon M1 and 521 by M2 stimuli. Gene ontology studies revealed adipokine signaling and antigen presenting and processing pathways are enriched in gene sets that are altered in M1 activation (>2 folds). Further, our study also identified several membrane proteins that are differentially presented on either M1 or M2 macrophages, thus may serve as potential cellular markers for identifying macrophage populations with polarized activation status. Our analysis found 240 long non-coding (lncRNAs) RNAs are actively regulated during macrophage polarization as annotated in the mm10 dataset. Scanning the chromosome region of 132 differentially expressed lncRNAs, we found that several lncRNAs are located in the loci with enriched gene clusters involved in inflammation, lipid metabolism and insulin resistance. Thus, this study provides a comprehensive profile of transcriptome that can be of great importance to understand the functions of ATMs in regulating adipose tissue function, especially obesity associated adipose tissue inflammation and insulin resistance

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186-LB

Hyperglycemia without Insulin Deficiency Promotes Expression of Inflammatory Genes, S100A8/S100A9, and Acyl-CoA Synthetase 1 (ACSL1) in White Blood Cells (WBC)

MARIANE ABDILLAHI, MANALI YAVATKAR, JOHN LOIKE, KARIN E. BORNFELDT, RACHEL J. PERRY, GERALD I. SHULMAN, IRA J. GOLDBERG, *New York, NY, Seattle, WA, New Haven, CT*

Patients with type 1 and type 2 diabetes mellitus are at an increased risk of developing cardiovascular disease but the mechanisms remain unclear. Increased levels of calcium binding inflammatory proteins S100A8 and S100A9 have been correlated with increased incidence of diabetes complications. In addition, studies in diabetic mice have implicated the fatty acid metabolic enzyme ACSL1 as an inflammatory mediator. We therefore examined whether hyperglycemia (HG) alone alters WBC gene expression of S100A8, S100A9 and TNFα. Gene expression was evaluated in-vitro by incubating whole human blood under normal and high glucose conditions and then isolating neutrophils and monocytes using Ficoll gradients. HG (15mM and 30mM glucose levels) increased expression of S100A8 (>3 fold) and S100A9 (>4 fold) in neutrophils, but not monocytes. TNFα expression was unchanged. mRNA levels of genes involved in fatty acid transport (CD36) and oxidation (CPT1) were decreased by ~50% with HG, while GLUT1 expression increased >4-fold at 15mM and 30mM in both cell types. The in-vivo effect of HG without insulin deficiency was also evaluated by performing hyperglycemic clamps on Sprague-Dawley rats using continuous infusions of a glucose solution. Glucose was increased to over 15 mM by 2 hours and remained elevated until completion of the study at 8 hours. Insulin levels increased from ~50 μU/ml to 700μU/ml. WBCs were isolated after 8 hours and mRNA levels assessed. Significant increases in S100A8 and S100A9 mRNA were observed in WBCs during HG (3 fold and 5 fold, respectively). TNFα mRNA levels were unchanged. HG increased ACSL1 mRNA levels in rat WBCs (7 fold), and in human monocytes and neutrophils (8 and 4 fold, respectively). Thus, HG alone induces significant increases in S100A8/S100A9 expression, which are more prominent in neutrophils than monocytes. Our data indicates that neutrophils may be the primary trigger of inflammation in diabetes.

187-LB

Eukaryotic Translation Initiation Factor 5a Inhibition Reduces the Proinflammatory Cytokines and ER Stress in Beta-Cell Micro-environment in a Humanized Transgenic Model of Type 1 Diabetes

SHAHNAWAZ IMAM, PRATHIBHA SANAL KUMAR, RAGHAVENDRA G. MIRMIRA, JUAN JAUME, *Madison, WI, Indianapolis, IN*

Type 1 diabetes (T1D) is a complex interplay of immune cells and pancreatic β cells. Upon activation T-cells releases proinflamatory cytokines viz. IFNg, IL17 and induce β cell dysfunction and eventual death. Deoxyhypusine synthase catalyses the crucial hypusine modification of eIF5A which promotes the translation of proinflamatory cytokines and induces intracellular stress in the pancreatic beta cell micoenvironment. Inducible Double-transgenic mice carrying DQ8-GAD65 gene were immunized with adenoviral vectors carrying GAD65 for diabetes induction. Animals were subsequently treated with deoxyhypusine synthase (DHS) inhibitor GC7 and monitored for diabetes development over time. Our result show that down regulation of eIF5A through inhibition of DHS and DOHH, altered the physiopathology as it reduces the potent inflammatory cytokine CD3+CD4+IL17 population and help in reducing the ER stress in pancreatic beta cells micro-environment, leads to significantly increase in the Fasting insulin production. Results of glucose tolerance test also explain that administration of GC7 provide tolerance and maintain the insulin production upto 30 mins in an animal model that closely resembles human T1D.

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188-LB

ERK Regulates TLR4 Endocytosis and Pro-inflammatory Responses in Macrophages

FANG-MEI CHANG, DANIEL ACEVEDO, SARA M. REYNA, *Edinburg, TX, San Antonio, TX*

Type 2 diabetes (T2D) is associated with low circulating levels of lipo-polysaccharide (LPS) resulting in endotoxemia that has been linked to insulin resistance. Binding of LPS to TLR4 leads to the activation of two TLR4 signaling pathways: MyD88-dependent and TRIF-dependent. Activation of the TRIF-dependent pathway requires TLR4 endocytosis. TLR4 endocytosis in macrophages leads to the activation of pro-inflammatory signaling pathways and production of factors linked to the development of T2D. However, the molecular mechanisms involved in regulating TLR4 endocytosis remain elusive. The extracellular signal-regulated kinase 1 and 2 (ERK1/2) module is activated downstream of TLR4 and associated with insulin resistance. We examined whether inhibition of ERK activity blocked TLR4-mediated inflammatory responses. RAW 264.7 macrophages were pre-treated with a MAPK inhibitor, U0126 (50 microM, 1 hr), and then treated with LPS (100 ng/ml, 6 hr). Inhibition of LPS-induced ERK activity decreased the release of MyD88-dependent MCP-1 (15±0.9 fold) and TRIF-dependent RANTES (49±4.0 fold), compared to macrophages exposed to LPS alone. Because inhibition of LPS-induced ERK activity did not affect total TLR4 protein or mRNA, we examined if ERK modulates the cell surface expression of TLR4. By using the loss of cell surface expression by flow cytometry as readout for TLR4 endocytosis, LPS decreased TLR4 surface expression by 65±0.3%, but when ERK was inhibited with 10, 25, or 50 microM U0126 in the presence of LPS, TLR4 surface expression increased in a dose-dependent manner (34±1.0%, 54±1.3%, and 63±1.6%, respectively). In addition, incubation of macrophages with UO126 blocked LPS-induced activation of IRF3, a TRIF-dependent transcription factor. In summary, ERK regulates TLR4 signaling pathways and endosomal trafficking in macrophages. We propose that ERK positively regulates TLR4-mediated inflammatory responses and inhibition of ERK signaling will protect against insulin resistance.

189-LB

Nanoparticle Biodistribution in a Mouse Model of Type 1 Diabetes: The Role of Macrophage Uptake and Homing in the Pancreatic Micro-environment

CHRISTINA KRIEGEL, KEVAN C. HEROLD, TAREK FAHMY, *New Haven, CT*

Imaging inflammation and monitoring the course of disease after an intervention remains a highly sought after goal for diagnostics and drug development. For this purpose, we designed novel "theranostic" reagents using fluorescently labeled biodegradable nano-scale polymeric particles (NP). We observed that fluorescing NP, but not the fluorophore in its free form, substantially accumulated in the pancreatic microenvironment of diabetic animals. Notably, only a moderate to low signal was detected in pre-diabetic or non-inflamed control mice. We hypothesized that NP accumulation in inflamed tissues may be due to either retention in the inflamed microvasculature or due to macrophage uptake and trafficking to these sites.

To elucidate the mechanism of NP retention in sites of inflammation, NPs were either incubated with macrophages of NOD mice and systemically administered or directly injected into either non-inflamed NOD/SCID control animals, pre-diabetic or diabetic NOD mice, or diabetic NOD mice subjected to in vivo macrophage depletion. Biodistribution of NP was evaluated using optical fluorescence on a Multispectral Bruker In Vivo imaging system. We observed an equally strong signal when NP were directly injected or delivered by macrophages. Most importantly, NP retention was dependent on macrophages since macrophage-depleted mice showed only minimal uptake in the pancreas after direct administration, whereas injection of ex vivo loaded macrophages led to significant NP accumulation in this group.

Our results indicate that macrophages play a crucial role in NP trafficking to the site of inflammation in a model of type 1 diabetes. Therefore, utilization of macrophages as a "Trojan Horse" might be advantageous in the development of innovative, targeted therapies for treatment of immune-mediated conditions at the site of inflammation, reducing the risk of undesirable off-target effects.

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TRANSPLANTATION

190-LB

Preservation of Beta-Cell Function following Pancreatic Islet Autotransplantation

PIOTR WITKOWSKI, *Chicago, IL*

The aim of the study was to assess the number of patients remaining insulin free after total pancreatectomy and islet autotransplantation in our center.

Total pancreatectomy followed by islet autotransplantation was performed in 10 patients with the age of 34 (11-53) and BMI of 28 (18-35). Eight patients had chronic pancreatitis with intractable pain, remain patients had a benign pancreas tumor or small ampullary cancer. PRSS1 or SPINK1 gene mutations were present in 3 patients. Exogenous insulin therapy was implemented for at least 6 weeks after the autotransplantation to support islet graft recovery and engraftment and subsequently weaned off, if possible. Follow up was 28 (2-60) months.

The islet tissue pellet volume was 6ml (2-30). Viability was 95% (81-98). Five (50%) patients are currently off insulin with excellent glucose control and HbA1c below 6. The remaining 5 patients still require insulin injections, however none of them experiences "brittle" form of diabetes mellitus; no severe hypoglycemic episodes were reported. Transplanted beta cell mass was significantly higher- in patients currently insulin free comparing to those with insulin therapy, 202kIEQ (149k-340kIEQ) vs. 64kIEQ (48-260), respectively. Islet mass per kilogram of patient body weight was also substantially higher in the same group- 3,300IEQ/kg (1,611-4,800) vs. 1,078kIEQ/kg (556-4,277), respectively. Islet gradient purification was applied in 3 cases and resulted in insulin independence in 2 individuals. BMI as well as time of chronic pancreatitis prior to operation did not differ in patients who became insulin free and insulin dependent. None of the patients developed long-term complications related to the islet transplant procedure.

Islet autotransplantation efficiently preserved beta cell function in patients after total pancreatectomy allowing for insulin independence in half of them and stable glucose control in remaining. The success was correlated with higher islet mass transplanted.

191-LB

Composition and Function of Macro-Encapsulated Human Embryonic Stem Cell-derived Implants Meet Characteristics of Clinical Human Islet Cell Grafts

EVI MOTTÉ, EDIT SZEPESSY, KRISTA SUENENS, GEERT STANGÉ, MYRIAM BOMANS, DANIEL JACOBS-TULLENEERS-THEVISSEN, ZHIDONG LING, EVERT KROON, DANIEL PIPELEERS, *Jette, Belgium, San Diego, CA*

Shortage of good quality human pancreases for use in organ and islet cell transplantation has led to development of large-scale laboratory sources that generate insulin-producing implants. Prior work showed that human embryonic stem (huES) cells can be differentiated in vitro to pancreatic endoderm that forms beta cell containing implants in immune-deficient mice. The present study reports a higher endocrine purity in encapsulated versus non-encapsulated subcutaneous implants, with enrichment in alpha-beta-delta cells when placed in TheraCyte-macro-devices and in alpha cells when alginate-micro-encapsulated. We compared endocrine composition and glucose-regulated functions of macro-huES-implants with the characteristics of cultured human islet cells as used in clinical transplantation. At post-transplant week 20-30, macro-huES-implants generated higher plasma C-peptide levels than human islet cell grafts with similar cell number at start. Their endocrine purity was higher, containing single-hormone-positive alpha and beta cells that exhibited rapid secretory responses to increasing and decreasing glucose concentrations, as was also the case during perifusion of cultured human islet cell preparations. Their insulin secretory amplitude was however lower, in part attributable to a lower cellular hormone content; it was associated with lower rates of glucose-induced insulin biosynthesis, but not with lower glucagon-induced release, signs that are indicative for an immature functional state of the huES-derived beta cells at the time of analysis. These data support the therapeutic potential of macro-encapsulated huES-implants. Their comparison with clinical-grade human islet cell grafts sets references for further development and clinical translation.

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INSULIN ACTION—ADIPOCYTE BIOLOGY

192-LB

Grb10 Promotes Lipolysis and Thermogenesis by Phosphorylation-dependent Feedback Inhibition of mTORC1

MEILIAN LIU, JULI BAI, SIJIA HE, JOHN BLENIS, PHILIPP E. SCHERER, LILY Q. DONG, FENG LIU, *Albuquerque, NM, San Antonio, TX, Boston, MA, Dallas, TX*

Identification of key regulators of lipid metabolism and thermogenic functions has important therapeutic implications for the current obesity and diabetes epidemic. Here we show that Grb10, a newly identified direct substrate of mechanistic/mammalian target of rapamycin (mTOR), is expressed highly in brown adipose tissue, and its expression in white adipose tissue is markedly induced by cold exposure. In adipocytes, mTOR-mediated phosphorylation at Ser501/503 switches the binding preference of Grb10 from the insulin receptor to raptor, leading to the dissociation of raptor from mTOR and down-regulation of mTOR complex 1 (mTORC1) signaling. Fat-specific disruption of Grb10 increased mTORC1 signaling in adipose tissues, suppressed lipolysis, and reduced thermogenic function. The effects of Grb10 deficiency on lipolysis and thermogenesis were diminished by rapamycin administration in vivo. Our study has uncovered a novel feedback mechanism regulating mTORC1 signaling in adipose tissues and identified Grb10 as a key regulator of adiposity, thermogenesis, and energy expenditure.

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193-LB

Hyperglycemia-induced HMGB1 Expression: A Potential Role in Adipose Tissue Inflammation

SANDEEP SINHA, DANIEL FRANCO, MICHAEL QUOC NGUY, PETER D. REAVEN, *Phoenix, AZ*

The nuclear protein HMGB1 has recently been identified as an inflammatory alarmin that can be secreted by inflammatory cells and is increased in chronic inflammatory and autoimmune diseases. Little is known about whether adipose tissue (AT) may be a source of the alarmin HMGB1 and whether this is enhanced during hyperglycemia. To investigate this, we performed subcutaneous fat biopsies on 4 subjects before and after 6 hr infusions of glucose (20%) to raise plasma glucose to steady state levels of ~ 300 mg/dl and compared these with infusions of mannitol (20%) in a cross-over fashion. Western-blots were performed on protein lysates from these tissues. HMGB1 protein expression was several-fold higher in post-glucose infusion AT ($p<0.01$ vs. pre-infusion biopsy). NF-κB translocation to the nucleus was also markedly increased ($p<0.02$) in post-glucose infusion AT. To clarify whether the HMGB1 increase was due to hyperglycemia *per se*, we also examined *ex vivo* consequences of direct addition of glucose to pre-infusion AT. Ex-vivo AT exposure to glucose for 6 hours also increased HMGB1 protein expression (vs. 5mM glucose, $p<0.01$) and increased nuclear translocation of NF-κB ($p<0.03$). Moreover, enhanced HMGB1 secretion into the media was observed in high glucose (25 mM) treated AT. Adding this conditioned media to THP-1 cells induced proinflammatory cytokine (e.g., IL-6, TNFα) gene expression, which was reduced with depletion or inactivation of HMGB1 by ethyl pyruvate (HMGB1 secretion inhibitor) and glycyrrhizic acid, respectively. These *in vivo* and *in vitro* data strongly suggest that AT secretes HMGB1 in response to hyperglycemia, which may in turn contribute to AT inflammation.

194-LB

Acute Loss of Insulin and IGF-1 Signaling in Adipose Tissue Results in a Severe, but Transient, Metabolic Syndrome

MASAJI SAKAGUCHI, C. RONALD KAHN, *Boston, MA*

Both obesity and lipodystrophy are accompanied by insulin resistance and inflammatory changes in adipose tissue. To investigate the effect of acute insulin resistance in adipose tissue, we created mice carrying IR and IGF1R floxed alleles and the tamoxifen-inducible Cre ERT2 recombinase under the adiponectin promoter. Within 2-3 days of tamoxifen treatment these FindIGIRKO mice demonstrate a major loss of IR and IGF1R in both white and brown fat tissues. This resulted in acute, severe resistance insulin with marked hyperglycemia (>400 mg/ml) and hyperinsulinemia (6.8-fold increase), marked glucose intolerance, severely impaired insulin tolerance tests, as well as a significant decrease in size of subcutaneous (SC), perigonadal (PG), and retroperitoneal (Ret) white fat (WAT) and interscapular brown (BAT) adipose depots. This was associated with decreased levels of adiponectin, leptin, and resistin mRNA, particularly in the SC depot, and an increased expression of IL-6 and TNFα in Ret WAT, without evidence of macrophage invasion. By day 9 after tamoxifen treatment, FindIGIRKO exhibited massive degeneration and inflammatory changes in SC, PG and BAT fat tissues accompanied by fatty liver and marked hyperplasia of pancreatic β cells. Surprisingly, however,

after 2 weeks, serum glucose levels returned toward normal, and by 4 weeks glucose tolerance and insulin tolerance tests began to return toward normal in FindIGIRKO mice, despite the continued loss of adipose tissues. These data indicate the critical role of insulin and IGF-1 signaling in maintenance of adipose mass and function, but also demonstrate difference in acute versus chronic response to insulin and IGF-1 resistance of fat tissues, and the ability of these alterations in adipose tissue to initiate systemic compensatory responses, including β-cell hyperplasia. This new model of adipose tissue insulin resistance allows an opportunity to dissect these acute and chronic responses.

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195-LB

Inhibition of PDE3 and PDE4D Activates Brown Adipogenic Program

DING AN, M.Y. CHOUINARD, ABBY WATANABE, T.J. UNGER, TODOR DIMITROV, JENN LACHEY, JEFF SAUNDERS, DAVID WHITE, *Watertown, MA*

Emerging evidence suggests that browning of white/beige adipocytes or activation of brown adipocytes increases energy expenditure and reduces obesity. A classical way to induce browning or activation is through the adrenergic receptor pathway which is mediated by cAMP. Cyclic nucleotide phosphodiesterases (PDEs) degrade cAMP, thereby decreasing the duration and magnitude of adrenergic signaling. In the present study, we explored whether inhibition of adipose tissue specific PDE isoforms can induce browning/activation of adipocytes, resulting in increased mitochondrial respiration. We measured gene expression of 8 PDE isoforms in 18 tissues and identified that PDE3B is highly and selectively expressed in both white and brown adipose tissues (WAT and BAT), whereas PDE4D is selectively expressed in BAT. Mice on high fat diet showed a 70% and 87% increase in PDE3B and PDE4D respectively in inguinal WAT but interscapular BAT expression was unchanged. We next determined if inhibition of PDE3B and/or PDE4D regulates the brown adipogenic program. C3H10T1/2 white and DE2-3 brown adipocytes were incubated with the pan-PDE3 inhibitor cilostazol or the PDE4D specific inhibitor GEBR7B separately or in combination. Neither Cilostazol nor GEBR7B effects on ap2, UCP1, FGF21 or PPAR-α. Interestingly, under basal conditions, combination of Cilostazol and GEBR7B increased UCP1, PGC1α, FGF21 and PPAR-α expression without altering ap2. Under β-adrenoceptor stimulation, combination of Cilostazol and GEBR7B potentiate the expression of UCP1, PGC1α and FGF21 by 2.2-, 2.8- and 14.3-fold respectively in DE2-3 cells, and PGC1α and PPAR-α by 2.5 and 3.7 respectively in C3H10T1/2 cells. Finally, combination of PDE3 and PDE4D inhibitors potentiated isoproterenol-induced basal and uncoupled respiration in DE2-3 cells. Taken together, our results suggest that targeting PDE3 and PDE4D activates a brown adipogenic program, and may provide a therapeutic opportunity to increase energy expenditure and treat obesity.

196-LB

Fat-Specific Deletion of Insulin Receptor Leads to Severe Lipoatrophic Diabetes

JEREMIE BOUCHER, ABDELFATTAH EL OUAAMARI, GRAHAM SMYTH, SAMIR SOFTIC, ROHIT N. KULKARNI, C. RONALD KAHN, *Boston, MA*

To determine the relative roles of insulin and IGF-1 action in adipose tissue development, we created mice lacking either the insulin receptor (IR), IGF-1 receptor (IGF1R), or both using a Cre recombinase driven by the fat-specific adiponectin promoter. Mice lacking IR in fat alone (F-IRKO), or in combination with IGF1R deficiency (F-IR/IGFRKO) displayed a lipodystrophic phenotype, with a 95 to 100% reduction in all white adipose tissue (WAT) depots, associated with a severe reduction in circulating adipokines.

F-IRKO and F-IR/IGFRKO mice developed hyperglycemia at 3 weeks of age, and glucose levels were >500 mg/dl in 5 week-old mice. These mice displayed dyslipidemia with 2 to 5 fold increases in circulating triglyceride, free fatty acid and cholesterol levels. Both lipodystrophic models developed hepatosteatosis and hepatomegaly, > 10 fold increase in insulin levels and dramatic beta-cell mass expansion, already apparent in 3 week-old animals, and worsening with aging. Food intake was double that of control mice and was associated with a 10% decrease in energy expenditure. Chronic leptin treatment restored circulating glucose to normal levels within one week in both F-IRKO and F-IR/IGFRKO mice. Interestingly, serum glucose, triglycerides and free fatty acids normalized spontaneously by 1 year of age. At this age, these mice displayed an increased glucagon response, ruling out liver failure and impairment in gluconeogenesis as a reason for the normalization of glycemia in older KO mice.

While IR-deficient mice had almost no WAT, brown adipose tissue (BAT) was increased by 50%, but was absent in F-IR/IGFRKO mice. IGF1R deficiency in fat alone (F-IGFRKO) however, led to a ~25% reduction in both WAT and BAT. This indicates that although insulin/IGF-1 signaling is essential for fat development, IGF1R is sufficient and IR dispensable for BAT formation, and IR is essential and IGF1R dispensable for WAT formation. Consequently, a fat-specific and lifelong deletion of IR leads to severe lipoatrophic diabetes.

Supported By: ADA (7-09-MN-22)

197-LB

Browning and Inflammation of Subcutaneous White Adipose Tissue in Rhesus: Wellness vs. Dysmetabolism

FRANKLIN LIU, *Kenilworth, NJ*

The presence of BAT and browning of subcutaneous white adipose tissue (SubQ WAT) in rodents and humans has been correlated with changes in expression of many different genes known to contribute to energy metabolism, nutrient uptake and inflammation. Indeed, recent publications suggest that induction of browning correlates with repression of inflammation in SubQ WAT in high-fat diet mice. To establish the status of browning and inflammation in Rhesus we have evaluated gene signatures of browning and inflammation in SubQ AT of dysmetabolic/insulin resistant versus lean Rhesus. Analysis of the BAT gene signature showed a significant reduction in ucp1, adrb-3, pgc1a, cidea, dio2 and bmp-7 (ranging from 5 to 2-fold) in dysmetabolic rhesus compared to healthy. In addition, a striking decrease in browning gene markers such as tmem26, cox7a1, epac1 and cide-3 (ranging from 4 to 2-fold) was observed in SubQ WAT. This loss of a browning phenotype in SubQ WAT was accompanied by more than 10-fold increase in pro-inflammatory genes such as pai-1, c4a, ccl3 and osteopontin (abstract 2014-A-1921-Diabetes), and decreased adiponectin and insulin receptor gene expression. This apparent "visceralization" of the SubQ WAT might reflect the pathophysiological state of these animals. Dysmetabolic Rhesus compared to healthy had increased body weight (16.97 ± 3.2 vs. 9.6 ± 0.86 g), increased percent of body fat (44.2 ± 5.9 vs. 5.3 ± 0.97%) and increased pro-inflammatory plasma markers (IL-6, MCP-1 and CRP). In addition, they had decreased fasting levels of HDL (64.7 ± 23 vs. 89.7 ± 17.1 mg/dL), increased triacylglycerols (114.8 ± 59.3 vs. 30 ± 7.8 mg/dL) insulin (33 ± 32.8 vs. 20.3 ± 11.9 mg/dL) and glucose (75.2 ± 9.5 vs. 69.3 ± 8 mg/dL). In summary, we report for the first time the presence of a BAT/browning gene signature in SubQ WAT of Rhesus that negatively correlates with increased systemic inflammation and insulin resistance.

198-LB

Adipose-specific Inhibition of BCKDH Activity Alters Substrate Flux in Metabolic Tissues to Mimic the "Metabolic Signature" of Insulin Resistance (IR)

JENNIFER LEE, ARCHANA VIJAYAKUMAR, YUPING XU, OLGA ILKAYEVA, ODILE PERONI, CHRISTOPHER B. NEWGARD, CHRISTOPHER J. LYNCH, MARK A. HERMAN, BARBARA B. KAHN, *Boston, MA, Hershey, PA, Durham, NC*

A "metabolic signature" associated with IR includes higher circulating branched-chain amino acids (BCAAs) and their metabolites C3/C5 acylcarnitines (ACs), and muscle medium-long-chain ACs (products of incomplete β-oxidation). BCAA metabolism in white adipose tissue (WAT) is down-regulated in obesity and IR. To determine whether impaired WAT BCAA metabolism contributes to the "metabolic signature" associated with IR we generated adipose-specific branched chain ketoacid dehydrogenase E1β subunit knockout (AdBCKDHKO) mice. WAT BCKDHE1β expression was decreased by 97% and valine oxidation by 74% in AdBCKDHKO mice vs. controls (wild type and BCKDH flox mice). High fat/high sucrose (HFHS) feeding caused obesity and elevated fasting blood glucose (FBG) but not overt glucose intolerance or IR in either genotype. HFHS control mice had 1.7-2X higher circulating BCAAs and branched-chain ketoacids (BCKAs) vs. chow controls. HFHS AdBCKDHKO mice had similar adiposity and FBG to HFHS controls and further elevations in plasma BCKAs but not BCAAs. HFHS feeding did not raise C5-OH/C3-DC ACs but this analyte was 2.2X and 1.3X higher in liver and muscle of HFHS AdBCKDHKO mice vs. chow and HFHS controls. Some WAT long-chain ACs were decreased < 50% in HFHS AdBCKDHKO mice vs. HFHS controls. Yet muscle medium-long-chain ACs and liver medium-chain ACs showed modest elevations with diet in controls and were 1.5-2X higher in HFHS AdBCKDHKO vs. HFHS controls. In sum, HFHS feeding caused obesity, impaired FBG, higher plasma BCAAs and changed the tissue AC profile in controls. HFHS AdBCKDHKO mice have similar obesity and FBG to HFHS controls, yet higher plasma BCKAs, C3/C5 ACs in muscle and liver, and they accumulate β-oxidation intermediates in a tissue-specific manner. Thus, down-regulation of WAT BCAA metabolism is sufficient to alter substrate flux in metabolic tissues to induce elements of the "metabolic signature" associated with IR.

199-LB

Regulation of Insulin Resistance and Adiponectin Signaling in Adipose Tissue by Liver X Receptor Activation Highlights Cross-Talk with PPAR?

FENPING ZHENG, SAIFEI ZHANG, XUEYAO YIN, QIANQIAN PAN, DAN YU, HONG LI, *Hangzhou, China*

Liver X receptors (LXRs) have been recognized as a promising therapeutic target for atherosclerosis; however, their role in insulin sensitivity is controversial. Adiponectin plays a unique role in maintaining insulin sensitivity. Here, we investigated the role of LXR activation in insulin resistance based on adiponectin signaling and mechanisms.

C57BL/6 mice maintained on a regular chow received the LXR agonist, T0901317 (30 mg/kg.d) for 3 weeks by intraperitoneal injection, and differentiated 3T3-L1 adipocytes were treated with T0901317 or GW3965. T0901317 treatment induced significant insulin resistance in C57BL/6 mice. It decreased adiponectin gene transcription in epididymal fat, as well as serum adiponectin levels. Activity of AMPK, a key mediator of adiponectin signaling, was also decreased, resulting in decreased Glut-4 membrane translocation in epididymal fat. In contrast, adiponectin activity was not changed in the liver of T0901317 treated mice. In vitro, both T0901317 and GW3965 decreased adiponectin expression in adipocytes in a dose-dependent manner, an effect which was diminished by LXRα silencing. ChIP-qPCR studies demonstrated that T0901317 decreased the binding of PPARγ to the PPAR-responsive element (PPRE) of the adiponectin promoter in a dose-dependent manner. Furthermore, T0901317 exerted an antagonistic effect on the expression of some PPARγ-target genes both in EP fat and adipocytes. In luciferase reporter gene assays, T0901317 dose-dependently inhibited PPRE-Luc activity in HEK293 cells co-transfected with LXRα and PPARγ. These results suggest that LXR activation induces insulin resistance with decreased adiponectin signaling in epididymal fat, probably due to negative regulation of PPARγ signaling. These findings indicate that the potential of LXR activation as a therapeutic target for atherosclerosis may be limited by the possibility of exacerbating insulin resistance-related disease.

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200-LB

A New Model System to Study Akt Isoform Metabolic Functions

EVA GONZALEZ, ESI KAJNO, TIMOTHY E. MCGRAW, *New York, NY*

Insulin metabolic action is largely mediated by the Akt kinase family. Akt2 is the most abundant Akt isoform in metabolic tissues and deletion or impairment of Akt2, but not Akt1, leads to altered glucose metabolism and insulin resistance in mice and humans. However, due to differential expression levels of Akt isoforms and the potential contribution of compensatory mechanisms upon deletion of Akt kinases, Akt isoform specific effectors and metabolic functions are still poorly understood. To elucidate Akt1 and Akt2 function in insulin regulated metabolism we combined the MK-2206 Akt pharmacological inhibitor and engineered drug-resistant forms of Akt1 and Akt2 to develop a new model system that allows for acute and specific inhibition of Akt isoforms. We generated 3T3-L1 adipocytes expressing endogenous levels of epitope Flag-tagged WT or MK-2206-resistant forms of Akt1 or Akt2. Drug-resistant Akt kinases were phosphorylated in response to insulin similar to their WT counterparts. MK-2206 treatment led to a dose-dependent inhibition of phosphorylation of WT Akt kinases and their targets AS160 and FoxO1, however insulin-induced phosphorylation of AS160 and FoxO1 was preserved in adipocytes expressing drug-resistant Akt1 or Akt2. Our model system revealed that both Akt1 and Akt2 drug-resistant forms control insulin-mediated FoxO1 nuclear exclusion and the translocation of GLUT4 glucose transporters to the plasma membrane. On the contrary, only Akt1 activation promotes 3T3-L1 adipocyte differentiation, as assed by lipid content and the expression profile of adipogenic genes. EdU (5-ethynyl 2'-deoxyuridyne) incorporation analyses revealed that Akt1, but not Akt2, regulates the mitotic clonal expansion that precedes terminal adipocyte differentiation, supporting a specific role for Akt1 signaling in adipogenesis. Our studies provide a new model system to elucidate Akt isoform metabolic functions, revealing overlapping and specific roles for Akt isoforms in adipocyte differentiation and metabolic function.

Supported By: AHA (to E.G.)

INSULIN ACTION—CELLULAR AND MOLECULAR METABOLISM

201-LB

IL-1 Receptor Associated Kinase-1 (IRAK-1) Null Mice Have Increased Whole-Body Insulin Sensitivity

XIAO-JIAN SUN, SOOHYUN PARK KIM, LIWU LI, MICHAEL J. QUON, *Baltimore, MD, Blacksburg, VA*

IRAK-1, downstream from Toll-Like-Receptors, promotes cross-talk between innate immune signaling and insulin signaling by phosphorylating IRS-1 at Ser^{24}. Preliminary data showed that 20 week old IRAK-1 null mice have improved glucose tolerance and insulin sensitivity as assessed by IPGTT and QUICKI. Therefore, we hypothesized that IRAK-1 contributes to insulin resistance mediated by pro-inflammatory signaling. To rigorously test this *in vivo*, we used the hyperinsulinemic euglycemic glucose clamp (reference method) to evaluate whole body insulin sensitivity in male IRAK null mice (IRAK1-KO) and C57BL/6 wild-type littermate control mice (WT) on normal chow diet at 29 ± 0.9 wk of age. Immunoblotting of liver and adipose tissue confirmed the absence of IRAK-1 in IRAK1-KO mice. As expected, IRAK-1 was readily detectable in tissues from WT mice. To achieve clamp conditions, insulin was infused intravenously at a rate of 2.5 mU/kg/min. Blood glucose levels were measured every 5 min and an intravenous glucose infusion rate (GIR) was adjusted to maintain blood glucose at a constant level (clamp glucose levels = 127 ± 4, n = 5 for WT and 129 ± 6, n = 6 for IRAK1-KO, $p > 0.9$). After ~1 h, we typically approached a steady-state clamp period and used a subsequent 30 min interval where coefficient of variation for blood glucose and GIR < 0.05 to define the clamp interval. We defined an insulin sensitivity index SI_{clamp} = GIR normalized for body weight and clamp glucose levels. SI_{clamp} for IRAK1-KO mice was ~40% higher than SI_{clamp} for WT control mice (0.422 ± 0.051 vs. 0.295 ± 0.025 dl/kg·min, $p < 0.05$). Thus, IRAK1-KO mice had unequivocally higher whole body insulin sensitivity than WT mice. This is consistent with our previous biochemical and cellular data that suggested a mechanism for IRAK-1 to impair insulin sensitivity through serine phosphorylation of IRS-1 at Ser^{24}. We conclude that IRAK-1 impairs whole body insulin sensitivity. These results may have therapeutic implications for treatment of diabetes.

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202-LB

Potentiation of Insulin-mediated Glucose Lowering without Elevated Hypoglycemia Risk by a Small Molecule Insulin Receptor Modulator

MARGARET WU, GE DAI, JUN YAO, SCOTT HOYT, LIANGSU WANG, JAMES MU, *Kenilworth, NJ*

Insulin resistance is the key feature of type 2 diabetes and is manifested as attenuated insulin receptor (IR) signaling in response to same levels of insulin binding. Several small molecule IR activators have been identified and reported to have insulin sensitization effects. One of these molecules, TLK19781 (Cmpd1), was investigated to examine its IR sensitizer action *in vivo*. Our data demonstrated that Cmpd1, at doses that had minimal efficacy by itself, potentiated insulin action during an OGTT in non-diabetic mice and enhanced insulin-mediated glucose lowering in STZ-induced diabetic mice. Interestingly, different from insulin dose rising studies, Cmpd1 dose escalation in combination with fixed level of insulin showed good efficacy without increased hypoglycemia risk. To explore the underlying mechanism for the apparent glucose sensitive effects, tissue insulin signaling was compared in healthy and diabetic mice. Cmpd1 enhanced insulin's effects on IR phosphorylation in both healthy and diabetic mice. In contrast, the compound potentiated insulin's effects on Akt phosphorylation in diabetic but not non-diabetic mice. Cmpd1-mediated differential effects on signaling corresponding to varied glucose levels could be part of the reason for reduced hypoglycemia risk. To confirm the specificity of Cmpd1 action, glucose lowering efficacy studies were conducted in inducible IR knocked-down (IR-iKD) mice. While insulin or its combination with Cmpd1 did not lower glucose in IR-iKD mice, anti-diabetic agents utilizing IR-independent mechanisms were fully efficacious in this model. The results from these studies support the idea of targeting IR for insulin sensitization, which carries low hypoglycemia risk by standalone treatment and could improve the effectiveness of insulin secretion therapies.

203-LB

NF-KappaB-inducing Kinase and TLR4-mediated Skeletal Muscle Inflammation in Obesity and Type 2 Diabetes

MANDEEP BAJAJ, PADMA SATHYANARAYANA, JONGOH KIM, ABSALON GUTIERREZ, LAWRENCE CHAN, RONALD TILTON, SANJEEV CHOUDHARY, *Houston, TX, Galveston, TX*

Despite substantial evidence that excessive inflammation via NF-κB pathway is an underlying mechanism for insulin resistance, the precise mechanisms for skeletal muscle NF-κB activation are not well understood. We investigated the role of a key NF-κB regulatory enzyme, NF-κB-inducing kinase (NIK), in skeletal muscle inflammation induced by obesity and type 2 diabetes (T2DM) and its relationship to Toll-like Receptor 4 (TLR4). We studied lean nondiabetic subjects (BMI 23.6 ± 0.5, n=4), obese subjects (BMI 32.0 ± 2.4, n=6), and T2DM subjects (BMI 38.5 ± 2.5, n=5), who underwent vastus lateralis muscle biopsies. Muscle NIK and TLR4 protein was increased in both obese subjects ($p<0.001$) and type 2 diabetics ($p<0.001$) compared with lean subjects. Plasma adiponectin (AD) was decreased in obese (6.4 ± 0.5 μg/ml, $p<0.05$) and T2DM subjects (4.4 ± 0.4 μg/ml, $p<0.05$) compared to lean controls (11.2 ± 3.0 μg/ml), while plasma FFA were higher in obese ($p<0.01$) and T2DM ($p<0.05$). NIK correlated positively with muscle TLR4 ($R=0.95$, $P<0.001$), and plasma FFA ($R=0.55$, $p<0.03$) and negatively with AD ($R=-0.61$, $p<0.02$). PU.1 has been reported to be a master regulator of multiple TLRs such as TLR2, -4, and -9. To determine if increasing conc. of PU.1 as observed in insulin resistant states can interact with NIK to alter its transcriptional activity, 293 cells were co-transfected with 2 μg of NIKwt and increasing conc. of either full length PU.1 or PU.1dTAD (PU.1 lacking transactivation domain). Results show that immunoprecipitated NIK specifically binds to full length PU.1 and not the truncated form suggesting that NIK interacting domain of PU.1 could overlap its transactivation domain. We conclude that muscle NIK correlates strongly with TLR4 and FFA and inversely with adiponectin. NIK interacting domain of PU.1 could overlap its transactivation domain, suggesting that elevated levels of NIK in obese and diabetic muscle could amplify the inflammatory signal by regulating TLR4 expression.

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204-LB

TRAIL: A Link between Inflammation, Insulin Resistance, and Vascular Complications

HANIS HARITH, BELINDA DI BARTOLO, LEI DANG, SHANE THOMAS, SIAN CARTLAND, MARY KAVURMA, *Sydney, Australia, Newtown, Australia*

TNF-related apoptosis-inducing ligand (TRAIL) has protective effects in cardiovascular disease and diabetes; its role in insulin resistance is unclear. Here we examined the effect of TRAIL on insulin resistance, and determined whether this may influence vascular function *in vivo* and *in vitro*.

Six week old male mice were placed on a high fat diet (HFD) for 12 w. In response to the HFD, wildtype (WT) mice had increased aortic TRAIL, IL-6, MCP-1 and TNF-α mRNA expression. In contrast, plasma TRAIL levels were reduced. Compared to WT, $TRAIL^{-/-}$ mice at 12 w had increased plasma glucose, insulin, and cholesterol levels, with no change in body weight. No change in glucose tolerance between genotypes was observed; however $TRAIL^{-/-}$ mice had impaired insulin sensitivity. $TRAIL^{-/-}$ aortas not only displayed impaired insulin-induced vasodilation *ex vivo*, they also had reduced phospho-Akt protein expression, with no change in total Akt, after an insulin challenge. Vascular smooth muscle cells (VSMC) are the main cell type in blood vessels. Insulin promoted proliferation of aortic VSMC isolated from WT mice, but not $TRAIL^{-/-}$ VSMC. Notably, this correlated with reduced insulin receptor expression. Consistent with these, impaired insulin sensitivity and insulin-induced vasodilation were evident in $TRAIL^{-/-}$ mice, even prior to a HFD. This was associated with reduced insulin-induced glucose uptake in $TRAIL^{-/-}$ muscle *ex vivo*.

Together, these findings suggest that a HFD increases expression of inflammatory markers, but has differential effects on circulating vs. tissue-specific TRAIL. Further, TRAIL-deficiency augments insulin resistance via impaired insulin signalling, exacerbated by a HFD. Thus, TRAIL may have therapeutic potential for diet-induced insulin resistance.

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205-LB

Exercise Improves Insulin Sensitivity and Glucose Metabolism in Myotubes from Severely Obese Subjects

YUAN Z. FENG, NATASA NIKOLIĆ, SIRIL S. BAKKE, EILI T. KASE, JØRAN HJELMESÆTH, VIGDIS AAS, ARILD C. RUSTAN, G. HEGE THORESEN, *Oslo, Norway*

Exercise leads to improved insulin sensitivity and oxidative capacity in skeletal muscles. However, molecular mechanisms underlying these adaptations are poorly understood. The purpose of the present study was to examine glucose and lipid metabolism after electrical pulse stimulation (EPS) as an *in vitro* model of exercise of myotubes established from healthy, lean subjects (LD) and myotubes originating from severely obese subjects (BMI ≥ 40) with (SO-T2D) or without type 2 diabetes (SO-nD).

Insulin sensitivity, measured as insulin-stimulated uptake of [^{3}H]deoxyglucose, phosphorylation of Akt and glycogen synthesis, and metabolism of [^{14}C] oleic acid (OA) and [^{14}C] glucose were studied in myotubes from LD, SO-nD and SO-T2D after chronic, low-frequency EPS (48 h, single, bipolar pulses of 2 ms, 30 V and 1 Hz). Without EPS, insulin-stimulated phosphorylation of Akt tended to be lower in myotubes from SO-T2D compared to cells from LD and SO-nD subjects. Furthermore, insulin-stimulated glucose uptake was abolished in myotubes from SO-T2D indicating that the myotubes maintained their T2D phenotype in culture. However, after EPS, insulin-stimulated phosphorylation of Akt was increased in myotubes from all donors. This effect was higher in myotubes from SO-T2D, and in line with this, insulin-stimulated glycogen synthesis was also increased after EPS in myotubes from SO-T2D. EPS increased glucose oxidation in myotubes from both LD and SO subjects. However, OA oxidation after EPS was only increased in myotubes from LD donors, and OA oxidation after EPS correlated negatively with BMI of the subjects.

In conclusion, EPS improved insulin sensitivity in myotubes, and this effect was most evident in myotubes established from severely obese subjects with T2D. EPS enhanced oxidative capacity of glucose in myotubes from all subjects, while OA oxidation was only improved in myotubes from lean subjects.

INSULIN ACTION—GLUCOSE TRANSPORT AND INSULIN RESISTANCE IN VITRO

206-LB

Novel Class of Naturally Occurring Lipids with Antidiabetic and Anti-inflammatory Effects

ISMAIL SYED, MARK M. YORE, PEDRO M. MORAES-VIEIRA, TEJIA ZHANG, EDWIN HOMAN, MARK A. HERMAN, RAJESH T. PATEL, JENNIFER LEE, ABHA DHANESHWAR, ODILE D. PERONI, ANN HAMMARSTEDT, ULF SMITH, TIMOTHY E. MCGRAW, ALAN SAGHATELIAN, BARBARA B. KAHN, *Boston, MA, Cambridge, MA, New York, NY, Gothenburg, Sweden*

Increased adipose tissue (AT) lipogenesis is associated with enhanced insulin sensitivity. Mice overexpressing Glut4 in AT (AG4OX) have elevated AT lipogenesis and increased glucose tolerance in spite of obesity and elevated circulating fatty acids. To determine if the lipid profile contributes to improved glucose homeostasis in AG4OX, we performed lipidomic analysis of AT. This revealed a 16-18-fold increase in a novel class of lipids in AG4OX AT vs. wildtype (WT) mice. Using a targeted MS approach, we identified 16 novel lipid family members with multiple isomers based on structural variations. Novel lipid levels are highest in brown adipose tissue followed by subcutaneous (SQ) and perigonadal (PG) white AT (WAT). Levels in liver, pancreas, kidney, muscle, heart and brain are substantially lower than AT. Levels of these lipids are acutely regulated by fasting. Most isomers are reduced 50-65% in serum and AT of insulin-resistant vs. insulin-sensitive people. Nearly all isomers in humans correlate remarkably strongly with insulin sensitivity determined by clamp. Lipid isomers are also reduced in SQ WAT in mice fed HFD. Oral administration of these lipids lowers ambient glycemia and enhances glucose tolerance in aged chow-fed mice and mice with diet-induced obesity while stimulating GLP1 and insulin secretion. These lipids enhance glucose-stimulated insulin secretion 1.5-fold in human pancreatic islets and GLP1 secretion 3-fold in enteroendocrine cells. In cultured adipocytes, they enhance glucose uptake and insulin-stimulated GLUT4 translocation. These lipids also suppress inflammatory processes in dendritic cells. Biological effects of these lipids are mediated through lipid-responsive GPCRs and knockdown of specific GPCRs blocks the effects on glucose transport and GLUT4 translocation. In sum, we identified a novel lipid class that improves glucose-insulin homeostasis. Restoration of the low levels in insulin-resistant people may be effective to treat type 2 diabetes.

207-LB

KLF4 Up-regulating MFN2 Expression Contributes to the Alleviation of High-Fat-induced Insulin Resistance in Hepatic Cells

AN SONG, CHAO WANG, GUANGYAO SONG, KEXIN GAN, *Jinan, China, Shijiazhuang, China*

Kruppel-like factor 4 (KLF4) is a crucial transcription factor implicated in multiple cell events,while mitofusin 2 (MFN2) protein is involved in mitochondrial metabolism and insulin resistance (IR) regulation. However, the role of KLF4 in high-fat-induced IR and MFN2 expression in hepatic cells remain unknown.

Hepatic cells HepG2 were treated with control or palmitic acid, the cell insulin sensitivities were evaluated by glucose consumption measured with glucose oxidase method. Then cells were infected with control or KLF4 expression adenovirus and/or MFN2 siRNA expression adenovirus. The expression levels of KLF4, MFN2, insulin receptor (INSR), insulin receptor substrate 2 (IRS2) and glucose transporter type 2 (GLUT2) were detected by quantitative RT-PCR and Western-blot. MFN2 promoter luciferase reporter plasmid was constructed and reporter gene assays were performed to detect its transcriptional activities by cotransfection in HepG2 cells. The interaction of KLF4 with MFN2 promoter region in HepG2 cells was assayed by chromatin immunoprecipitation (ChIP).

The results show, that KLF4, MFN2, INSR, IRS2 and GLUT2 were down-regulated and the insulin sensitivities of HepG2 cells decreased by palmitic acid incubation. By over-expression of KLF4, the insulin sensitivities of HepG2 cells improved, and the expression levels of MFN2, INSR, IRS2 and GLUT2 were up-regulated. While after knock-down the expression of MFN2 by specific siRNA expression adenovirus, KLF4 over-expression could not ameliorate the impaired insulin sensitivities of HepG2 cells effectively. The results of ChIP and reporter gene assays indicated that KLF4 interacted with MFN2 promoter region and activated the transcription of MFN2 in HepG2 cells.

In conclusion, KLF4 could alleviate high-fat-induced insulin resistance by up-regulating MFN2 expression directly in hepatic cells.

INSULIN ACTION—SIGNAL TRANSDUCTION, INSULIN, AND OTHER HORMONES

208-LB

Fatty Liver and Insulin Resistance in the Liver Specific Knockout Mice of Mitogene Inducible Gene (Mig)-6

WON HOON JUNG, BYUNG KIL PARK, EUN-AH LEE, HEE-YOUN KIM, JUN CHOUL LEE, KOON SOON KIM, KI YOUNG KIM, BON JEONG KU, SANG DAL RHEE, *Daejeon, Republic of Korea*

Mitogen inducible gene 6 (Mig-6) is a feedback inhibitor of EGFR signaling pathway. Thus, deletion of the Mig-6 gene leads to activation of EGFR signaling pathway. The liver-specific knock-out mice of the Mig-6 gene showed hepatomegaly and increased plasma concentration of cholesterol, indicating the roles of Mig-6 gene in the metabolic syndrome. In this study, it was analyzed the biomarkers of insulin resistance and the effects of high fat diets in the wild (Mig-$6^{f/f}$) and liver specific K.O. (Mig-$6^{d/d}$) mice of Mig-6. The fasting plasma concentrations of glucose, triglyceride, cholesterols, free fatty acids and HOMA-IR were measured and the glucose tolerance and insulin resistance tests were perfomed in the 25-week-old Mig-$6^{f/f}$ and the Mig-$6^{d/d}$ mice. The protein levels of active components of insulin signaling pathway and gluconeogensis were analyzed in the liver and fat. The fasting plasma cholesterol and glucose concentration were higher in the Mig-$6^{d/d}$ mice than the wild mice with increased fat deposition in the liver. But the Mig-$6^{d/d}$ mice had the improved glucose intolerance and insulin resistance without increased amount of p-IR after insulin infusion in the liver. The hepatic concentration of Pepck, a key enzyme in the gluconeogenesis was increased in fasting Mig-$6^{d/d}$ mice. The feeding of high-fat diet accelerated the plasma lipids profiles and HOMA-IR in the Mig-$6^{d/d}$ mice but had no differential effects in oral glucose tolerance and insulin tolerance in both genotypes. These results suggest that the activated EGFR signaling might mainly increase the fasting plasma glucose concentration through inducing the hepatic steatosis and the improved whole body insulin resistance in the K.O. mice might be caused by decreased fat deposition in fat tissues.

209-LB

Obestatin Stimulates Insulin Secretion Under Glucose-stimulated Condition

GEETALI PRADHAN, YUXIANG SUN, *Houston, TX*

Obestatin, a 23 amino acid peptide derived from the ghrelin gene, is expressed in various tissues including stomach and pancreas. Obestatin is known to reduce food intake and body weight, improve memory and regulate sleep, but has no effect on secretion of growth hormone and corticosterone. Obestatin is also known to increase mass and survival of pancreatic β cells but it's effect on insulin secretion remains unclear.

We studied the effect of obestatin on insulin secretion under glucose-stimulated conditions both *in vitro* and *ex vivo* using rat insulinoma INS-1 cells and mouse pancreatic islets. To determine whether the effect of obestatin on insulin secretion is mediated through the ghrelin receptor, growth hormone secretagogue receptor (GHS-R), we transiently knocked down GHS-R in INS-1 cells and generated pancreatic β cell-specific GHS-R knockout mouse model (MIP-Cre $GHSR^{f/f}$).

Our results indicate that obestatin has profound stimulator effect on insulin secretion in both INS-1 cells and mouse pancreatic islets. Moreover, treatment of obestatin in GHS-R knockdown INS-1 cells also showed significant increase of insulin secretion under glucose-stimulated condition. Similarly, incubation of pancreatic islets from β cell GHS-R deficient MIP-Cre $GHSR^{f/f}$ mice with obestatin produced almost doubled the amount of insulin secretion compared to controls.

In conclusion, our studies indicate that obestatin is a potent insulin secretagogue under glucose-stimulated condition. This effect of obestatin is not likely mediated via its receptor GHS-R in pancreatic β cells, which is in agreement with the binding studies that obestatin doesn't activate GHS-R. Obestatin's stimulatory effect on insulin secretion and promoting effect on β cell survival together make obestain a powerful therapeutic candidate for Type 2 diabetes.

210-LB

Stem Cell Factor Stimulates Glucose Uptake and GLUT4 Expression In Vitro and In Vivo

MEHMET M. ALTINTAS, NESTOR DE LA CRUZ-MUNOZ, GABRIEL GAIDOSH, LEOPOLDO AROSEMENA, VINEET GUPTA, ALI NAYER, *Chicago, IL, Miami, FL*

The glucose transporter 4 (GLUT4) mediates insulin-stimulated glucose uptake and accounts for 90% of glucose transporters in skeletal muscle and adipose tissue. AMP-activated protein kinase (AMPK) is involved in GLUT4 expression and cellular glucose uptake. Considering the structural and functional homology between insulin and c-Kit tyrosine kinase receptors, we asked whether c-Kit and its ligand, stem cell factor (SCF), are involved in glucose homeostasis. We demonstrated that c-Kit and SCF proteins are expressed in adipose tissue and skeletal muscle in mice and humans. In mice, adipose c-Kit expression correlated directly with adipose GLUT4 expression and inversely with blood glucose concentration. Intraperitoneal administration of recombinant SCF resulted in an acute and dose-dependent decline in blood glucose concentration in mice. Similarly, recombinant SCF treatment stimulated glucose uptake into cultured 3T3-L1 adipocytes and C2C12 myotubes. Recombinant SCF treatment resulted in activating phosphorylation of AMPK, but not the insulin receptor, and increased GLUT4 protein expression in cultured adipocytes and myotubes. In line with these findings, c-kit knockout mice demonstrated greater fasting blood glucose and serum insulin levels than congenic wild-type mice did. Moreover, insulin-stimulated glucose disposal was attenuated in c-kit knockout mice. In addition, c-kit knockout mice demonstrated diminished GLUT4 protein expression in adipose tissue and skeletal muscle. In conclusion, recombinant SCF stimulates glucose uptake and GLUT4 expression in vitro and in vivo. These effects are independent of the insulin receptor and may involve AMPK. The salutary effects of recombinant SCF on glucose homeostasis may be used in the treatment of hyperglycemic states including diabetes mellitus.

211-LB

The Effects of Vaspin on NF-κB and PI3K/Akt Signaling Pathway in HUVEC

SHIWEI LIU, YUANBIN LI, YI PEI, MINGMING WANG, JUN WANG, LI ZHANG, LINLIN GAO, YUJIE HE, *Taiyuan, China*

Aims: In this study, we investigated the effects of visceral adipose tissue-derived serpin (vaspin) on nuclear factor-kappa B (NF-κB) and Phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway in human umbilical vein endothelial cells (HUVECs) stimulated by tumor necrosis factor-α (TNF-α) to elucidate the role of vaspin in human endothelial cells of inflammation and insulin resistance.

Methods: Human umbilical vein endothelial cells were islated and cultured in vitro. A NF-κB luciferase reporter system was constructed and transiently transfected into human umbilical vein endothelial cells. Following transfection, HUVECs were pretreated with various concentrations of vaspin (0-320 ng/ml) before 10μg/ml TNF-α stimulation. The transcription activity of NF-κB was determined using luciferase reporter assay. The level of Akt phosphorylation was checked by western blot. Expression levels of NF-κB downstream inflammatory cytokines IL-1 and IL-6 were measured by enzyme-linked immunosorbent assay (ELISA). mRNA and protein expression levels of intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1) were determined by quantitative real-time PCR (qRT-PCR) and western blotting inrespectively.

Results: Results showed that vaspin inhibited TNF-α mediated activation of NF-κB and its downstream molecules in a concentration-dependent manner ($P<0.05$). Vaspin significantly increased Akt phosphorylation in TNF-α stimulated endothelial cells in a concentration-dependent manner ($P<0.05$), which effects were abolished by pretreatment with the PI3-kinase inhibitor, Wortmannin ($P<0.05$).

Conculsions: Our results suggested that vaspin protected endothelial cells from TNF-α induced inflammation and insulin resistance by combination the inhibition of NF-κB, its downstream molecules and the upregulation of the PI3-kinase/Akt signaling pathway.

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INTEGRATED PHYSIOLOGY—INSULIN SECRETION IN VIVO

212-LB

Disturbed Glucose Homeostasis after Sleep Restriction Is Independent of the Chronobiological Time-Point of Sleep

FELIX MACHLEIDT, DENISA TROST, NELLI FORCK, MAREN WALTL, HENDRIK LEHNERT, SEBASTIAN M. SCHMID, *Luebeck, Germany*

Short sleep duration has been shown to detrimentally affect glucose metabolism in humans. However, little is known about the influence of chronobiological time-points of sleep on insulin sensitivity, i.e. in which part of the night sleep takes place. Against this background we investigated effects of sleep duration and sleep time-points on glucose metabolism in men. In a balanced cross-over design 15 healthy normal weight men underwent 3 different sleep conditions. We conducted two conditions of sleep restriction with only 4 hours of sleep per night: early (sleep between 11 p.m. - 3 a.m.) vs. late (sleep between 3 a.m. - 7 a.m.) condition. In the control condition participants were allowed to sleep for 8 hours (11 p.m. - 7 a.m.). After each condition we performed a Botnia clamp combining an intravenous glucose tolerance test with a subsequent hyperinsulinemic-euglycemic clamp. Thus it is possibly to assess acute β-cell secretory performance (first phase insulin response) as well as insulin sensitivity. Insulin sensitivity was defined as the ratio of glucose infusion rate and mean insulin plasma levels during steady state during the last 60 minutes of the clamp (M-Value). Baseline parameters were comparable between all conditions. Both, after the early and late condition of sleep restriction M-Values were significantly lower compared to controls reflecting reduced insulin sensitivity ($p<0.05$). Furthermore, first phase insulin response tended to be diminished after both conditions of sleep restriction as compared to regular sleep ($p=0.089$). There were no differences in glucose metabolism between the early and late sleep restriction. Taken together, we could demonstrate that acute sleep restriction impairs glucose homeostasis independent of chronobiological time-points of sleep. The detrimental effects of sleep restriction are mainly due to reduction of insulin sensitivity and—to a lower extent—to disturbed acute secretory performance of the β-cell.

213-LB

Patients with Long-Duration Type 2 Diabetes Have Blunted Glycemic and β-Cell Function Improvements after Bariatric Surgery

VISHESH KHANNA, STEVEN K. MALIN, JAMES F. BENA, BETH ABOOD, CLAIRE E. POTHIER, DEEPAK L. BHATT, STEVEN E. NISSEN, STACY A. BRETHAUER, PHILIP R. SCHAUER, JOHN P. KIRWAN, SANGEETA R. KASHYAP, *Cleveland, OH, Boston, MA*

Although bariatric surgery improves glycemic control, it is unclear if glucose regulation is improved comparably in short vs. long duration type 2 diabetes (T2D). Therefore, we evaluated the effect of T2D duration on glycemic control and glucose regulation (insulin secretion and sensitivity) in subjects who were randomized to bariatric surgery (RYGB n=12 and SG n=15). Twenty-seven adults (18F/9M, age: 51.0y [41.4,57.3], BMI: 34.6kg/m^2 [34.5,37.9], HbA1c: 9.1% [8.6,10.5]) with short (n=14; ≤5 y, 46% SG) and long-duration (n=13; ≥10 y, 53% SG) T2D received a mixed-meal tolerance test at baseline and 24 months (m) post-surgery. Body composition (BMI, body fat via DXA), insulin sensitivity (Matsuda Index), 1st and 2nd phase meal-stimulated insulin secretion (MSIS, C-peptide iAUC/glucose iAUC (1st, 0-30min) and (2nd, 60-120min), disposition index (DI or β-cell function); MSIS x Matsuda Index) and incretin (GLP-1, GIP) responses were examined. Before surgery, while both early and long-duration T2D had similar BMI, HbA1c, and % insulin use (all $p>0.2$), long-duration T2D required more oral medications and had lower fasting C-peptide compared with early T2D ($p<0.02$). At 24 m, both early and long-duration T2D had similar improvements in BMI, body fat, insulin sensitivity and meal-stimulated incretin responses (all $p>0.10$). However, early T2Ds had better HbA1c (-3.0[-4.9,-2.1] vs. -1.6[-3.1,-0.8]%, $p=0.003$) and greater 1st (0.14[0.1, 0.3] vs. 0.02[-0.01,0.1]) and 2nd phase DI (0.4[0.2,0.6] vs. 0.03[-0.02,0.2], both $p<0.02$), compared with long-duration T2D. Indeed, baseline T2D duration correlated with smaller reductions in HbA1c ($r=0.39$, $p<0.04$) and 1st ($r=-0.53$, $p=0.003$) and 2nd DI ($r=-0.51$, $p=0.001$). Therefore, despite equal weight loss and changes in incretin hormones to short duration T2D, inadequate β-cell function in people with long duration T2D appears key in explaining better glycemic control responses to bariatric surgery.

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214-LB

Most People with Long-Duration Type 1 Diabetes Are Insulin Microsecretors and Produce Their Own Endogenous Insulin

TIMOTHY J. MCDONALD, RICHARD A. ORAM, EWAN R. PEARSON, BEVERLEY SHIELDS, ANDREW T. HATTERSLEY, *Exeter, United Kingdom, Dundee, United Kingdom*

Ultrasensitive assays that can detect C-peptide under 5 pmol/L allow detection of very low levels of c-peptide. We aimed to use urine c-peptide creatinine ratio (UCPCR) to assess endogenous insulin in a large cross-sectional population-based study of patients with Type 1diabetes (T1D).

We recruited 944 patients from primary and secondary care in 2 UK centres. All diagnosed under 30years, duration >5 years, clinical diagnosis of T1D. Median(IQR) age of diagnosis 11(6-17)y, duration 18(11-26)y, HbA1c 8.7(7.9-9.8)%, insulin dose 0.78(0.60-0.97)u/kg/24hr, and BMI 25.6(23.3-28.6)Kgm-2. All provided a home post-meal UCPCR.

81% (790/944) had detectable endogenous production (median(IQR) UCPCR 0.012 (0.004-0.038)nmol/mmol). Most had very low, historically undetectable, levels (492/944, 53%, UCPCR >0.001-0.03 nmol/mmol). 8% had C-peptide levels above the DCCT cut off of significant endogenous insulin. Absolute UCPCR levels fell with duration but the proportion with detectable UCPCR never fell below 73% (maximum duration 47 years). Age of diagnosis and duration independent predictors of C-peptide in multivariate modelling.

The majority of patients with long duration T1D are insulin microsecretors and have detectable urine c-peptide. Some rare individuals with T1D maintain higher levels of endogenous insulin for many years after diagnosis of diabetes. The fact that some beta cells remain in most with longstanding T1D may reflect escape from immune attack, or beta cell regeneration. Understanding this may lead to a better understanding of pathogenesis in T1D and open new possibilities for treatment.

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215-LB

A Potent, Efficacious, and Selective GPR40 (FFAR1) Agonist Provides Immediate and Durable Glucose Control in Rodent Models of Insulin Resistance and Type 2 Diabetes

YANYUN CHEN, MIN SONG, XIANBU PENG, CHARLIE HU, DONALYN SCHEUNER, KRISTER B. BOKVIST, PRANAB MAITI, CHAFIQ HAMDOUCHI, ANNE REIFEL MILLER, *Indianapolis, IN, Bangalore, India*

LY2881835 (LY) is a high affinity, potent and efficacious GPR40 agonist when examined in hGPR40 binding and FLIPR assays. A statistically significant (SS) increase in insulin secretion was demonstrated when LY was examined in primary islets from mice, rats and humans; although, insulin secretion was not seen when LY was tested in primary islets from GPR40 KO mice. OGTTs performed in wild type (WT), GPR40 KO and GPR120 KO mice following oral administration of LY at 30 mg/kg demonstrated SS reductions in glucose AUCs in WT and GPR120 KO mice but not in GPR40 KO mice. These findings demonstrate that LY induces specific GPR40-mediated anti-diabetic activity when examined ex-vivo and in-vivo. LY was administered orally at 30 mg/kg to diet-induced obese (DIO) mice, an early model of T2D due to insulin resistance, for 14 days with OGTTs performed on days 1 and 14. SS reductions in glucose AUCs were seen on days 1 and 14. Interestingly, glucose levels were also SS reduced at time 0 of the OGTTs (60 minutes after LY was administered); although, glucose levels never fell below 100 mg/dl in any mouse during the study. A similar study was performed in streptozotocin (STZ)-treated DIO mice to explore glucose control in a model of type 2 diabetes (T2D). In this model, pancreatic insulin content was reduced ~80% due to STZ-treatment plus the mice were insulin resistant due to the high fat content of their diet. Glucose AUCs were SS reduced during OGTTs performed on days 1, 7 and 14 compared to control mice. In conclusion, these results demonstrate that LY functions as a GPR40-specific insulin secretagogue mediating immediate and durable glucose control in rodent models of insulin resistance and T2D. The findings suggest that a GPR40 agonist could benefit glucose control in individuals with insulin resistance and substantially reduced beta-cell function.

216-LB

Mosapride, a Serotonin 5-ht4 Receptor Agonist, and Alogliptin, a Selective Dipeptidyl Peptidase-4 Inhibitor, Exert Additive Effects on Plasma Active GLP-1 Levels in Mice

KATSUNORI NONOGAKI, *Sendai, Japan*

Aims: Mosapride citrate, a selective serotonin 5-HT4 receptor, typically activates gastrointestinal tract motility. The aim of the present study was to determine the effects of mosapride with or without alogliptin, a selective dipeptidyl peptidase-4 inhibitor, on feeding-dependent and -independent glucagon-like peptide-1 (GLP-1) secretion in mice.

Methods: In the first experiment, mosapride citrate was administered intraperitoneally to C57BL6J mice treated over 4 days with or without alogliptin (0.05%). The mice were food-deprived after mosapride citrate administration. One hour later, the mice were decapitated and blood was obtained to determine the plasma active GLP-1 levels. In the second experiment, mosapride citrate was administered intraperitoneally after 24-h food deprivation to C57BL6J mice treated over 4 days with or without alogliptin (0.05%). The mice were then provided food pellets and 1 h later the mice were decapitated and blood was obtained to determine the plasma active GLP-1 and insulin levels.

Results: Despite food deprivation, systemic administration of mosapride citrate significantly increased plasma active GLP-1 levels in mice. In addition, mosapride citrate significantly increased plasma active GLP-1 and insulin levels after refeeding following 24 h of fasting. Moreover, alogliptin treatment enhanced the feeding-dependent and -independent increases in the plasma active GLP-1 levels induced by mosapride citrate, as well as the refeeding-induced insulin secretion compared with saline controls.

Conclusions: 5-HT4 receptors upregulate active GLP-1 secretion independent of feeding. Pharmacologic stimulation of 5-HT4 receptors and the pharmacologic inhibition of DPP-4 exert additive effects on plasma active GLP-1 levels in mice.

217-LB

Across Glucose Tolerance (GT) Spectrum, Men (M) Display Greater Decreases in Insulin Secretion (IS) Than Women (W): A Cross-Sectional Analysis

RALPH RAYMOND, DANNY CHEN, CLAUDIO COBELLI, CHIARA DALLA MAN, DOUGLAS S. LEE, R. PAUL ROBERTSON, SUDHA S. SHANKAR, DARKO STEFANOVSKI, MARIA T. VASSILEVA, DAVID FRYBURG, FOR BETA CELL TEAM OF FNIH BIOMARKERS CONSORTIUM, *Skillman, NJ, Groton, CT, Padova, Italy, Cambridge, MA, Seattle, WA, Indianapolis, IN, Los Angeles, CA, Bethesda, MD, East Lyme, CT*

Little is known about gender differences in IS. As part of a project examining utility of Beta cell function tests, we studied effect of gender on IS response to arginine (ARG) stimulation test (AST) and the mixed meal tolerance test (MMTT) in overnight fasted, obese M and W with normal glucose tolerance (NGT), prediabetes (PDM) and type 2 diabetes (T2DM). For AST, acute IS (AIRarg) was measured over 5 min at baseline glucose after an IV ARG bolus (5 gm over 30 sec). Immediately following these samples, a 60 min infusion (900 mg/min) of glucose was initiated; ARG was administered again after 50 min of the glucose infusion; IS samples repeated (AIRmax). For MMTT, IS (κot and DItot) were measured in response to a standardized 450 kCal meal and estimated using minimal model.

The table below summarizes results. *Within* each gender significant declines in IS were detected for all 4 parameters (NGT and PDM largely similar v. T2DM). To compare the *changes* in IS of W to M across GTs, an ANCOVA model was developed. Of covariates tested (BMI and age), only age was included in model. ANCOVA showed that in both AST and MMTT, decline in IS for M>W.

				ARGININE TEST		MMTT	
	Age (Yr) (mean±SD)	BMI (kg/m2) (mean±SD)	Baseline Glucose (mg/dL) (mean±SD)	AIRarg (μU/ml)	AIRMAX (μU/ml)	MMTT Φ tot (10^{-9}/min)	MMTT DI tot (10^{-13}/ ((μU/ml)(min^2))
NGT (W) N=11	42.6±9.4	31.0±2.4	92±5	73.6 (61.0-88.8)	351.3 (263.3-468.9)	93.0 (77.4-111.6)	478.4 (380.8-601.1
NGT (M) N=12	41.2±7.4	31.8±3.2	93±5	95.9 (82.9-110.9)	440.5 (367.0-528.8)	112.4 (90.0-140.4)	450.4 (312.2-649.6)
PDM (W) N=6	45.5±12.4	32.4±1.4	109±11	86.8 (68.8-109.5)	362.8 (307.0-428.8)	106.5 (90.0-126.1	260.0^ (193.2-349.8)
PDM (M) N=2	49.0±2.3	31.6±0.8	116±2	116.1 (54.2-248.5)	419.5 (298.0-590.5)	99.4 (70.2-140.8)	188.1 (78.2-452.4)
T2DM (W) N=11	56.8±7.0	32.6±3.9	156±21	43.7^# (33.7-56.6)	103.2*† (78.0-136.5)	19.1*† (14.4-25.4)	33.6*† (21.5-52.3)
T2DM (M) N=11	52.5±8.6	32.9±3.9	156±29	28.9*† (23.2-36.0)	70.4*† (55.7-88.9)	12.4*† (9.9-15.7)	9.0*† (5.4-15.0)
ANOVA WITHIN women OR men for IS and across populations. Within M and W (but not between): ^p † p < 0.001 vs. PDM, #p				WOMEN: p=0.01 MEN: p<0.001	WOMEN: p<0.001 MEN: p<0.001	WOMEN: p<0.001 MEN: p<0.001	WOMEN:p<0.001 MEN: p<0.001
ANCOVA analysis comparing the change in IS BETWEEN men and women across GT				p < 0.05	p = 0.08	p < 0.05	p < 0.05

We conclude that 1) in a cross-sectional analysis of M and W with NGT, PDM, and T2DM, IS declines in both genders; 2) From NGT to T2DM, M show a greater decline than W in 2 different tests of IS. These results may have implications for gender balance in study designs.

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218-LB

Imaging of Insulin Exocytosis in Human Pancreatic Islets

JOANA ALMACA, ALEJANDRO CAICEDO, *Miami, FL*

Insulin exocytosis in the β-cells is a critical step in the whole process of hormone secretion that regulates blood glucose levels. To directly monitor insulin secretion in vitro, we used the exocytosis sensor phluorin, consisting of a mutated GFP protein sensitive to pH. In particular, under acidic pH, such as the one inside the exocytic granules, the protein is not fluorescent but its fluorescence strongly increases when the vesicles fuse with the plasma membrane and their content is released (pH increases). We fused phluorin with Neuropeptide Y (NPY), a peptide reported to be present with insulin in the same granules (NPY-phluorin). Human pancreatic islets were infected with adenoviruses encoding NPY-phluorin for at least 5 days and vesicle fusion with the plasma membrane could be observed either by 50 mM KCl depolarization or by increasing glucose concentration to 16 mM. Insulin granules appeared and quickly fused with the plasma membrane in a pulsatile manner with a frequency of pulse at about 3-5 min in the same cell. This process was tightly coordinated because different cells from the same islet (or regions in the islet) responded to glucose at the same time. This behaviour is in agreement with the well established pulsatility and synchronicity observed for activated β-cells and supports the use of this technique to monitor insulin secretion in vitro and in vivo using infected islets transplanted in the anterior chamber of the mouse eye.

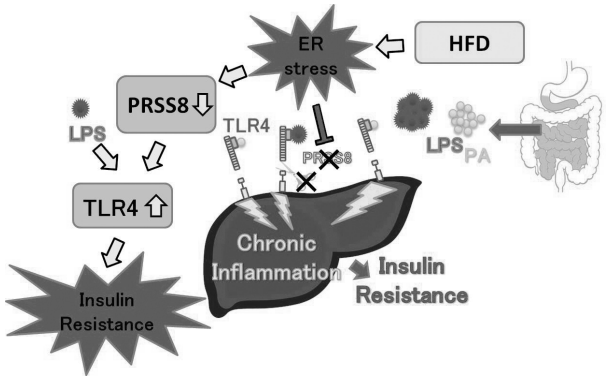
INTEGRATED PHYSIOLOGY—LIVER

219-LB

The Serine Protease Prostasin Regulates Hepatic Insulin Sensitivity by Modulating TLR4 Signaling

KOHEI UCHIMURA, MANABU HAYATA, TERUHIKO MIZUMOTO, YOSHIKAZU MIYASATO, YUTAKA KAKIZOE, KAZUKI FUKUDA, TATSUYA KONDO, TAKESHI MATSUMURA, EIICHI ARAKI, KIMIO TOMITA, KENICHIRO KITAMURA, *Kumamoto, Japan*

Although the effects of a high fat diet (HFD) and postprandial endotoxemia on the development of type 2 diabetes have been extensively studied, the precise mechanisms are not fully understood. Here we show that a serine protease prostasin (PRSS8) regulates hepatic insulin sensitivity by modulating Toll-like receptor 4 (TLR4)-mediated signaling. We demonstrate that HFD triggers the suppression of PRSS8 expression by inducing endoplasmic reticulum (ER) stress and increases TLR4 levels in the liver. PRSS8 released the ectodomain of TLR4 by cleaving it at the Lys^{560}/Lys^{561} residues, which resulted in a reduction in the full-length form at the plasma membrane and reduced activation of TLR4 by its ligands. Liver-specific PRSS8 knockout (LKO) mice developed hepatic insulin resistance associated with an increase in hepatic TLR4. Restoration of PRSS8 expression in the liver of HFD, LKO, and db/db mice decreased TLR4 levels and ameliorated hepatic insulin resistance. Furthermore, we demonstrated that a major component of serum PRSS8 may originate from the liver and that the serum PRSS8 levels were negatively correlated with body mass index (BMI) and homeostasis model assessment-insulin resistance (HOMA-IR) in healthy human subjects. Our results identify a novel role for PRSS8 and provide a new insight into the development of diabetes resulting from HFD or metabolic endotoxemia.



220-LB

Selective Silencing of NFκB in Kupffer Cells Improves Systemic Insulin Sensitivity in Obese Mice

MICHAELA TENCEROVA, MYRIAM AOUADI, PRANITHA VANGALA, SARAH M. NICOLORO, JOSEPH YAWE, JESSICA COHEN, YUEFEI SHEN, LORENA GARCIA-MENENDEZ, DAVID J. PEDERSEN, MICHAEL P. CZECH, *Worcester, MA*

Obesity is often accompanied by liver inflammation that could promote fatty liver disease and insulin resistance. Activation of liver macrophages, known as Kupffer cells (KCs), may contribute to hepatic lipid accumulation and impairment of insulin signaling. However, this hypothesis has not been directly tested due to lack of technology to manipulate gene expression specifically in KCs without targeting other cell types or organs. To address this question, we developed a system based on glucan-encapsulated siRNA particles (GeRPs) to selectively deliver siRNA to KCs in vivo. Following intravenous administration in obese mice, GeRPs were internalized by KCs in liver but were not detected in hepatocytes or macrophages within other tissues. Importantly, GeRPs loaded with an siRNA targeting NFκB, a major regulator of inflammation, selectively silenced its expression in KCs, while hepatocytes were unaffected. GeRP-mediated silencing of NFκB resulted in a decreased expression of downstream cytokines, including IL-1β. Strikingly, silencing NFκB in KCs, over a 14-day period, improved glucose tolerance in genetically obese mice. Taken together, these results demonstrate a major contribution of KCs in the development of insulin resistance. Furthermore, the GeRP technology provides a unique method to validate novel therapeutic targets expressed by KCs involved in hepatic inflammation and insulin resistance.

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221-LB

The b-ZIP Transcription Factor E4BP4 as a Novel Regulator of Hepatic Glucose Metabolism in Obesity

LEI YIN, XIN TONG, DEQIANG ZHANG, BLAKE ARTHURS, HUGH BRADY, *Ann Arbor, MI, London, United Kingdom*

Increased gluconeogenesis in the liver is one of the key pathological changes in diabetic patients. FOXO1-dependent activation of gluconeogenic enzymes such as Pepck and G6Pase has been shown to contribute significantly to increase gluconeogenesis of diabetic mouse models. However, it remains unclear how liver FOXO1 activities are persistently enhanced in diabetic conditions. A previous study suggests an interaction between FOXO1 and E4BP4, a b-ZIP transcription factor, in cancer cells. In our lab, we observed that the mRNA and protein levels of E4BP4 were elevated in the liver tissues of both ob/ob mice and high-fat diet-fed mice. Whether E4BP4 can influence FOXO1 expression and gluconeogenesis in diabetic condition has not been investigated yet. Here we reported that E4BP4 controls hepatic gluconeogenesis by regulating FOXO1 protein expression and activity in a diet-induced mouse model. Genetic deletion of E4bp4 protects mice from high-fat-diet-induced hyperglycemia and insulin resistance. Compared with wild-type mice, E4bp4-/- mice displayed about 50% reduction in hepatic G6pase expression and G6PASE enzymatic activity in vivo. Acute depletion of E4bp4 expression in primary mouse hepatocytes reduces G6pase expression and glucose production, whereas acute over-expression of E4bp4 increases G6pase expression and glucose production, supporting a cell-autonomous role of E4BP4 in regulating gluconeogenesis in hepatocytes. E4bp4 depletion suppresses the FOXO1-induced G6pase-luc activity while reducing the protein abundance of FOXO1. Further analysis showed acute E4bp4 knockdown promotes FOXO1 protein polyubiquitination and subsequent proteasome-dependent degradation in cultured hepatocytes. In summary, our results highlight a critical role for E4BP4 in regulating FOXO1 expression and hepatic gluconeogenesis in diabetic conditions, indicating that inhibition of E4BP4 expression or function might be a novel venue to treat hyperglycemia in diabetes.

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222-LB

Elevated Systemic Soluble Amyloid Precursor Protein β as a Risk Factor for the Development of Type 2 Diabetes Mellitus

CHRISTIAN PEHMOLLER, ASHLEY ROBSHAW, CRISTIANO GUIMARAES, MIN WAN, PAUL L. HUANG, CHARLES E. NOLAN, LIYA KANG, TONI WHITTARD, CRAIG L. HYDE, M. JULIA BROSNAN, DAVID RIDDELL, OLIVIER BEZY, *Cambridge, MA, Boston, MA*

Epidemiological studies have shown that type 2 diabetes mellitus (T2D) is highly correlated with Alzheimer's disease (AD). T2D doubles the risk of developing AD and, conversely, individuals with AD are more likely to exhibit impaired fasting glucose levels. It has been suggested that insulin resistance may represent a common pathological link connecting these two chronic diseases. To date, the most reliable marker for AD progression remains the proteolysis of amyloid precursor protein (APP) into amyloid peptide Aβ and soluble APPβ (sAPPβ). To determine if there is a mechanistic connection between these circulating factors and peripheral insulin resistance, we collected plasma samples from a subset of participants in the Pfizer/Massachusetts General Hospital sponsored

Cardiology and Metabolic Patient Cohort (CAMP Cohort). The CAMP Cohort consists of > 4,000 phenotyped subjects that include lean and obese individuals with and without insulin resistance and T2D. Analysis of the plasma samples revealed a positive correlation between Aβ and glucose levels ($r=0.429$, $p < 1.0e-06$) and a negative correlation between Aβ and total plasma cholesterol, HDL and LDL after adjusting for T2D status and BMI ($p = 0.001$ for HDL, $p < 0.05$ for all 3). We then explored diet induced insulin resistance in APP over expressing mice (Tg2576). When placed on a high-fat diet, APP overexpressing mice (Tg2576) had greater body weight gain, impaired glucose and insulin tolerance, and increased hepatic insulin resistance compared to wild type animals. Treatment of human or murine primary hepatocytes with recombinant human sAPPβ strongly impaired insulin signaling. Comparison of the copper-binding domain of human sAPPβ with human insulin revealed striking structural similarities suggesting sAPPβ could directly interfere with insulin action. These observations provide a potential molecular explanation for the peripheral and central insulin resistance observed in T2DM and AD patients.

223-LB

PLA2G5 Regulates Glucose and Fatty Acid Metabolism in Human Hepatocytes

CHRISTIAN PEHMOLLER, JESSICA CALLOWAY-JONES, LANBA ADHIRAJ, NICHOLAS B. VERA, CECILE VERNOCHET, OLIVIER BEZY, *Cambridge, MA*

Cardiac metabolism in obesity and type 2 diabetes (T2D) has been proposed to regulate whole body energy homeostasis through the secretion of group V phospholipase A2 (PLA2G5). Recent data from the laboratory of Eric Olsen, Dallas, TX, indicate heart specific over-expression of PLA2G5 causes obesity, and reduces liver, muscle and adipose fatty acid oxidation; implicating systemic PLA2G5 as a regulator of energy homeostasis. Using human recombinant PLA2G5 (hrPLA2G5), we examined the role of this secreted phospholipase in the development of metabolic disease. When added to serum from healthy donors, hrPLA2G5 recapitulated the dramatic increase in the lysophosphatidylcholine (LPC) and free fatty acid (FFA) profile observed in serum from obese T2D patients. *In vitro* treatment of human hepatocytes with hrPLA2G5 resulted in rapid (≤ 10 minutes) internalization of hrPLA2G5 and a similar FFA profile exclusively released into the cytoplasm of hepatocytes. To further assess the effect of PLA2G5 on hepatocyte metabolism, we performed metabolic flux analysis (Seahorse Flux Analyzer) following overnight hrPLA2G5 exposure. Our data revealed an increase in both oxygen consumption rate (OCR) and fatty acid oxidation (FAox). Consistent with the increase in FAox, extracellular acidification rates (ECAR) indicated glycolysis was significantly reduced following hrPLA2G5 incubation. Gene expression analysis indicated a down regulation of genes involved in glycolysis and TCA cycle in response to PLA2G5 and up-regulation of gluconeogenesis. These data further establish PLA2G5 as a key regulator of energy homeostasis and suggest PLA2G5 is an important regulator of hepatocyte metabolism.

224-LB

The Relationship between Sarcopenia and Non-alcoholic Fatty Liver Disease: The Korean Sarcopenic Obesity Study

HYE JIN YOO, HO CHEOL HONG, SIN GON KIM, NAN HEE KIM, SEI HYUN BAIK, DONG SEOP CHOI, KYUNG MOOK CHOI, NAM HOON KIM, SUN HWA KIM, *Seoul, Republic of Korea*

Previous studies have shown that non-alcoholic fatty liver disease (NAFLD) and sarcopenia may share pathophysiological mechanisms, such as insulin resistance, inflammation, vitamin D deficiency, and decreased physical activity. However, their direct relationship has not been investigated. The association between NAFLD and sarcopenia was examined in 452 apparently healthy adults enrolled in the Korean Sarcopenic Obesity Study (KSOS), an ongoing prospective observational cohort study. The liver attenuation index (LAI), which measured using abdominal computed tomography (CT), was used as a parameter for the diagnosis of NAFLD. Sarcopenia was defined using a skeletal muscle mass index (SMI) [SMI (%) = total skeletal muscle mass (kg) / weight (kg) x 100] that was measured by dual energy X-ray absorptiometry (DXA). After adjusting for age and sex, both SMI and LAI were negatively correlated with the homeostasis model assessment of insulin resistance (HOMAIR) ($P<0.001$) and high sensitivity C-reactive protein (hsCRP) ($P<0.001$) as well as brachial ankle pulse wave velocity (baPWV), an indicator of arterial stiffness. Furthermore, SMI and LAI had positive relationships with HDL-cholesterol, but both had a negative relationship with triglyceride, alanine aminotransferase (ALT), and total body fat. In a multiple logistic regression analysis, the odds ratio for NAFLD risk was 5.16 (95% CI = 1.63-16.33) in the lowest quartile of

SMI compared to the highest after adjusting for potential confounding factors. Conclusion: Individuals with lower muscle mass exhibited increased risk of NAFLD. This result may provide a novel insight into the mechanism linking between sarcopenia and NAFLD.

225-LB

AAV8-mediated SIRT1 Gene Transfer to the Liver Prevents High Carbohydrate Diet-induced Non-alcoholic Fatty Liver Disease

IVET ELIAS, LAIA VILÀ, CARLES ROCA, ALBERT RIBERA, TURA FERRÉ, ALBA CASELLAS, RICARDO LAGE, SYLVIE FRANCKHAUSER, FATIMA BOSCH, *Barcelona, Spain*

Non-alcoholic Fatty Liver Disease (NAFLD) is the most common hepatic disease worldwide, and evidence suggests that it promotes insulin resistance and type 2 diabetes. To date, the only treatment capable of counteracting or ameliorating liver steatosis is based on lifestyle intervention by means of caloric restriction (CR). The protein deacetylase Sirtuin1 (SIRT1), which is activated by CR, increases catabolic metabolism and decreases lipogenesis and inflammation, both involved in the development of NAFLD. Here we show that adeno-associated viral vectors of serotype 8 (AAV8)-mediated liver-specific Sirt1 gene transfer prevents the development of NAFLD induced by a high carbohydrate (HC) diet. Long-term hepatic SIRT1 overexpression led to up-regulation of key hepatic genes involved in beta-oxidation such as Peroxisome proliferative activated receptor gamma, coactivator 1 alpha (Ppargc1a), Long-chain acyl-Coenzyme A dehydrogenase (Acadl), Very long chain acyl-CoA dehydrogenase (Acadvl), Sirtuin 6 (Sirt6) and Sirtuin 3 (Sirt3), prevented HC diet-induced lipid accumulation, reduced macrophages infiltration and liver inflammation. AAV8-Sirt1-treated mice showed improved insulin sensitivity, increased oxidative capacity in skeletal muscle and reduced white adipose tissue inflammation. Moreover, HC feeding induced leptin resistance, which was also attenuated in AAV8-Sirt1-treated mice. Therefore, AAV-mediated gene transfer to overexpress SIRT1 specifically in the liver may represent a new gene therapy strategy to counteract NAFLD and related diseases such as type 2 diabetes.

226-LB

Argininosuccinate Synthetase Regulates Hepatic AMPK Activity Linking Protein Catabolism and Ureagenesis to Hepatic Glucose Metabolism

ANILA K. MADIRAJU, XIAN-MAN ZHANG, GARY W. CLINE, SANJAY BHANOT, VARMAN T. SAMUEL, RICHARD G. KIBBEY, GERALD I. SHULMAN, *New Haven, CT*

AMP-activated protein kinase (AMPK) is a key sensor of cellular energy status and plays a critical role in the regulation of major metabolic processes. AMPK activation relies on allosteric interaction with AMP via binding at the γ subunit, which increases Thr172 phosphorylation. The urea cycle enzyme argininosuccinate synthetase (ASS1) produces a single AMP per turn of the urea cycle, a predominant pathway in the liver. Here we show that ASS1 activity regulates hepatic AMPK activity, revealing a central role for urea cycle flux in the regulation of cellular metabolism via AMPK. Antisense oligonucleotide (ASO) knockdown of hepatic ASS1 gene expression in awake rats reduced liver AMPK activation by 57±6% (P=0.05), and decreased phosphorylation of the downstream AMPK target acetyl-coA carboxylase (ACC) by 27±7% (P<0.05). ASS1 ASO treatment increased plasma glucose concentrations (106±5 mg/dL vs. 141±6 mg/dL, P<0.01), without altering rates of endogenous glucose production. Acute intravenous treatment of rats with L-citrulline [30 mg/kg], the substrate of ASS1, increased hepatic AMPK activation by 41±3% (P<0.01) and increased ACC phosphorylation by 35±10% (P=0.06). L-citrulline treatment decreased fasting plasma glucose concentrations (120±2 mg/dL vs. 110±1 mg/dL, P<0.01), inducing the inverse effect of hepatic ASS1 ablation. Significantly, immunopreciptation (IP) of hepatic ASS1 protein pulled down AMPK, and IP of AMPK brought down ASS1, providing evidence for a direct physical interaction between AMPK and ASS1. Taken together these findings demonstrate that the urea cycle enzyme ASS1 resides in a complex with liver AMPK and can lead to direct activation of AMPK via increased production of AMP. This interaction may link increased protein catabolism and ureagenesis with hepatic AMPK activation and alterations in hepatic glucose metabolism.

227-LB

Treatment with a Monoclonal Antibody Blocking the Glucagon Receptor Is Not Associated with Perturbations in Liver Function or Lipid Metabolism

ALISON FORGIE, EILEEN BLASI, QUAN ZHENG, TERRENCE PARK, BORA HAN, MARK EVANS, RUN YU, JAVIER CHAPARRO-RIGGERS, JOHN LIN, *South San Francisco, CA, La Jolla, CA, Los Angeles, CA*

Blockade of the elevated glucagon signaling in patients with type 2 diabetes mellitus (T2DM) is emerging as an attractive potential treatment for this condition. Clinical trial data have shown robust HbA1c lowering in T2DM patients receiving glucagon receptor (GCGR) antagonists, however, this has been accompanied by elevations in liver function tests (LFT), and in some cases, increases in LDL-cholesterol (LDL-C), leading to the notion that blockade of glucagon signaling in humans may be obligately connected to these deleterious changes. As these changes have been observed upon treatment with small molecule antagonist drugs only, an alternate explanation may be hepatic pharmacophore accumulation and toxicity. Hence to address the role of mechanism versus drug modality, a monoclonal antibody (mAb), shown to fully block the GCGR, was administered to non-human primates (NHP). Clinical chemistry parameters were measured. No significant changes in LFT's, LDL-C, or triglycerides (TG) were observed following repeat dosing of this mAb, comparing to both the treated animals' baseline values and to a cohort receiving only vehicle. These data are in agreement with the observation that a human patient, who carries a homozygous GCGR P86S mutation resulting in significantly reduced glucagon signaling, presents normal LFT's, LDL-C and TG's. Additional experiments were conducted in lean and disease mouse models using another mAb with cross-reactivity to murine GCGR. No treatment-related changes in LFT's were observed in any model following chronic dosing. LDL-C showed variable and inconsistent responses to treatment, in contrast to the NHP and human data described, and likely reflects well known species differences in lipid metabolism. In summary these data suggest glucagon signaling can be fully blocked without undesirable effects on LFT's and LDL-C, and point to monoclonal antibodies as the potential modality of choice in the treatment of T2DM.

228-LB

Prevention of Diet-induced Hepatic Insulin Resistance by Antisense Oligonucleotides Targeted to mINDY

DOMINIK PESTA, RACHEL PERRY, DONGYAN ZHANG, MICHAEL J. JURCZAK, ANDREAS L. BIRKENFELD, SANJAY BHANOT, VARMAN T. SAMUEL, GERALD I. SHULMAN, *New Haven, CT, Berlin, Germany, Carlsbad, CA*

INDY as part of the SLC13 protein family is a high-affinity di- and tricarboxylate plasma membrane transporter involved in citrate import. In Drosophila, genetic deletion of INDY alters energy metabolism and extends lifespan. Mice lacking INDY are protected from both diet-induced and age-associated hepatic insulin resistance. Here, we examined the impact of selective hepatic knockdown of mammalian Indy protein (mINDY) expression using anti-sense oligonucleotides (ASOs) on hepatic glucose metabolism in 4 week high fat fed rats (n=15 per group) assessed by hyperinsulinemic-euglycemic (HEC) clamp studies. After 4 weeks of ASO treatment, mINDY mRNA expression was reduced by 91% (P<0.001) in the treatment group. The mINDY ASO treated rats showed a 34% reduction in fasting plasma insulin concentrations compared to the control group (14.5 vs. 9.6 µU/ml, P<0.05) and was associated with ~30% reduction in basal rates of endogenous glucose production [5.9 ± 0.6 vs. 8.4 ± 0.8 mg/(kg-min), Furthermore hepatic insulin responsiveness was increased in the mINDY ASO rats as reflected by increased suppression of hepatic glucose production during the HEC [19.7 vs. 61.6%, P<0.05]. Taken together these data suggest that hepatic mINDY may be a novel therapeutic target for the treatment of hepatic insulin resistance and type 2 diabetes.

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229-LB

The ER Stress Sensor IRE1alpha Controls Fasting-induced Metabolic Adaptation Response in the Liver

MENGLE SHAO, BO SHAN, YANG LIU, CHENG YAN, YING WU, LIU YANG, YONG LIU, *Shanghai, China*

In eukaryotes, accumulation of unfolded/misfolded proteins in the endoplasmic reticulum (ER) activates the cellular unfolded protein response (UPR). The ER-localized transmembrane signal transducer IRE1 (inositol-requiring enzyme 1) is an ancient ER stress sensor that possesses both protein Ser/Thr kinase and endoribonuclease (RNase) activities. Activated through trans-autophosphorylation and dimerization/oligomerization upon ER stress, IRE1 initiates a key branch of the UPR by non-conventional splicing regulation of the transcription factor XBP1 (X-box binding protein 1). Despite that

the mammalian IRE1alpha-XBP1 branch has been implicated in metabolic processes, the exact metabolic role of IRE1alpha remains largely elusive. We found that hepatic IRE1alpha is a catabolic sensor that regulates the metabolic adaptation response to prolonged fasting. Deprivation of food or consumption of a ketogenic diet could activate the IRE1alpha-XBP1 pathway in mouse livers. Hepatocyte-specific ablation of Ire1alpha resulted in impairment of fatty acid-oxidation and ketogenesis under chronic fasting or ketogenic conditions. Liver-specific restoration of XBP1s reversed the defects in IRE1alpha knockout mice. Furthermore, XBP1s could directly bind to and activate the promoter of PPARalpha, the master regulator of starvation responses. These findings suggest that hepatic IRE1alpha promotes starvation-induced adaptive shift of fuel utilization through the XBP1s-PPARalpha pathway.

230-LB

An Immuno-affinity Method to Separate Chylomicrons from VLDL and to Ascertain the Conversion of Sugar to Fat by De Novo Lipogenesis in the Human Intestine

GRACE MARIE JONES, EWAN F. SINCLAIR, CLIVE PULLINGER, RUSSELL CACCAVELLO, TERESA KHOFRI, MICHAEL WEN, KATHY MULLIGAN, ALEJANDRO GUGLIUCCI, JEAN-MARC SCHWARZ, *Vallejo, CA, San Francisco, CA*

The kinetics of VLDL and chylomicron lipoprotein particles as well as their respective triglyceride (TG) content are important to understand the mechanisms by which dietary or pharmacological interventions modify particle size, lipid profile and cardiovascular risk. Ultracentrifugation cannot separate remnant chylomicrons from large VLDL particles. Therefore, we devised an immuno-affinity method to separate VLDL (apoB100) from chylomicron (apoB48) particles in triglyceride-rich lipoproteins (TRL) using an apoB100 antibody.

The separated lipoproteins were analyzed by Silver Stain and revealed a depletion of apoB100 in the sequential flow-through fraction and the elution of apoB100 contained no apoB48. To further validate the separation process we examined the TG content of the separated VLDL and chylomicrons by GC-MS and LC-MS/MS analysis. Traditional GC-MS analysis was used to validate a triglyceride-specific palmitate enrichment LC-MS/MS technique. The incorporation of 1-13C-acetate into palmitate, using mass isotopomer distribution analysis, was used to calculate fractional de novo lipogenesis (DNL) in VLDL and chylomicrons.

Both LC/MS-MS and GC-MS analysis revealed a difference in the incorporation of 13C-acetate in palmitate between TG in the VLDL versus chylomicron particles. Additionally, LC/MS-MS analysis revealed a difference in the types of fatty acids incorporated in palmitate-containing TG in VLDL as compared to chylomicrons.

Together, these results demonstrate that we have developed and validated methods that: 1) allow for the isolation of apoB48 particles from apoB100 particles in human TRL samples, 2) permit the discernment of the fatty acid composition in palmitate containing TG and 3) support intestinal conversion of sugar to fatty acids by DNL. The physiological significance of enterocyte DNL on postprandial lipid profiles remains to be explored.

231-LB

Effect of Antisense Oligonucleotide Knockdown of Hepatic AMP Deaminase 2 Expression on AMPK Activity and Hepatic Fat and Glucose Metabolism

YASMEEN RAHIMI, MAX C. PETERSEN, ANILA K. MADIRAJU, DANIEL F. VATNER, DOMINIK PESTA, RACHEL J. PERRY, SANJAY BHANOT, GARY W. CLINE, VARMAN T. SAMUEL, GERALD I. SHULMAN, *New Haven, CT, Carlsbad, CA*

AMP activated kinase (AMPK) is a key regulator of hepatic fat oxidation and lipid synthesis through its regulation of acetyl CoA carboxylase (ACC) 1 and 2 activity. Furthermore, inhibition of AMPK activity is associated with hepatic fat accumulation through increasing hepatic lipogenesis and decreasing fat oxidation. Given that AMP is a key activator of AMPK, it has been suggested that inhibition of hepatic AMP deaminase 2 (AMPD2), a key enzyme that converts AMP to IMP, would be a potential therapeutic target for nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2D). To test this hypothesis, we examined the effects of knockdown of hepatic AMPD2 expression using antisense oligonucleotides (ASO) in four week high-fed fat rats. AMPD2 ASO treatment did not alter fasting plasma glucose concentrations but surprisingly led to an increase in basal rates of endogenous glucose production [7.5 ± 0.4 vs. 5.8 ± 0.2 mg/(kg·min); $P < 0.05$]. Furthermore AMPD2 ASO treatment did not lead to activation of AMPK or downstream targets [(ACC1 and 2 phosphorylation, hepatic malonyl-CoA concentrations (0.41 ± 0.05 control-ASO, 0.6 ± 0.1 pmol/mg AMPD2-ASO; $P>0.05$), suggesting that fatty acid oxidation in the liver was unaltered. Consequently AMPD2 ASO treatment did not impact hepatic insulin responsiveness, as reflected by similar suppression rates of endogenous glucose production during the hyperinsulinemic-euglycemic clamp, as well as hepatic triglyceride content (25 ± 2 mg/g Control ASO vs. 21 ± 2 mg/g AMPD2 ASO, $P > 0.05$). Conclusion: These findings demonstrate that AMPK activity is not regulated by AMPD2 and that AMPD2 may not have therapeutic potential for NAFLD and T2D.

Supported By: T32

232-LB

Endoplasmic Reticulum Stress and miRNA-122/370 Expression in Mice Offspring: Effects of Maternal Consumption of High-Fat Diet

ARINE M. MELO, RAFAELA O. BENATTI, FERNANDA O. BORGES, SIMONE F. LEMES, LAIS A.P. SIMINO, LICIO A. VELLOSO, ADRIANA S. TORSONI, MARCIO A. TORSONI, *Limeira, Brazil, Campinas, Brazil*

Maternal consumption of high fat diet (HFD) has been associated to changes in lipid metabolism, hepatic steatosis and impairment in insulin signaling in hypothalamus and liver in the offspring. HFD also can modify the expression of miRNAs related to fatty metabolism and to active cellular response to endoplasmic reticulum stress (ERS) leading to obesity and insulin resistance. Our objective was to evaluate the miRNAs and ERS in the offspring before the development of obesity. To answer this question we used male offspring mice recently weaned (d28) from dams fed with HFD (HFD-O) or standard chow (SC-O) during pregnancy and lactation. We evaluated unfolded proteins response (UPR) activation, as an indicator of ERS, the expression of miR-122/370 and enzymes related to lipid metabolism in liver. Body weight, mass of white adipose tissue, food intake, and hepatic triglycerides were increased in HFD-O compared to SC-O mice (1.3, 3.0, 1.1, 1.5-fold, respectively). Furthermore, hypothalamic and hepatic level of p-PERK and p-eIF2alpha were increased in HFD-O (1.4, 2.1, 1.8, 3.8-fold, respectively), as well as hypothalamic GRP94, GRP78 and XBP1s proteins compared to SC-O (3.3, 2.7, 2.2-fold, respectively). In addition HFD-O mice showed reduced hypothalamic p-AKT stimulated by insulin (2.1-fold), increased level of p-JNK1 (2.2-fold), and immunostaining to CD11+ cells and TNFalpha. Liver SCD1 was increased in HFD-O mice (3-fold), indicating an increase in phospholipids synthesis that contributes to ERS and liver triglycerides storage. Furthermore liver AGPAT expression increased (1.7-fold) while CPT1 and ACADVL expression was reduced in HFD-O compared to SC-O mice (40% and 30%, respectively). In addition, liver from HFD-O showed reduced expression of miR-122 (25%) and increase in miR-370 (3-fold) compared to SC-O. Taken together these results suggesting that recently weaned mice present metabolic and epigenetic changes before the development of obesity.

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233-LB

Clinical Utility of Serum Fibroblast Activation Protein in the Risk Assessment of Severe Liver Fibrosis Secondary to Non-alcoholic Fatty Liver Disease in Diabetes and Obesity

KATHRYN H. WILLIAMS, ANA JULIA V. DE RIBEIRO, EMILIA PRAKOSO, ANNE-SOPHIE VEILLARD, NICHOLAS SHACKEL, YAGMIN BU, BELINDA BROOKS, ERIKA CAVANAGH, JIM RALEIGH, SUSAN MCLENNAN, GEOFFREY MCCAUGHAN, WILLIAM BACHOVIN, FIONA KEANE, AMANY ZEKRY, MARK D. GORRELL, STEPHEN M. TWIGG, *Sydney, Australia, Boston, MA*

Non-alcoholic fatty liver disease (NAFLD) is common in diabetes and obesity, sometimes occurring as non-alcoholic steatohepatitis (NASH) with fibrosis. Non-invasive methods to assess for NASH risk are needed. Objectives: To determine whether blood levels of the pro-fibrotic enzyme, fibroblast activation protein (FAP), have clinical value in assessing for significant fibrosis, particularly when combined with the established NAFLD Fibrosis Score (NFS). Research Design: Two adult cohorts were examined: 106 with type 2 diabetes who had transient elastography (Cohort 1) and 146 with morbid obesity who had liver biopsy (Cohort 2). Results: In Cohort 1, FAP level was an independent risk factor for median liver stiffness (MLS) ≥10.3 kPa (consistent with severe fibrosis) with odds ratio (per SD increase) of 2.0 (95% CI 1.2-3.4), p=0.006. There was 8.1 fold (95% CI 1.6-39.7) odds ratio of MLS ≥10.3kPa for those in the highest compared with the lowest FAP tertile (p=0.010). FAP levels below 730pmol AMC/min/mL had 95% negative predictive value for significant fibrosis. Low FAP re-classified 41% of 64 patients from "intermediate risk" of severe fibrosis by NFS, to "low risk." In Cohort 2, per SD increase in FAP, there was 1.7 fold (95% CI 1.1-2.8) increased odds of significant fibrosis (F≥2), p=0.021, and low FAP correctly reclassified 49% of 73 patients from "intermediate risk" of severe fibrosis by NFS, to "low risk." Conclusions: Circulating FAP co-segregates with liver fibrosis in NAFLD and lower FAP combined with NFS has clinical utility in excluding severe fibrosis in populations with type 2 diabetes and obesity.

Supported By: NHMRC

INTEGRATED PHYSIOLOGY—MACRONUTRIENT METABOLISM AND FOOD INTAKE

234-LB

Dysregulation of Intestinal Glucose Transporters to Systemic and Luminal Glucose Cues in Type 2 Diabetes

RICHARD L. YOUNG, TONGZHI WU, NEKTARIA PEZOS, MICHAEL HOROWITZ, CHRISTOPHER K. RAYNER, *Adelaide, Australia*

Expression of intestinal sweet taste receptors (STRs) is dysregulated in type 2 diabetes (T2D), in association with augmented glucose absorption. [1] Here, we determined whether expression of the glucose transporters (GTs) sodium-glucose co-transporter-1 (SGLT-1) and glucose transporter-2 (GLUT2) were (i) regulated acutely by changes in luminal and blood glucose in non-diabetic subjects (ND), (ii) modified in T2D, and (iii) associated with changes in expression of the STR, T1R2. Eleven ND subjects (8M:3F, 31 ± 3y, BMI: 25 ± 2 kg/m^2) and 12 T2D patients (4M:8F, 65 ± 2y, BMI 28 ± 1 kg/m^2) were studied during euglycemia (6 mmol/L) and hyperglycemia (12 mmol/L) on 2 study days. Duodenal biopsies were collected at baseline and after a 30 min duodenal glucose infusion (30g/150ml water + absorption marker 3-O-methylglucose (3-OMG)) to assess transcript levels. Patients with T2D showed dysregulated transcription of intestinal GTs following luminal glucose, and a lack of suppression in response to elevated blood glucose (see table). Responses of SGLT-1 to luminal glucose indicate a specific contribution of this GT to augmented glucose absorption during hyperglycemia in T2D patients. Changes in T1R2 transcript levels were related to glucose absorption in T2D patients (3-OMG, $P \leq 0.05$), however, GT transcription is regulated acutely by factors other than STRs in humans.

	SGLT-1		GLUT2		T1R2	
	6 mmol/L	12 mmol/L	6 mmol/L	12 mmol/L	6 mmol/L	12 mmol/L
ND						
baseline	reference	23%↓$^{\delta}$	reference	24%↓$^{\#}$	reference	← →
post-infusion	← →	46%↑*	← →	← →	35%↑*	42%↓*
T2D						
baseline	reference	← →	reference	← →	reference	← →
post-infusion	29%↓$^{\#}$	38%↑*	← →	22%↓*	53%↑*	29%↑*

*P < 0.05, # < 0.01, δ < 0.001.

1. Young RL et al Diabetes 2013 62:3532-41.

Supported By: NHMRC; Diabetes Australia

235-LB

A Moderate Calorie Restriction and Intermittent Fasting Prevent Type 2 Diabetes in a Diabetic Mouse Model by Increasing Fatty Acid Oxidation in Glycolytic Muscles

CHRISTIAN BAUMEIER, DANIEL KAISER, JÖRG HEEREN, LUDGER SCHEJA, CLARA WEIGELT, HANS-GEORG JOOST, ROBERT WOLFGANG SCHWENK, ANNETTE SCHÜRMANN, *Potsdam, Germany, Hamburg, Germany*

Calorie restriction (CR) and intermittent fasting (IF) are known to have several beneficial effects on health, longevity and prevention of type 2 diabetes (T2D). The aim of the present study was to clarify detailed mechanisms on the suppression of T2D by these dietary interventions.

We tested if moderate CR and elongated fasting periods prevent the onset of T2D in New Zealand Obese (NZO) mice, a model for polygenic obesity and diabetes. At 4 weeks of age male NZO mice were fed a high-fat diet (HFD, 35% calories from fat) ad libitum (AL), or were subjected to 10% CR. Additionally, one group had access to HFD AL but was fasted every other day (IF). Body weight development, as well as blood glucose, body composition and diabetes prevalence were determined. Furthermore, we measured oral glucose tolerance and the respiratory quotient at week 8 and analyzed muscular lipid composition as well as fatty acid oxidation at 12 weeks of age.

Both 10% CR and IF resulted in lower body weight (48.0 ± 1.7 g vs. 45.5 ± 0.6 g vs. 41.3 ± 0.9 g; AL vs. CR vs. IF; week 10) and prevented development of hyperglycemia as detected in AL mice (diabetes prevalence in week 14: 43% vs. 0% vs. 0%; AL vs. CR vs. IF). CR reduced the lean mass rather than the fat mass, while IF reduced both in comparison to the AL fed control group. Glucose tolerance and insulin sensitivity was improved in animals subjected to CR and IF, and measurements of the respiratory quotient indicated an increased metabolic flexibility, especially in mice of the IF group. Moreover, ex vivo studies revealed an increased fatty acid oxidation in glycolytic muscles of IF mice which was accompanied by a reduction of diacylglycerol species.

In conclusion our data demonstrate that both, moderate CR and IF are suitable to prevent or at least delay the onset of T2D in NZO mice by increasing metabolic flexibility and lipid oxidation.

236-LB

A Human Model of Oral Saturated Fatty Acid Induced Insulin Resistance

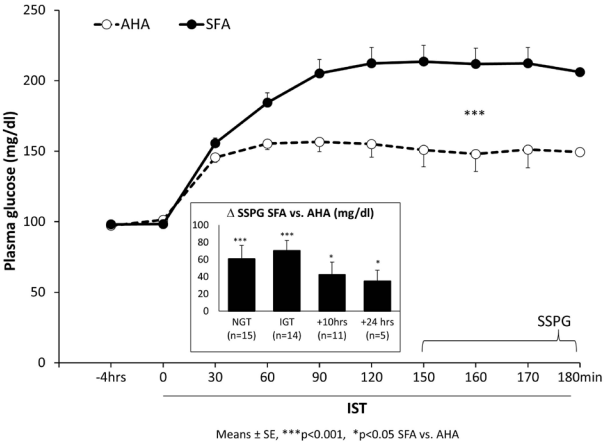
JURAJ KOSKA, HODA GHANEM, JAMES DEER, ARLINE SALBE, SHERMAN M. HARMAN, PETER D. REAVEN, *Phoenix, AZ, Dublin, CA*

Models of lipid-induced insulin resistance (IR) in humans often rely on acute infusion of fatty acid (FA) mixtures to study mechanisms of IR and its potential treatments. Limitations of this method of inducing IR include bypassing the gastrointestinal tract, non-physiological acute plasma FA elevation and use of a more soluble unsaturated FA, rather than the saturated FA (SFA) present in the typical Western diet. We therefore developed an oral human model of a SFA-enriched diet induced IR.

In a series of cross-over studies, subjects with normal or impaired glucose tolerance (NGT or IGT) consumed a SFA-rich, high-calorie diet compared to a standard American Heart Association (AHA) diet for 24 hours (breakfast to breakfast) or daylong (breakfast to bedtime). IR was determined 4, 10 and 24 hours after completion of each diet from steady state plasma glucose (SSPG) levels during the final 30 minutes of a 3-hour insulin suppression test (IST).

SSSPG was increased 61% 4 hours (Figure) after 24-hour of a SFA diet. IR increased in both NGT and IGT, and persisted 10 (overnight) or 24 hours after the last SFA meal (Figure insert).

In summary, we developed a human model of diet-induced IR by use of short-term oral administration of SFA. The SFA diet induced IR in both NGT and IGT subjects and persisted for at least 24 hours. This model offers unique opportunities for identifying mechanisms and potential treatments of diet induced IR.



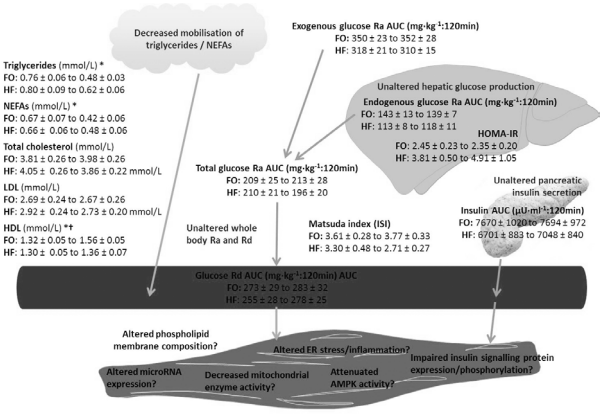
Supported By: U.S. Dept. of Veterans Affairs

237-LB

Six Days High-Fat Overfeeding Does Not Alter Whole-Body Insulin Sensitivity in Young, Healthy Males

SOPHIE L. WARDLE, LINDSAY S. MACNAUGHTON, CHRIS S. MCGLORY, OLIVER C. WITARD, ARNY A. FERRANDO, STUART D.R. GALLOWAY, COLIN N. MORAN, KEVIN D. TIPTON, *Stirling, United Kingdom, Little Rock, AR*

We aimed to investigate the whole body mechanisms associated with consumption of high fat, high energy diets in healthy males using dual stable isotopic tracer methodology. A secondary aim was to consider whether increased fish oil (FO) intake could protect against diet induced insulin resistance and to examine the mechanisms for this effect. Twenty healthy males (22 ± 1 y; 71.24 ± 2.16 kg) were matched to 1 of 2 groups; all underwent 6 d of high fat overfeeding (150% of total kcal, 60% FAT, 25% CHO, 15% PRO). One group received 10 % of fats from FO (FO; n = 10) while the other consumed mostly SFAs and MUFAs (HF; n = 10). The overfeeding was bookended by two trial days; identical in all respects. Following an overnight fast participants underwent a primed continuous [6,6-2H2] glucose infusion followed 1h later by an OGTT (73 g glucose + 2 g [U13C] glucose) with blood samples drawn at 10 min intervals. Whole blood fatty acid profiling by GCMS revealed a significant elevation of basal EPA and DHA in the FO group only ($p < 0.05$) confirming dietary compliance. Insulin sensitivity, indicated by Matsuda and HOMA-IR, and plasma glucose kinetics (CI-GCMS) were unaltered by high fat overfeeding (Image 1). Despite changes in plasma fatty acid composition, six days of high fat overfeeding does not alter whole body insulin action in healthy males. However, changes in tissue specific mechanisms may precede whole body insulin resistance development.



All statistical analyses were conducted using two-way ANOVA with Bonferroni post-hoc tests conducted in the case of statistical significance. * denotes statistically significant from baseline (irrespective of group); p < 0.05, † denotes statistically significant interaction effect; p < 0.05. Ra = Rate of appearance, Rd = Rate of disappearance/disposal.

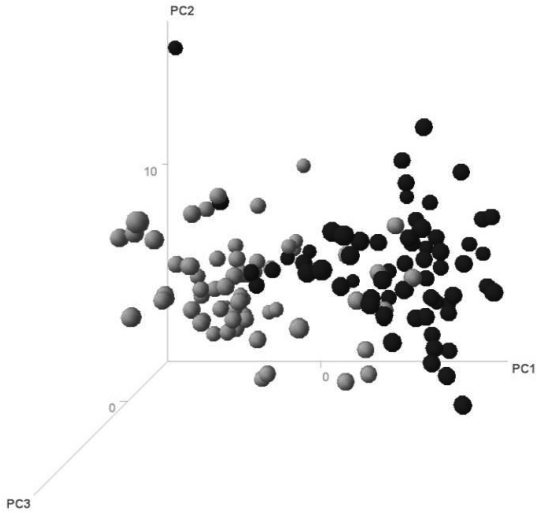
Supported By: Diabetes Research and Wellness Foundation

238-LB

Standardizing Diet Significantly Reduces Inter-subject Variability in Metabolomic Profiles

ROSE CHRISTIAN, YI LUO, PETIA SHIPKOVA, SERHIY HNATSHYN, MICHAEL REILY, *Princeton, NJ*

Metabolomic profiling is used in clinical trials to detect treatment effects of anti-diabetic compounds, but inter-subject variability may reduce precision and reproducibility. The purpose of this study was to assess the value of standardizing diet prior to metabolomic profiling. Plasma was collected from 64 healthy fasting subjects on admission (street diet) and after consuming 6 identical meals over 48 h in a research unit (standard diet). Metabolomic analyses were performed by liquid chromatography - mass spectrometry (LC-MS) on Thermo Exactive systems. Raw mass spectral data were processed with in-house metabolomic software. Peak areas reported for 192 individual metabolites were analyzed for inter-subject variability and outliers by open source R scripts. Inter-subject variability (%CV) for the 192 metabolites was significantly higher on street diet than on standard diet, 59% CV vs. 40% CV ($p < 0.001$), figure shows principle component analysis. Feeding an identical diet for 48h prior to sample collection caused 19% absolute reduction and 32% relative reduction in inter-subject variability and 50% reduction in outliers ($p<0.002$). Standardizing the diet of study subjects in phase I-II drug trials may enhance precision and reproducibility of metabolomic profiling by reducing inter-subject variability.



239-LB

Mutation of Leucine-rich Pentatricopeptide Repeat Containing Protein (LRPPRC) Leads to Impaired AMPK Regulation in Leigh Syndrome French Candian Type (LSFC) Fibroblasts

YVETTE MUKANEZA, MARIE-ÈVE RIVARD, JULIE THOMPSON-LEGAULT, CHRISTINE DES ROSIERS, LISE CODERRE, LSFC CONSORTIUM, *Montreal, QC, Canada*

LSFC is a rare mitochondrial disease caused by mutations in the *LRPPRC* gene. This leads to a decrease in both the LRPPRC protein and mitochondrial respiratory chain enzyme cytochrome c oxidase (COX) activity. Mitochondrial diseases increase the risk of developing diabetes. We hypothesized that mitochondrial dysfunction in LSFC patients would induce alterations in energy- and nutrient-signaling pathways similar to those found in insulin-resistant and diabetic patients. Using skin fibroblasts as a model, we examined AMPK activation, a key pathway involved in energy homeostasis, under various stress conditions. Basal AMPK activity was similar in control and LSFC cells. In control cells, acute nutrient overload (1 mM palmitate + 10 mM lactate for 4 h) increased AMPK and acetyl CoA carboxylase (ACC) phosphorylation by 90% ($p<0.01$) and 154% ($p=0.06$), respectively. Palmitate/lactate also increased the expression of SIRT1, a downstream target of AMPK, by 57% ($p<0.05$), LRPPRC by 23% ($p=0.045$) and COXIV by 19% ($p<0.05$). All these effects were absent in LSFC cells. We also evaluated the effect of chronic AMPK activation on these signaling pathways using a specific activator of AMPK, ZMP (0.5 mM, 48 h). The effects of ZMP pretreatment were additive to those of palmitate/lactate, leading to further increases in the phosphorylation of ACC (364%, $p<0.001$) and SIRT1 (120%, $p<0.05$), as well as increased expression of SIRT1 (75%, $p<0.01$), LRPPRC (63%, $p<0.001$) and COXIV (38%, $p<0.001$). Again, all these effects were absent in LSFC cells. However, AMPK could be activated in response to chemical hypoxia induced by dinitrophenol (0.1 mM, 10 min) in LSFC fibroblasts. In conclusion, LSFC cells showed impaired AMPK activation in response to nutrient overload. The reduction in nutrient-induced AMPK activation may contribute to the development of insulin resistance in these patients and ultimately predispose them to diabetes.

Supported By: CIHR

INTEGRATED PHYSIOLOGY—MUSCLE

240-LB

Sixteen Weeks of Caloric Restriction in Abdominally Obese Adults Improves Skeletal Muscle Insulin Sensitivity and Preserves Mitochondrial Function

MATTHEW L. JOHNSON, KLAUS DISTELMAIER, IAN LANZA, K. SREEKUMARAN NAIR, *Rochester, MN*

Reductions in body weight and abdominal fat by caloric restriction (CR) improve insulin action, which is often impaired in overweight and obese individuals. Improvements in the efficiency of fuel utilization by mitochondria are hypothesized to be an underlying mechanism responsible for CR's insulin sensitizing effects. The purpose of this study was to investigate the effect of CR on insulin sensitivity and mitochondrial function in abdominally obese men and women (45-65 years) before and after a 16-week CR program or Control (CON) period. Fifteen (15) abdominally obese participants undertook a CR program (9) managed by the dietetics staff at the Mayo Clinic Clinical Research Unit that resulted in weight loss averaging 9.5% ± 1.4% of total bodyweight or CON (6). Percent body fat declined from 45.4 ± 1.9% to 41.8 ± 1.5% ($P<0.05$) with reductions in total fat mass (42.0 ± 2.9kg vs. 35.0 ± 2.5kg; $P<0.05$) and no change in lean body mass (50.7 ± 3.9kg vs. 49.0 ± 3.8kg) in CR, while the CON group did not change. These changes resulted in body mass index declining from 33.8 to 30.8 ($P<0.05$) in CR with no change 34.1 to 34.7 in CON. The CR program lowered post absorptive overnight fasting blood glucose levels from 107.4 ± 3.1 mg/dL to 102.6 ± 3.0 mg/dL ($P<0.05$) and increased the glucose infusion rate required to maintain glycemia during a 6-hour two-stage hyperinsulemic-euglycemic clamp ($P<0.05$), while the CON showed no change. No change in response to the 16-week intervention for state 3 skeletal muscle mitochondrial capacity (452.8 ± 34.5 vs. 393.8 ± 52.1 in CR and 505 ± 42.1 vs. 510.3 ± 44.6 in CON pmol/s/mg tissue) or respiratory control ratio (6.8 ± 0.6 vs. 5.8 ± 0.4, CR and 6.2 ± 0.6 vs. 7.3 ± 0.6 in CON) was found as measured by high-resolution respirometry of mitochondria isolated from vastus lateralis muscle biopsies. In conclusion a 16-week CR program in abdominally obese individuals increases skeletal muscle insulin sensitivity and preserves mitochondrial function.

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241-LB

Enhanced mTOR Signaling Attenuates Cardiac Injury in OVE26 Diabetic Mice

XIANMIN XU, KAI CHEN, SATORU KOBAYASHI, DEREK TIMM, YUAN HUANG, WEINIAN SHOU, QIANGRONG LIANG, *Sioux Falls, SD, Old Westbury, NY, Indianapolis, IN*

Diabetic cardiomyopathy is an important causative factor for the heightened risk of heart failure in diabetic patients. Yet, our understanding of the underlying mechanism has been limited, making it difficult to design effective strategies for preventing diabetic heart failure and reducing the high mortality in diabetic patients. The serine/threonine protein kinase mammalian target of rapamycin (mTOR) has been implicated in the pathogenesis of several types of heart disease. mTOR signaling is activated in diabetic heart. However, the functional significance of mTOR in the diabetic heart remains unclear. We addressed this question by crossing the OVE26 type 1 diabetic mice with transgenic mice expressing a constitutively active (CA) mTOR or dominant negative (DN) mTOR in the heart. Diabetes-induced cardiac damage was substantially attenuated in CA-mTOR mice as shown by improved cardiac function as well as reduced levels of oxidative stress, interstitial fibrosis and myocyte apoptosis. Conversely, diabetic cardiac damage was markedly exacerbated in DN-mTOR mice, suggesting that the increased mTOR signaling is an adaptive response that limits cardiac dysfunction in type 1 diabetes. CA-mTOR expression inhibited autophagic flux in the heart, while DN-mTOR accelerated this process, consistent with the regulatory role of mTOR in autophagy. Since autophagy is detrimental in type 1 diabetic heart, mTOR-induced cardioprotection may be mediated, at least in part, by its inhibitory effect on autophagy. Together, these findings demonstrate that the enhanced mTOR signaling protects from cardiac injury in type 1 diabetes likely through the inhibition of autophagy.

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242-LB

Molecular Link between Insulin Resistance and Muscle Impairment in Myotonic Dystrophies

LIVIO LUZI, ILEANA TERRUZZI, ANNA MONTESANO, PAMENLA SENESI, ROSANNA CARDANI, LAURA RENNA, ROBERTO COLOMBO, GIOVANNI MEOLA, *Milan, Italy, San Donato Milanese, Italy*

Insulin resistance is mainly present in skeletal muscle in non-obese patients with myotonic dystrophies (DMs). DMs are autosomal dominant disorders exhibiting insulin resistance or diabetes, a variety of multisystemic features among which muscular dystrophy, myotonia, and dilated cardiomyopathy. Known type 1 and 2 forms of DMs are caused by dynamic and unstable expanded microsatellite sequences (CTG and CCTG) considered liable for the misregulation of insulin receptor (IR) splicing causing an altered ratio between IR-A and IR-B (with lower and higher insulin affinity respectively). Our previous studies showed that DM2 myotubes presented predominant level of IR-A but the same differentiation degree than myotubes from healthy subjects. We hypothesized that the DMs insulin resistance is not directly caused by a genetically impaired myogenesis but by molecular mechanisms involved in cellular insulin response. To verify this hypothesis we grew satellite cells from muscle biopsies of control, DM1 and DM2 subjects in growth media unsupplemented or supplemented with the well-known insulin mimetic thioctic acid. Then we treated neo formed myotubes with 100nM insulin for 0, 10, 15 and 30 minutes. Immunofluorescence and Western Blot analysis showed that DMs insulin response was altered in DMs myotubes. In particular, AKT/p70 S6 kinase signaling pathway, regulator of the protein synthesis and degradation and muscle mass remodeling, is down regulated. To confirm these *in vitro* data, we evaluated AKT phosphorylation levels in muscle biopsies from normal and DMs patients. Our results strengthened our *in vitro* data: AKT is down-regulated in DMs patients, suggesting a possible molecular link between muscle damage and insulin signaling defects. Further investigations can be performed to clarify this important molecular relationship in order to focus new possible pharmacologic targets in the treatment of DMs muscle injury and in pathological condition characterized by insulin resistance.

243-LB

Activation of 4E-BP1 in Skeletal Muscle Protects against High Fat Diet- and Age-induced Metabolic Dysfunctions

SHIHYIN TSAI, BRIAN KENNEDY, *Novato, CA*

Obesity is a major risk factor driving the global type II diabetes pandemic. Yet, the molecular factors linking obesity to disease remain to be fully elucidated. It is unclear why only a subset of obese individual progress to metabolic syndromes and the others do not. Gender differences are also apparent in humans and in murine models. For instance, male and female mice fed a high fat diet (HFD) similarly become obese, but males are prevalence to develop insulin resistance and glucose intolerance, the hall marks of type II diabetes. Here we report gender differences in expression of eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1) upon HFD feeding. 4E-BP1 expression is significant reduced in skeletal muscle and adipose tissue of male mice, but not female mice. Strikingly, transgenic whole body 4E-BP1 expression protects male but not female mice against HFD-induced obesity and insulin resistance suggesting that 4E-BP1 is a gender-specific suppressor of metabolic dysfunctions. 4E-BP1 represses cap-dependent mRNA translation initiation by sequestering eIF4E and is a master effector on protein translation controlled by mTOR. We explore possible mechanisms that underlie the health benefits of reduced mTOR signaling with altered activity of 4E-BP1. We found that the selective activation of 4E-BP1, which is resistant to mTOR regulation, in mouse skeletal muscles, instead of adipose tissue, is protective against high fat diet-induced type II diabetes in both genders. These mice has increased energy expenditure, altered adipose tissue distribution including reduced white adipose accumulation and preserved brown adipose mass, and protected from hepatic steatosis. The results presented here suggest that (1) 4E-BP1 may be the critical target of downstream of mTOR that relates to metabolic diseases and (2) interventions activating 4E-BP1 may have therapeutic potential on diet or aging induced metabolic diseases.

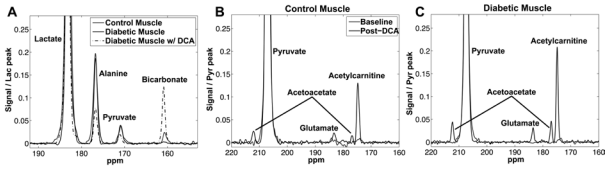
Supported By: Ellison Medical Foundation

244-LB

Mitochondrial Metabolism of Diabetic Skeletal Muscle Measured by Hyperpolarized 13C MR Spectroscopy

JAE MO PARK, SONAL JOSAN, RALPH E. HURD, JAMES L. GRAHAM, PETER J. HAVEL, DIRK MAYER, DAVID BENDAHAN, DANIEL M. SPIELMAN, THOMAS JUE, *Stanford, CA, Menlo Park, CA, Davis, CA, Baltimore, MD, Marseille, France*

We have performed *in vivo* experiments using hyperpolarized [1-^{13}C] lactate (Lac), [2-^{13}C]pyruvate (Pyr), and dichloroacetate (DCA) to examine in control (CRL) and T2DM skeletal muscle the pyruvate dehydrogenase (PDH) and tricarboxylic acid cycle, which reflects oxidative metabolism activity. Sprague-Dawley (SD) rats with UCD-T2DM and CRL SD rats were scanned using a 3T MR scanner. Immediately after a 40-mM hyperpolarized [1-^{13}C]Lac bolus injection, ^{13}C MR signal was acquired from CRL (n=6) and T2DM rats (n=5), and 3 of the T2DM rats were additionally scanned following another 40-mM Lac injection 1h after a DCA infusion. A separate group of animals were scanned after injecting 80-mM hyperpolarized [2-^{13}C]Pyr (n=3 for each group). Bicarbonate (Bic), which reflects the PDH activity, was significantly lower ($P<0.02$) in T2DM than in CRL when [1-^{13}C]Lac was injected. However, DCA remarkably increased Bic, indicating that PDH in T2DM muscle can be activated. When [2-^{13}C]Pyr was injected [1-^{13}C]acetyl-carnitine (ALC), [1-^{13}C] acetoacetate (ACC), [5-^{13}C]glutamate (Glu) appeared in CRL and T2DM muscle after DCA infusion. Surprisingly, PDH was more activated by DCA in diabetic models than in CRL. While Glu was comparable between T2DM and CRL, ALC and ACC in T2DM muscle were about twice higher than in CRL, indicating that PDH activity and oxidative metabolism differ in T2DM vs. CRL skeletal muscles.



Supported By: NIH (P41EB015891); Berkeley-France Fund; Lucas Foundation

INTEGRATED PHYSIOLOGY—OTHER HORMONES

245-LB

Gallbladder Emptying and Single-Dose Metformin Elicit Robust and Additive Glucagon-like Peptide-1 Responses

ULRICH ROHDE, DAVID P. SONNE, MORTEN HANSEN, ANDREAS BRØNDEN, MIKKEL CHRISTENSEN, JENS F. REHFELD, JENS J. HOLST, TINA VILSBØLL, FILIP K. KNOP, *Hellerup, Denmark, Copenhagen, Denmark*

Preclinical studies suggest that gallbladder emptying and subsequent activation of the bile acid receptor TGR5 on enteroendocrine L cells leads to glucagon-like peptide-1 (GLP-1) secretion. Drugs affecting bile acid binding (colesevelam (COL)) or reabsorption (metformin (MET)) seem to increase postprandial GLP-1 secretion in humans. We hypothesized that gallbladder emptying stimulates human GLP-1 secretion and that COL and MET, respectively, would potentiate any GLP-1 secretion induced by gallbladder emptying.

Ten subjects (age (mean±SD): 23.4±3.8 years; BMI: 21.9±1.8 kg/m2; HbA1c: 5.1±0.3%) were studied on 6 randomized days. In a double-blind fashion the subjects received 1) COL (3.75 g); 2) MET (1.5 g); or 3) placebo (PLA) in 50 ml water admixed 1.5 g acetaminophen (for evaluation of gastric emptying) administered via nasogastric tube, with a concomitant 60-minute iv infusion of saline and cholecystokinin-8 (CCK), respectively. Blood was sampled for 4 hours for measurements of plasma GLP-1, glucose, insulin, C-peptide and glucagon. Gallbladder emptying was measured by ultrasound. Food intake was assessed at the end of each day.

CCK infusion during PLA induced complete gallbladder emptying and a significant GLP-1 response (incremental area under curve) compared to saline infusion (392±173 (mean±SEM) vs. -277±94 pM×min, P=0.02). MET without CCK elicited a significant GLP-1 response (215±87 vs. -277±94 pM×min (saline+PLA), P=0.002), which was potentiated by CCK-induced gallbladder emptying (963±202 pM×min (CCK+MET), P=0.03). COL did not elicit significant GLP-1 responses. Plasma glucose was not affected by the interventions, nor was insulin, C-peptide, glucagon or food intake.

CCK-induced gallbladder emptying and single dose MET, respectively, elicit robust and additive GLP-1 responses in humans. We, therefore, speculate that MET's mode of action includes stimulation of GLP-1 secretion by both bile acid-dependent and independent mechanisms.

246-LB

Ghrelin Antagonizes GLP-1 as well as Glucose-stimulated Insulin Secretion in Healthy Humans

JENNY TONG, AHRAR HAQUE, AMALIA GASTALDELLI, DAVID A. D'ALESSIO, *Cincinnati, OH, Pisa, Italy*

The gastric hormone ghrelin suppresses insulin secretion and causes glucose intolerance in humans. Paradoxically these effects occur during meal absorption when ghrelin also increases GLP-1 secretion. We hypothesized that blocking GLP-1 action by Exendin-9 (Ex-9) would magnify the effect of ghrelin to impair glucose tolerance in healthy individuals. Eight healthy non-obese subjects (5 females, 3 males, aged 25±4 [mean±SD] y) were randomly assigned to receive acyl ghrelin (2 µg/kg/h), Ex-9 (0.15 mg/kg/h), the combination of ghrelin and Ex-9, or saline on 4 different days. Ghrelin and Ex-9 were given as primed, continuous iv infusions for a total of 4.5 hours before and after consumption of a standardized mixed meal. Glucose and insulin were sampled continuous throughout the 240 min of the meal tolerance test (MTT). Ghrelin ($p<0.01$) and ghrelin plus Ex-9 administration ($p<0.001$) impaired glucose tolerance (AUCglucose 0-240 min) (Ghrelin: 9092±4030; Ex-9 plus ghrelin: 11348±4200; saline: 3897±2147) and the combination treatment reduced postprandial insulin secretion adjusted for glucose (incremental AUCinsulin/glucose) (70.1±41 vs. 41.0±19, p=0.037). No difference was found between ghrelin and Ex-9 plus ghrelin treatment. Ex-9 infusion alone did not alter glucose tolerance or insulin secretion. In conclusion, blocking endogenous GLP-1 action by Ex-9 did not further impair postprandial glucose tolerance or insulin secretion induced by ghrelin administration. These findings indicate that the effects of ghrelin to suppress insulin secretion are not modulated by its action to increase plasma GLP-1. This suggests that ghrelin antagonizes GLP-1- as well as glucose-stimulated insulin secretion.

Supported By: 1R01DK097550

247-LB

Effects of Sitagliptin on Blood Pressure and Heart Rate in Response to Intraduodenal Glucose Infusion in Type 2 Diabetes: A Potential Role for GIP

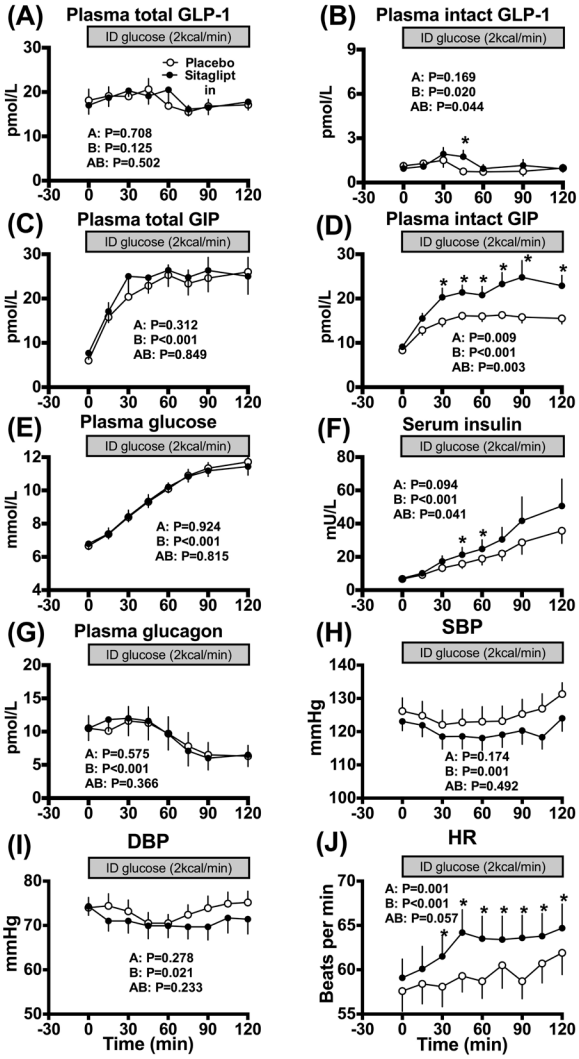
TONGZHI WU, LAURENCE G. TRAHAIR, MICHELLE J. BOUND, CAROLYN DEACON, MICHAEL HOROWITZ, CHRISTOPHER K. RAYNER, KAREN L. JONES, *Adelaide, Australia, Copenhagen, Denmark*

Meal ingestion induces secretion of GLP-1 and GIP, which may play a role in the regulation of postprandial blood pressure (BP) and heart rate (HR). We evaluated, in type 2 patients, the effects of the DPP-4 inhibitor, sitagliptin, on BP and HR during intraduodenal (ID) glucose infusion at 2kcal/min - a rate where GIP is the major incretin in the circulation.

10 type 2 patients were studied on two occasions 30min after oral ingestion of sitagliptin (100mg) or placebo. ID glucose was infused at 2kcal/min (60g over 120min). BP, HR, plasma incretins, glucose and glucagon, and serum insulin were evaluated.

Sitagliptin increased HR (treatment effect: P=0.001) and serum insulin (treatment × time interaction: P=0.041), without affecting BP, plasma glucagon or glucose. During ID glucose infusion, there was a substantial increase in plasma total GIP on both days (P<0.001), but no increase in total GLP-1. After sitagliptin, plasma intact GLP-1 increased slightly (treatment × time interaction: P=0.044) and GIP substantially (P=0.003). The HR response to ID glucose was directly related to plasma intact GIP concentrations (r=0.75, P=0.008).

Sitagliptin increased the HR response to ID glucose at 2kcal/min in type 2 patients, associated with augmentation of plasma intact GIP concentrations. These observations suggest a potential role for GIP in the control of the "gut-heart" axis.



Supported By: Merck Sharp & Dohme Corp.

248-LB

Intravenous (IV) Arginine (ARG) Stimulates GLP-1 Release across the Spectrum of Glucose Tolerance (GT)

ADRIAN VELLA, RALPH RAYMOND, ROBERTO A. CALLE, CHARLIE CAO, DOUGLAS S. LEE, R. PAUL ROBERTSON, HARTMUT RUETTEN, SUDHA SHANKAR, MYRLENE STATEN, DARKO STEFANOVSKI, MARIA T. VASSILEVA, GORDON WEIR, DAVID FRYBURG, FOR BETA CELL TEAM OF FNIH BIOMARKERS CONSORTIUM, *Rochester, MN, Skillman, NJ, Cambridge, MA, Chicago, IL, Seattle, WA, Frankfurt, Germany, Indianapolis, IN, Bethesda, MD, Los Angeles, CA, Boston, MA, East Lyme, CT*

Meal-induced secretion of GLP-1 has been well-described, yet limited data exist on IV secretagogues of GLP-1. In a previous report, we showed that insulin secretion (AIRarg) responses to IV ARG differ across GT groups. In the same subjects, we report GLP-1 responses to IV ARG in 53 obese subjects with normal glucose tolerance (NGT), prediabetes (PDM) and type 2 diabetes (T2DM). Following an overnight fast, samples were acquired for total GLP-1 pre and for 10 min post an IV ARG bolus (5 gm over 30 sec) at basal glucose. Pre- and post-ARG GLP-1 samples were also acquired during a 60 min glucose infusion (900 mg/min).

Table summarizes results during basal glucose period; previously reported insulin responses are also included. Pre-ARG fasting GLP-1 differed across GT spectrum, highest in T2DM. IV ARG elicited GLP-1 secretion in all 3 GTs, with greater changes in PDM and T2DM than NGT (Delta GLP-1). Pre-ARG GLP-1 did not correlate with AIRarg, whereas *change* in GLP-1 correlated with AIRarg for NGT and T2DM but not PDM in basal glucose state (NGT/T2DM: r= 0.52/0.49

P<0.02; PDM r=0.16 NS). Similar responses observed during high glucose infusion (not shown).

	N	BMI	Basal Glucose (mg/dL)	AIRarg (μU/mL)	GLP-1 pre-ARG (pM)	GLP-1 post ARG (pM)	Delta GLP-1 (pM)
		(mean±SD)	(mean±SD)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Mean (95% CI)
NGT	23 (12M/11W)	31.5±2.8	93±5	9.9 (8.8,11.1)	3.8 (3.2, 4.6)	4.9 (4.3,5.7)	1.1 (0.6,1.5)
PDM	8 (2M/6W)	33.0±2.6	111±5	5.9** (5.3,6.5)	3.8 (2.3,6.3)	6.7 (5.2,8.5)	2.6** (1.8,3.4)
T2DM	22 (11M/11W)	32.8±3.9	156±5	4.0**# (3.6,4.3)	7.4*** (6.0, 9.0)	9.1*** (7.5,11.0)	1.8* (1.3,2.3)
	ANOVA across populations (*P*).		<0.001	<0.001	<0.001	<0.001	<0.01

*= P, ** P, *** P, # P.

We conclude that 1) IV ARG acutely stimulates GLP-1 secretion irrespective of glucose tolerance status; 2) Pre-ARG GLP-1 was not associated with insulin secretory response, but GLP-1 secretion after ARG positively tracks with insulin secretion in NGT and T2DM.

Supported By: ADA; FNIH Biomarkers Consortium

249-LB

Continuous Leptin Infusion Amplifies the Glucagon Response to Insulin-induced Hypoglycemia in Diabetic Rats

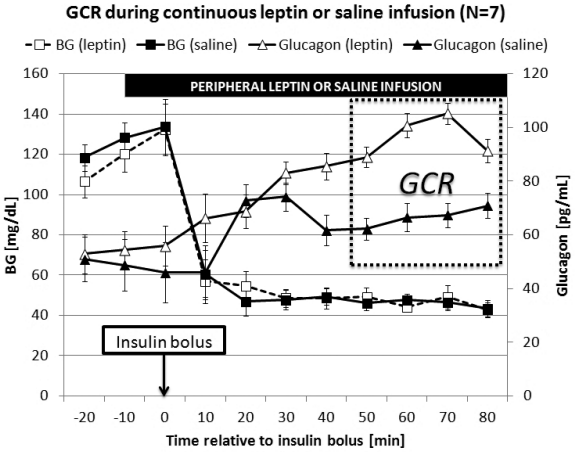
LEON S. FARHY, PATTIE HELLMANN, MURRY ADAMS, AIMEE Y. ZHANG, ANTHONY L. MCCALL, *Charlottesville, VA*

Glucagon counterregulation (GCR) is impaired in type 1 diabetes (T1DM). Our in vivo and in silico studies suggest that alpha-cell inhibitors (ACI) may enhance GCR by amplifying the pulsatile glucagon response to hypoglycemia. This study tests whether two ACIs, GLP-1 and leptin, can enhance GCR if given peripherally.

STZ-treated male Wistar rats were tested twice and used as their own controls. Blood glucose (BG) was lowered to ~115mg/dL(t=-20) followed by an i.v. infusion (t=-10min) of saline, GLP-1 (30 pmol/kg/min) or leptin (0.5 ug/min) and a 12U/kg i.v insulin bolus at t=0min. The ACI infusions were either switched off at hypoglycemia (60 mg/dL) or continued for the entire experiment. Blood samples were collected every 10min for BG and glucagon from t= -20 to 80min. GCR was estimated based on the glucagon levels from t=50 to t=80 min.

Compared to saline, continuous leptin infusion enhanced 1.5-fold the GCR (110±6.2 vs. 76±7.2 pg/mL, p<0.005) and the fold increase in glucagon over basal (2.0±0.25 vs. 1.5±0.20; p<0.05). In contrast, a switch-off of the leptin infusion at hypoglycemia did not improve GCR and peripheral infusion of GLP-1 with or without a switch-off was ineffective.

In conclusion, peripheral infusion of leptin enhances the defective GCR if given continuously in diabetic rats. This result could lead to new dual-hormone strategies for treatment of T1DM with enhanced hypoglycemia protection.



Supported By: NIH (RO1DK082805)

250-LB

Estradiol Suppresses Liver Fat Accumulation and Reduces Diabetes Prevalence in New Zealand Obese Mice

MARKO LUBURA, DEIKE HESSE, MARIA KRAEMER, LUDGER SCHEJA, JÖRG HEEREN, ANNETTE SCHÜRMANN, *Potsdam, Germany, Nuthetal, Germany, Hamburg, Germany*

In humans, as well as in rodents, prevalence to type 2 diabetes (T2D) is sexually dimorphic with an increased incidence in males. However, after menopause in women and ovariectomy in mice the T2D incidence matches that of male counterparts. Thus, we hypothesized that estrogen has protective effects and examined the influence of estradiol (E2) on onset of T2D in female New Zealand Obese (NZO) mice.

NZO females exhibited a diabetes prevalence of 43% in week 22 on a high-fat diet (HFD, 60% fat). Liver fat content, as determined by computed tomography (CT), at week 10 was used as a prediction marker for diabetes-prone (DP) and diabetes-resistant (DR) NZO females. For subsequent 10 weeks, both DP and DR mice were either supplemented with E2 (800 μg/kg HFD; DP-E and DR-E groups) or not (DP-C and DR-C groups). At week 20, an additional CT scan of the liver was conducted. Transcriptome analysis of DP and DR livers was performed in week 11.

E2 treatment reduced diabetes prevalence in both DP-E and DR-E groups by 73%. Moreover, E2 prevented an increase in liver fat content and β-cell loss under HFD and improved insulin signalling in pancreatic β-cells. Transcriptome analysis and Western blotting revealed an increased abundance of the MOGAT1 enzyme and the CD36 fat transporter in livers of DP mice, accompanied by increased hepatic diacylglycerol concentration. Furthermore, E2 treatment reduced the expression of CD36 and MOGAT1 in both DP-E and DR-E groups. In silico analysis indicated a high abundance of putative estrogen responsive elements in the promoter region of Mogat1.

Early elevation of CD36 and MOGAT1 in the liver caused an enhanced production and accumulation of triglycerides and diacylglycerols, presumably resulting in reduced hepatic insulin sensitivity. Continuous administration of E2 could prevent this effect. Moreover, E2 improved insulin signalling in pancreatic β-cells and reduced the diabetes prevalence in NZO females.

Supported By: DZD01GI0922

251-LB

Insulin Suppresses Fatty Acid Binding Protein and Omentin Levels

NANDITA K. SHANKAR, CLAYTON A. DEHN, ANGELICA GUERRERO, FRANKIE B. STENTZ, HELMUT O. STEINBURG, *Montclair, NJ, Tempe, AZ, Memphis, TN*

Circulating omentin (OM) and Fatty Acid Binding Protein (FABP) have been reported to be altered in insulin resistance (IR). However, the role of insulin (I) in the regulation of these adipokines remains unclear. We tested the hypothesis that I alters circulating OM and FABP, by measuring OM and FABP responses to elevated I in a group of healthy volunteers.

Following an overnight fast, subjects (N=9, age: 28±2 yrs, BMI: 21.8±7.3 kg/m^2, glucose: 85.6±28.5 mg/dL, I: 6.1±2.0 U/mL, C-peptide 1.1±0.1 ng/mL) underwent a hyperinsulinemic euglycemic clamp (target glucose 90mg/dL), at I of 10mU/m^2/min (low dose: LD: 0-180 min), followed by 40mU/m^2/min (high dose: HD: 180-360 min). Subjects underwent serial sampling for glucose, I, C-peptide, OM and FABP at baseline (BL) and during steady state (SS) of the LD and HD periods. Subjects underwent a second identical procedure after 14 days to assess reproducibility.

Data are presented as mean ± SEM. At SS, glucose levels were 89.7±0.7 (LD) and 92.6±1.3 mg/dl (HD), I were 5.6±1.0 (LD) and 13.0±1.6 U/mL (HD), and glucose disposal rates were 3.5±0.4 (LD) and 11.5±0.8 mg/kg/min (HD), and were reproducible between first and second clamp procedures (r^2 from 0.72 to 0.52). At BL, C-peptide levels correlated with FABP (r^2=0.72, p<0.01) and with OM (r^2=0.43, p=0.054). Significant (p<0.05) decreases from baseline were observed in plasma FABP and OM levels in response to hyperinsulinemia at LD and HD. FABP decreased from 9.5±3.2 (BL) to 7.8±2.6 (LD) and to 7.7±2.6 (HD) ng/mL. OM decreased from 484±161 (BL) to 421±140 (LD) and to 372±124 (HD) ng/mL. While OM levels decreased significantly from LD to HD, the difference in FABP between LD and HD was less robust. Reductions in FABP and OM were reproducible between clamp procedures (r^2 from 0.88 to 0.58).

Our results show for the first time that hyperinsulinemia reproducibly suppresses omentin and FABP in healthy humans, suggesting a potential role for I in regulating omentin and FABP. This may have implications for the regulation of these adipokines in IR.

252-LB

Eradication of Methane on Breath Testing and Reduction in Intestinal M. smihii Results in Improved Insulin Sensitivity and Lipid Profiles in Prediabetic Obese Subjects

RUCHI MATHUR, KATHLEEN SHARI CHUA, WALTER MORALES, DARKO STEFANOVSKI, GILLIAN M. BARLOW, STACY WEITSMAN, RICHARD BERGMAN, ZACHARY MARSH, MARK PIMENTEL, *Los Angeles, CA*

The methanogenic archaea are important colonizers of the gastrointestinal tract, and produce methane which can be detected on breath analysis. Methanobrevibacter smithii is the most common methanogen in the human gut. Studies suggest that methane positive (M+) subjects have a greater BMI. Here, we examine metabolic parameters before and after antibiotic treatment in subjects with M. smithii colonization and methane on breath test.

Using ADA criteria, we identified 11 pre-diabetic (9F, 2M) obese (BMI 35.2±7.7kg/m2) M+ subjects aged 47±9 yrs. Subjects underwent breath testing, OGTT, lipid profile and gastric transit analysis. They then received a 10 day course of antibiotics (neomycin 500mg bid/ rifaximin 550 mg tid), shown to eradicate methane on breath test in up to 85% of patients. Testing was repeated post intervention.

Baseline M. smithii levels measured by qPCR of stool correlated with breath methane (R=0.7, P=0.03). Eight subjects (73%) eradicated breath methane and showed reduced stool M. smithii (P=0.09). After therapy, cholesterol (P=0.03) and LDL (P=0.08) were lower, with more pronounced reductions in methane-eradicated subjects (P=0.01 and P=0.028, respectively). Insulin sensitivity (SI), estimated using Modified Minimal Model for OGTT analysis, showed significant improvement pre vs. post-treatment (0.62 ± 0.21 vs. 0.95 ± 0.17, P=0.05). Further, unit change in methane tended towards being inversely proportional to SI change (P=0.06). Gastric emptying was unchanged.

Eradication of methane on breath testing and reduction of M. smithii in stool is associated with improved glucose metabolism and SI improvement up to 50%. Lipid profiles also improved significantly with eradication. The mechanisms linking reductions in methanogens to improvements in insulin sensitivity need further elucidation.

Supported By: ADA (1-12-IN-28); NCATS (UL1TR000124)

253-LB

Role of Kinin B1 Receptor in Streptozotocin-induced Insulitis

NAJLA TIDJANE, LOUIS GABOURY, RÉJEAN COUTURE, *Montréal, QC, Canada*

Kinins are pro-inflammatory peptides whose effects are mediated by two GPCR, B1R and B2R. While B1R is virtually absent in sane tissues, it is highly inducible in diabetes and after exposure to pro-inflammatory cytokines. This study aims at investigating the mechanism by which kinin B1R partakes to insulitis. It is hypothesized that kinin B1R can either initiate the trafficking/ infiltration of immune cells into the pancreas or activate primary sensory C-fibers (CGRP and TRPV1 positive fibers) to cause neurogenic inflammation. Male rats were made diabetic with streptozotocin (STZ,65 mg/kg/ ip) and treated with B1R antagonist (SSR240612, 10 mg/kg/day for 7 days by gavage) or its vehicle. After sacrifice, the pancreas was harvested for studying insulitis. The expression of B1R, iNOS, TNF-α,macrophages,TCD4$^+$, CGRP and TRPV1 was measured in the pancreas by Western blot analysis, qRT-PCR and immunofluorescence. Number and size of Langerhans islets were measured by immunostaining with insulin antibody to evaluate the severity of damaged β-cells. Macrophages and TCD4$^+$ lymphocytes were present abundantly throughout the pancreas of STZ-diabetic rats but absent in control. Importantly, B1R was expressed and upregulated on these immune cells infiltrating the diabetic pancreas. B1R was not expressed on primary sensory C-fibers even if the expression of TRPV1 and CGRP was significantly enhanced in the diabetic pancreas. This finding is not supporting a primary neurogenic inflammatory component mediated by B1R. SSR240612 treatment prevented the infiltration of macrophages and TCD4$^+$ lymphocytes in addition to normalizing the upregulation of B1R, iNOS and TNF-α. Concomitantly, SSR240612 reduced significantly hyperglycemia and partially restored plasma insulin levels by preventing the loss of Langerhans islets. Data suggest that kinin B1 receptor is a key player in insulitis and its antagonism may offer a new strategy to prevent destruction of Langerhans islets by immune cells assault in this model of type 1 diabetes.

Supported By: CIHR

254-LB

Common Food Additive Carrageenan Inhibits GLP-1 Secretion by Enteroendocrine L-cells and Reduces Intestinal Epithelial Glut2 Expression

ALIP BORTHAKUR, SUMIT BHATTACHARYYA, JOANNE K. TOBACMAN, *Chicago, IL*

Studies in diabetic rat models have shown that Glut2 expression in liver is modulated by GLP-1, an incretin synthesized and secreted by intestinal L-cells. GLP-1 secretion by L-cells is modulated in response to both nutrients and non-nutrients in the gut lumen. Carrageenan (CGN), a sulfated polygalactan, is a common food additive used to improve texture of processed foods. CGN exposure predictably causes inflammation, mediated by both ROS and TLR4, and impairs glucose tolerance. Since GLP-1 secretion by L-cells is modulated by both nutrients and non-nutrient substances in the gut lumen, the effects of CGN exposure on GLP-1 secretion by L-cells and the consequences on Glut2 expression in intestinal epithelial cells (IEC) were examined in an *in vitro* co-culture model. The human intestinal L-cell line NCI-H716 was grown on transwell inserts on top of a monolayer of the epithelial cell line LS174T. NCI-H716 cells were treated with κCGN (1 µg/ml). GLP-1 levels in the spent media were measured by ELISA, and proglucagon (the precursor of GLP-1) and Glut2 mRNA levels were measured by QRT-PCR. Proglucagon mRNA levels in NCI-H716 cells decreased significantly in response to CGN treatment for 1h ($p<0.01$) and further at 24h ($p<0.001$). GLP-1 secretion by the L-cells declined by 31%, 46% and 43% at 10 min, 1h and 24h, respectively, of CGN exposure. Direct CGN treatment of intestinal epithelial LS174T cells did not change mRNA expression of Glut2 ($p>0.05$). In contrast, CGN treatment of L-cells grown on inserts on top of the LS174T monolayer reduced Glut2 mRNA levels in LS174T cells significantly ($p<0.01$) by 1h, with further reduction at 24h ($p<0.001$). These data indicate that carrageenan inhibits expression and secretion of GLP-1 in intestinal L-cells, leading to reduced stimulation of Glut-2 expression in co-cultured IEC. These findings further demonstrate that exposure to the common food additive carrageenan can profoundly affect glucose metabolism in human cells.

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255-LB

Effects of Biased GPR39 Ligands on Insulin Secretion, GLP-1 Secretion, and Cellular Differentiation In Vitro

OLIVER J. MACE, STEVE ANDREWS, ALASTAIR J. BROWN, MILES CONGREVE, ALI JAZAYERI, JAYESH PATEL, BEN TEHAN, FIONA MARSHALL, *Welwyn Garden City, United Kingdom*

GPR39 is a GPCR expressed in the GI tract, adipose, liver and pancreas and has been implicated in metabolic regulation and preservation of pancreatic islet function. Activation of GPR39 by Zn^{2+} stimulates multiple intracellular pathways (cAMP, IP_1, SRE). Here we present the *in vitro* characterisation of biased agonists for GPR39 identified using our StaR™ platform.

Eight GPR39 agonists were characterised across 3 different signalling pathways: Gas, Gaq and Ga13 and compared by calculating the relative activity (Ra) to Zn^{2+} (table 1). Most compounds exhibited bias for Gas over Gaq with notable exceptions being Zn^{2+} which generated a similar level of activation across all pathways and HTL91 which showed bias for IP_1 over cAMP signalling. Activation of GPR39 stimulated GSIS from NIT-1 cells (diminished by siRNA) and GLP-1 secretion from primary mouse L-cells. 6 out of 8 compounds stimulated SRE-dependent transcriptional activity and induced insulin biosynthesis in pancreatic ductal ARIP cells.

These data support the ability of small molecules targeting GPR39 to stabilise distinct receptor confirmations that are capable of signalling via distinct intracellular pathways. The discovery of biased ligands for GPR39 could provide a way to selectively target beneficial signalling pathways with therapeutic benefit.

Table 1. Potency and Efficacy of GPR39 Agonists.

	cAMP accumulation			IP_1 accumulation			SRE-luciferase		
	pEC_{50}	Emax (% Zn^{2+})	Ra	pEC_{50}	Emax (% Zn^{2+})	Ra	pEC_{50}	Emax (% Zn^{2+})	Ra
Zn^{2+}	5.90	100.00	1.00	5.30	100.00	1.00	4.61	100.00	1.00
HTL57	6.34	80.26	2.21	4.64	96.00	0.21	5.12	30.20	0.98
HTL36	6.61	90.47	4.60	4.63	93.99	0.20	nd	nd	—
HTL06	6.32	88.91	2.33	4.65	94.10	0.21	nd	nd	—
HTL05	6.21	91.17	1.87	4.64	93.20	0.20	3.54	173.86	0.15
HTL29	5.91	75.23	0.77	4.64	100.14	0.22	4.22	79.18	0.32
HTL89	5.74	103.24	0.71	4.64	97.17	0.21	3.38	87.91	0.05
HTL91	4.60	131.03	0.07	6.23	83.44	7.11	nd	nd	—
HTL84	5.70	104.40	0.67	4.62	90.28	0.19	4.71	176.01	2.22

OBESITY—ANIMAL

256-LB

Hypomorphism for RPGRIP1L, a Ciliary Gene Vicinal to the FTO Locus Associated with Increased Body Weight in Humans, Causes Increased Adiposity in Mice

GEORGE STRATIGOPOULOS, JAYNE F. MARTIN CARLI, DIANA R. O'DAY, LIHENG WANG, CHARLES A. LEDUC, PATRICIA LANZANO, WENDY K. CHUNG, DIETER EGLI, DANIEL A. DOHERTY, RUDOLPH L. LEIBEL, *New York, NY, Seattle, WA*

Common polymorphisms in the first intron of *FTO* are highly associated with ~1.5 Kg per-risk-allele increased body weight in adults. Previous studies have suggested that CUX1 regulatory elements in intron 1 of *FTO* control the expression of *FTO* and the nearby gene, *RPGRIP1L*. Given the implication of RPGRIP1L in the biology of the primary cilium, and the established role of ciliary genes in energy homeostasis, we explored the possibility that mice heterozygous for an *Rpgrip1l* null allele (*Rpgrip1l*$^{+/-}$) would display obesity susceptibility comparable to the dose-dependent effect that the *FTO* intronic polymorphisms have on adiposity in humans. *Rpgrip1l*$^{+/-}$ mice are hyperphagic, have more fat than *+/+* littermates, and display diminished suppression of food intake in response to exogenous leptin. Moreover, mice deleted for *Rpgrip1l* in specific hypothalamic neuronal subpopulations displayed a similar phenotype, suggesting that *Rpgrip1l* hypomorphism in the hypothalamus may be the main cause of the apparent hyperphagia and increased adiposity of *Rpgrip1l*$^{+/-}$ mice. Supporting these *in vivo* observations, we find that in the hypothalamus of *Rpgrip1l*$^{+/-}$ mice, and fibroblasts derived from humans segregating for hypomorphic mutations in *RPGRIP1L*, localization of ciliary marker ACIII is diminished, accompanied by impaired localization of the leptin receptor in the vicinity of the cilium, and diminished pSTAT3 levels in response to leptin administration. These findings suggest a mechanism by which apparently functional polymorphisms in intron 1 of *FTO* affects *RPGRIP1L* expression and influences energy homeostasis.

257-LB

Integrin Ligand Mfge8 Is a Key Regulator of Fatty Acid Uptake, Obesity, and Insulin Resistance

AMIN KHALIFEH-SOLTANI, WILLIAM MCKLEROY, STEPHEN SAKUMA, ANDREAS STAHL, KAMRAN ATABAI, *San Francisco, CA, Berkeley, CA*

Obesity and insulin resistance are key risk factors in the development of coronary artery disease, stroke, and adult-onset diabetes mellitus. Fatty acid uptake by cells is critical for fat storage and the development of obesity which then promotes insulin resistance. Dietary triglycerides are broken down into free fatty acids prior to uptake for both storage and consumption in peripheral tissues. The mechanisms by which fatty acids are taken up by cells remain incompletely understood. Inhibition of fatty acid uptake by cells is one approach to prevent the development of obesity and insulin resistance. Expression of the integrin ligand Mfge8 is increased in human obesity and in mice on a high-fat diet (HFD). The role of Mfge8 in obesity is unknown. We found that Mfge8 promotes the development of obesity by facilitating cellular uptake of fatty acids. Mfge8 deficient (Mfge8-/-) mice absorb less dietary triglycerides and are protected from weight gain, steatohepatitis and obesity-associated insulin resistance on a HFD. Mfge8-/- cells have impaired fatty acid uptake in vitro and in vivo. Mfge8 coordinates fatty acid uptake through alpha v beta 3 and alpha v beta 5 integrin-dependent phosphorylation of Akt by PI3 kinase and mTOR complex 2 (Rictor) leading to translocation of Cd36 and Fatp1 from cytoplasmic vesicles to the cell surface. From the therapeutic viewpoint, delivery of Mfge8 to the small intestine may aid in the treatment of malabsorption syndromes. Alternatively, inhibition of the Mfge8-dependent pathway provides a novel therapeutic target for the treatment of obesity that directly inhibits the molecular pathways of fatty acid uptake by the cells. Collectively, our results implicate a central role for Mfge8 in regulating fatty acid uptake and insulin resistance in multi organ systems.

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258-LB

Xbp1s in Pomc Neurons Connects ER Stress with Energy Balance and Glucose Homeostasis

KEVIN W. WILLIAMS, TIEMIN LIU, MAKOTO FUKUDA, YINGFENG DENG, XINGXING KONG, ERIC D. BERGLUND, PHILIPP E. SCHERER, JOEL K. ELMQUIST, *Dallas, TX, Boston, MA*

The molecular mechanisms underlying neuronal leptin and insulin resistance in obesity and diabetes remain unclear. Here we show that induction of the unfolded protein response transcription factor "spliced X-box binding protein 1" (Xbp1s) in pro-opiomelanocortin (Pomc) neurons alone is sufficient to protect against diet-induced obesity as well as improve leptin and insulin sensitivity—even in the presence of strong activators of ER stress. The improved body weight was accompanied by increased energy expenditure and heat production. We also demonstrate that constitutive expression of Xbp1s in Pomc neurons contributes to improved hepatic insulin sensitivity and suppression of endogenous glucose production. Together our results identify critical molecular mechanisms linking ER stress in arcuate Pomc neurons to acute leptin and insulin resistance as well as liver metabolism in diet-induced obesity and diabetes.

Supported By: NIH

259-LB

Chronic Postnatal Overfeeding in Female Mice Predisposes Development of Obesity in Their Offspring via an Altered Central Leptin Signaling

XIAOQIU XIAO, JINJIN JI, YANG YU, ZHI DONG, *Chongqing, China*

The prevalence of obesity among child-bearing female has increased significantly. Adverse consequences of maternal obesity on the descendants have been well accepted, but few studies have examined the underlying mechanisms. We investigated whether neonatal overfeeding in female mice alters metabolic phenotypes in their offspring and whether the hypothalamic leptin signaling is involved. The chronic postnatal overfeeding was induced by reducing the litter size to 3pups/litter, in contrast with normal litter size of 10pups/litter. Normal and neonatally-overfed female mice were bred with normal male mice, and offspring of chronic postnatal overfeeding mothers (OOM) and the control mothers (OCM) were generated. We examined body weight, daily food intake, leptin responsiveness, and the number of positive neurons for phospho-signal transducer and activator of transcription-3 (pSTAT3) and neuropeptide Y (NPY) in the arcuate nucleus of the hypothalamus (ARH) and NPY in the nucleus tractus solitarius (NTS) of the brain stem. The body weight and daily food intake of OOM were significantly higher than those of OCM. Leptin significantly reduced food intake and increased the number of pSTAT3 positive neurons in the ARH of OCM mice, whereas no significant changes in food intake and pSTAT3 neurons were found in the leptin-treated OOM mice. The number of NPY neurons in the ARH and NTS of the OOM mice was significantly higher than that of the OCM mice. Our studies indicated that maternal obesity can be passed into the subsequent generation which is possibly associated with hypothalamic leptin resistance.

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260-LB

Lipid Storage by Adipose Tissue Macrophages Regulates Systemic Glucose Tolerance

MYRIAM AOUADI, PRANITHA VANGALA, JOSEPH C. YAWE, MICHAELA TENCEROVA, SARAH M. NICOLORO, JESSICA L. COHEN, YUEFEI SHEN, MIKE P. CZECH, *Worcester, MA*

Adipose tissue (AT) inflammation and infiltration by macrophages is associated with insulin resistance and type 2 diabetes in obese humans. Using an siRNA delivery method to silence genes expressed by macrophages specifically localized within AT depots, while leaving macrophages in other tissues unaffected, we showed that AT macrophages (ATMs) directly contribute to systemic glucose intolerance in obese mice. We reported that intra-peritoneal administration of siRNA encapsulated by glucan shells (GeRPs), to selectively silence inflammatory genes in ATMs, caused significant improvement in glucose tolerance in obese mice. Here we show that ATMs may also be beneficial as repositories for excess lipid that adipocytes are unable to store. Selective silencing of ATM lipoprotein lipase (LPL) decreased foam cell formation in AT of obese mice, consistent with a reduced supply of fatty acids from lipoprotein hydrolysis. Unexpectedly, silencing LPL also decreased the expression of genes involved in fatty acid uptake (FFAs) and esterification in ATMs. This resulted in increased circulating serum FFAs. ATM LPL silencing also caused a marked increase in circulating fatty acid binding protein 4 (fabp4/aP2), an adipocyte-derived lipid chaperon previously reported to induce liver insulin resistance and glucose intolerance. Consistent with this concept, obese mice with LPL-depleted ATMs exhibited higher hepatic glucose production from pyruvate and glucose intolerance. Thus, lipid storage by ATMs promotes systemic glucose tolerance. Using the GeRP technology we showed that ATMs can express both beneficial and deleterious factors, and the overall effect under a given physiological condition is the integration of the effects of these multiple factors in real time.

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261-LB

Bone Marrow Adiposity: Lineage Origin and Differentiation Potential of Bone Marrow Resident Adipocyte Progenitor Cells

THOMAS AMBROSI, CARLA BOCIAN, TIM J. SCHULZ, *Nuthetal, Germany*

Aging results in increased bone marrow adiposity, i.e. the replacement of hematopoietic cells by adipocytes in the cavities of long bones. Current evidence suggests that increased marrow adiposity negatively affects the regenerative potential of osteogenic progenitors, hematopoietic stem cells, and metabolic homeostasis locally and systemically. While it has been demonstrated that marrow adipocytes arise from a population of presumably bi-potential, osteo-adipogenic progenitors, the developmental origin and the effects of aging on these cells remain poorly understood.

Developmental lineage tracing in the mouse reveals a mesenchymal, but non-hematopoietic and non-endothelial origin of the osteo-adipogenic cells that is consistent with corresponding adipogenic cells derived from adipose tissue. Interestingly, cells expressing common markers of bi-potential progenitors, such as platelet-derived growth factor receptor (PDGFR-)α, reside in two distinct anatomical locations, the endosteum and in proximity to sinusoids. Conversely, expression of zinc-finger protein (Zfp-)423, which exclusively marks adipogenic cells, is observed only in the sinusoidal location, suggesting that two distinct populations with either adipogenic or osteogenic potential exist within bone. Prospective, flow-cytometric isolation and culture reveals an age-related impairment of osteogenic potential whereas adipogenesis is unchanged or even increased. Microarray analysis further suggests that changes in extracellular matrix production play a role in this pro-adipogenic switch.

These findings taken together suggest the presence of distinct sub-populations with either osteogenic or adipogenic potential that arise from a common population of stem cells. Aging-related changes in the microenvironment favor adipogenesis over an osteogenic regeneration phenotype. This process could in turn impair hematopoiesis and metabolic health on a systemic level.

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262-LB

Monoacylglycerol Activation of Ppara Mediates White Adipose Browning in AB-Hydrolase Domain6-KO Mice

SHANGANG ZHAO, YVES MUGABO, JOSE IGLESIAS, CAMILLE ATTANÉ, DONGWEI ZHANG, RAPHAËL PRENTKI, MARIE-LINE PEYOT, ERIK JOLY, MARK BROWN, MURTHY MADIRAJU, MARC PRENTKI, *Montreal, QC, Canada, Winston-Salem, NC*

We recently showed that in beta-cells that monoacylglycerol (MAG) acts as a metabolic coupling factor for glucose induced insulin secretion and that signaling competent MAG levels are regulated by alpha/beta-domain hydrolase-6 (ABHD6). We now have studied the role of ABHD6 in energy homeostasis.

Whole body ABHD6-KO mice on high fat diet (HFD) show reduced food intake, body weight gain and basal glycemia, and enhanced glucose tolerance and insulin sensitivity, as compared to wild type mice. Metabolic studies indicate that HFD-fed ABHD6-KO mice show increased O2 consumption, heat production and locomotor activity. The KO mice also maintain normal body temperature for longer period, during cold exposure and showed induction of "browning" genes in both visceral and brown fat. Plasma adipokine analysis showed increased FGF21 and reduced resistin levels in ABHD6-KO mice.

Ex vivo and in vitro experiments indicate that increased MAG level in white adipocytes by either exogenous MAG, ABHD6 inhibitor, or ABHD6 deletion, is associated with elevated expression of UCP1 and other beige/ brown adipocyte marker genes, including PPARalpha and PGC1-alpha. Differentiation of preadipocytes from ABHD6-KO fat pads to adipocytes showed increased UCP1 expression compared to WT mice that is curtailed by PPARalpha antagonist. Further, we found that MAG species transactivate PPARalpha in luciferase-reporter gene studies, suggesting that MAG activates PPARalpha to promote browning of white adipocytes.

Collectively, the results provide evidence that ABHD6-accesible MAG regulates energy and glucose homeostasis possibly via activation of PPARalpha. ABHD6 is a promising target not only for promoting glucose-stimulated insulin secretion but also for metabolic syndrome, diabetes and obesity.

Supported By: CIHR

263-LB

The Gut Microbiota Induces Obesity, Reduces Leptin Sensitivity, and Decreases the Expression of the Obesity-Suppressing Neuropeptide Brain-derived Neurotrophic Factor (BDNF) in the Central Nervous System

JOHN-OLOV JANSSON, *Gothenburg, Sweden*

The gut microbiota contributes to fat mass and the susceptibility to obesity, but the underlying mechanisms are not completely understood. The brain-derived neurotrophic factor (Bdnf), regulates mood and memory. In addition, it has recently been found to be a potent anti-obesity substance in both humans and experimental animals, probably exerting these effects at the level of the hypothalamus, especially the ventromedial nucleus (VMN) and the brainstem. Interestingly, recent findings indicate that a BDNF mRNA variant with a long 3´ untranslated region (long 3´ UTR) is targeted toward dendrites of the neuron, and that this variant of Bdnf mRNA is essential for energy balance and responsiveness to leptin. We found that conventional mice on normal chow had decreased expression of the (anti-obesity form of) long 3´ UTR Bdnf mRNA in the hypothalamus and the brainstem, compared to germ free mice. Moreover, conventional mice on high fat diet had decreased expression of the long 3´ UTR Bdnf mRNA in the hypothalamus, compared to germ free mice on high fat diet. Leptin treatment caused less weight reduction in conventional mice compared with germ free mice.

In conclusion, the gut microbiota reduces the expression of the anti-obesity dendritic targeting form of long 3´ UTR Bdnf mRNA in the hypothalamus and the brainstem. This may contribute to gut microbiota induced leptin resistance and fat mass in mice.

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264-LB

CCR2 Deficiency Leads to Eosinophilia, Alternative Macrophage Activation, and TH2 Polarization in Adipose Tissue

W. REID BOLUS, DARIO A. GUTIERREZ, ALYSSA H. HASTY, *Nashville, TN, Heidelberg, Germany*

Adipose tissue (AT) inflammation during obesity is mediated by inflammatory immune cells and closely correlates with systemic insulin resistance and type 2 diabetes. In AT, inflammatory status is tightly associated with the number and type of infiltrating leukocytes. In lean AT, eosinophils are relatively abundant and are capable of promoting macrophage alternative activation via their production of IL4. In wild type (CCR2+/+) mice, obesity causes the proportion of eosinophils in AT to decline, potentially contributing to the classical activation of inflammatory AT macrophages. In the current study we show that CCR2 deficiency leads to eosinophilia in AT and the peritoneal cavity. In contrast to CCR2+/+ mice, eosinophilia in CCR2-/- AT is sustained and even amplified during high fat diet feeding. Interestingly, the majority of eosinophils in the AT of CCR2-/- mice are localized within crown-like structures. The accumulation of these immune cells was found to be independent of the ability of CCR2-/- precursor cells to differentiate into eosinophils. Rather, the proportion of eosinophils in AT was positively correlated with the expression of Il5, a potent eosinophil chemokine. The eosinophilia in CCR2-/- mice was detected in all fat pads, but was not found in bone marrow, blood, spleen, or liver. In CCR2-/- mice, AT eosinophilia coincided with macrophage alternative activation and increased TH2 gene expression. This is the first study to provide a link between CCR2 function and eosinophilia in AT.

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265-LB

Macrophage and Preadipocyte Interactions in Adipose Tissue Fibrosis

GABRIEL MARTINEZ-SANTIBANEZ, BRIAN ZAMARRON, KAE WON CHO, MARK ANTHONY LINGAYA, CAREY N. LUMENG, *Ann Arbor, MI*

Extracellular matrix (ECM) accumulation in adipose tissue is a feature of chronic obesity and adipose tissue fibrosis is associated with insulin resistance. The adipose tissue ECM in adipose tissue is a critical regulator of adipocyte function and metabolism and the loss of ECM remodeling flexibility promotes metabolic dysfunction. The mechanisms by which adipose tissue fibrosis is initiated and maintained with obesity are not completely understood. The goal of our studies is to assess the source of ECM production and how ATMs might regulate ECM remodeling in adipose tissue. Microarray analysis identified preadipocytes (CD31-CD45-Sca1+PDGFRα+) as enriched for ECM genes compared to ATMs in lean and obese mice. ECM genes were further induced in preadipocytes but not ATMs with diet-induced obesity (DIO). To identify the source of the collagen production in adipose tissue, intracellular flow-cytometry was used to identify preadipocytes as the primary Collagen Type 1 and Elastin expressing cells in adipose tissue in lean and obese mice. Collagen+ preadipocytes increased in number in obese visceral adipose tissue

and were identified in omental fat samples from obese patients. Weight loss by caloric restriction of obese mice was found to increase visceral adipose tissue fibrosis. This was associated with a sustained increase in Collagen+ preadipocytes and CD11c+ ATMs. To assess the contribution of ATM derived signals to preadipocyte ECM production, in vitro studies demonstrated that TNFα induced Collagen I protein expression in 3T3-L1 preadipocytes. M1 macrophage conditioned media had no effect or decreased preadipocyte ECM gene expression. M2 macrophage conditioned media increased ECM gene expression. Overall, our studies support a model by which preadipocytes are the primary regulated source of adipose tissue ECM production and that ATMs have to capacity to provide signals that enhance or suppress this function.

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266-LB

A Diabetic Monkey Model Can Be Used for Diabetes Therapy Evaluation

ZUNYUAN YANG, LI GONG, WEN ZENG, *Chengdu, China*

We have proved that the diabetes symptoms may appear in rhesus monkeys fed with high-calorie diet. To study the application of diabetic monkeys in drug evaluation, three anti-diabetic drugs of different mechanisms were tested in these monkeys. The results were compared with what were found in clinical trials.TAK-875 (GPR40 agonist). Before administration, IVGTT was conducted in four diabetic monkeys and the plasma glucose curve (AUC0-120 min) was calculated as baseline. A week later, the same test was conducted after 20mg/kg TAK-875 was injected respectively. Comparing with baseline, AUC0-120 min of monkeys injected with TAK-875 decreased by 17.51% in average. In a clinical OGTT, AUC0-3h of the T2DM patients injected with 400mg/day TAK-875 for 2 weeks decreased by 12.98%. Bydureon (a long acting formulation of exenatide). Five diabetic monkeys were injected with Bydureon at a dosage of 40 μg/kg/week and another 5 were injected with saline for 4 weeks. Body weight, FPG, 2h postprandial glucose (2hPPG) and HbA1c were measured. Comparing with saline group, body weight of the Bydureon group decreased by 6.98%, FPG decreased by 17.70%, the 2hPPG decreased by 22.78%, HbA1c decreased by 0.20%. A stronger action of Bydureon on the postprandial glucose than that on FPG was found. These results are consistent with reports in clinical literature. Pioglitazone. Five diabetic monkeys were orally dosed with pioglitazone at a dosage of 1 mg/kg/day and another 5 were dosed with placebo for 4 weeks. FPG, 2hPPG, HbA1c and Lipid levels were measured. Comparing with saline group, the FPG of pioglitazone group decreased by 20.09%, 2hPPG decreased by 11.75%, HbA1c decreased by 0.24% and LDL-c decreased by 7.90%. In a clinical report, after a 40 mg/day pioglitazone treatment for 12 weeks, FPG decreased by 18.38%, HbA1c decreased by 0.24% and LDLc decreased by 15.70%. The efficacy of these three anti-diabetic drugs in diabetic monkeys is similar to that in human. This diabetic monkey model will be useful for evaluating the diabetes therapy.

267-LB

Validation of Schad (Medium- and Short-Chain 3-I-Hydroxyacyl-coa Dehydrogenase) as a Target for Treatment of Obesity and Insulin Resistance

NADJA SCHULZ, STEPHAN SCHERNECK, OLIVER KLUTH, TIMO KANZLEITER, MICHAELA RATH, HANS-GEORG JOOST, ANNETTE SCHÜRMANN, *Nuthetal, Germany*

We have recently shown that SCHAD (gene name *Hadh*), which catalyzes the third reaction of the mitochondrial beta-oxidation is involved in thermogenesis, maintenance of body weight, and in the regulation of nutrient-stimulated insulin secretion (*Endocrinology* 152: 4641-4651, 2011). In order to assess SCHAD as a target for treatment of obesity, *Hadh*$^{-/-}$ mice on the B6.V-*Lep*^{ob} background were characterized on a ketogenic diet. At 10 weeks of age,*Hadh*$^{ob/ob-/-}$ mice exhibited 7.8 g lower body weight and 6.8 g lower fat mass than *Hadh*$^{ob/ob+//+}$ mice. Lean body mass was not affected. This effect associated with a significant reduction of blood glucose and fasted plasma insulin concentrations in *Hadh*$^{ob/ob-/-}$ mice. SCHAD generates NADH which is a substrate for complex1 of the respiratory chain through its enzymatic conversion of 3-L-hydoxyacyl CoAs to 3-L-ketoacyl CoAs. Mitochondria of livers from *Hadh*$^{-/-}$ mice contained lower amount of complex 1 enzymes (e.g. NDUFB8) than mitochondria from *Hadh*$^{+/+}$ mice. Furthermore, oxygen consumption rate (OCR) of hepatic mitochondria of *Hadh*$^{-/-}$ mice as measured with an extracellular flux analyzer was significantly reduced when respiration was stimulated with hexanoylcarnitine (*Hadh*$^{-/-}$: 30.5 ± 2.9 pmol*min^{-1} vs. *Hadh*$^{+/+}$: 85.3 ± 3.1 pmol*min^{-1}). OCR was not affected after stimulation with succinate-rotenone. Thus, our data indicate that SCHAD is a potential target for pharmacological interventions in obesity and diabetes, because its inhibition—in particular under conditions of fat overload—impairs fuel efficiency.

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268-LB

Obesity Changed the Expression Pattern of Extracellular RNAs in Circulation and in Adipose Tissue Niche

RICHARD CHENG-AN CHANG, HUI SONG, WEI YING, HAIQING WANG, SRIKANTH KANAMENI, TAYLOR SPLAWN, BEIYAN ZHOU, *College Station, TX*

Compelling evidence demonstrated that adipose-tissue-resident macrophages (ATMs) are critical coordinators in adipose tissue niche by regulating adipocyte functions, immune cell compartment, and subsequently metabolic homeostasis. As the major cell compartment in adipose stroma, ATMs exert profound regulatory effects by secreting large amount of molecules such as various cytokines and chemokines upon environmental cues. Recent study suggested that, in addition to protein and peptide molecules, RNAs can also be detected in the extracellular fluid and may function as a new type of cell communicating molecules. However, why these extracellular RNAs (exRNAs) are produced and how they function has not been investigated. In the context of obesity induced chronic adipose tissue inflammation and insulin resistance, the exRNA profile has not been generated.

To better understand the regulatory mechanism of ATMs on adipose tissue function, we generated exRNA profiles from 1) the plasma from obese and lean mice, 2) the conditioned medium from classically (macrophage type 1, M1) and alternatively (macrophage type 2, M2) activated murine bone-marrow-derived macrophage and from sorted lean and obese mice ATMs. Interestingly, our results revealed that exRNA profiles in the adipose tissue niche are distinct from circulation; the significant concentration difference of exRNAs from local and circulation is a cue that ATM-secreted exRNA might serve as cell-to-cell communicator in adipose tissue niche. Moreover, a group non-coding RNAs are differentially released by ATMs at polarized activation status; this evidence also supports that exRNAs secretion is a novel marker of macrophage secretion. In conclusion, our study provides the first sets of evidence to support that ATMs can regulate adipose tissue function by actively releasing exRNAs acting in a paracrine manner in the context of obesity-associated metabolic syndromes.

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269-LB

Chronic Effects of Exenatide vs. Metformin Treatment on Body Weight and Endogenous GLP-1 Secretion in High-Fat-Diet-induced Obese Rats

XIAO JUAN ZHANG, FANGLI ZHOU, YANG LONG, WEIYA WANG, SHANGFU ZHANG, XIANGXUN ZHANG, HONGLING YU, XIANG CHEN, ZHONG CHENG, HAOMING TIAN, *Chengdu, China*

The anorexic role of glucagon-like peptide-1 (GLP-1) may contribute to the weight loss effect of both exenatide and metformin. In the current study, we targeted to compare the chronic effects of exenatide vs. metformin on body weight loss and intragastric glucose induced endogenous GLP-1 secretion in high-fat diet induced obese rats and to investigate the mechanisms involved in regulating circulating GLP-1 levels. Forty eight male adult wistar rats were randomly divided into high-fat diet fed and normal chow fed groups. Four mouths later, diet induced obese rats were submitted to exenatide treated (EX, 3μg/kg, twice a day), metformin treated (M, 300mg/kg/d) and high-fat diet fed control groups (HF-C). After 1 month, endogenous GLP-1 secretion was measured by intragastric glucose tolerance test. Blood samples were also collected for the detection of insulin, leptin levels and DPP 4 activity. Intestinal tissues were harvested for the measurement of L cell numbers, the expressions of sweet taste molecules and leptin receptor. Our results showed that similar weight losses and food reduction were found after both treatments. Besides, they all exhibited a positive role in stimulating endogenous GLP-1 secretion. Intestinal L cell numbers were increased in EX rats but stayed unchanged in M rats. The changes of sweet taste molecule expressions were not the same in the two treatment groups. Insulin and leptin sensitivity augmented after both treatments. DPP 4 activity decreased in M rats, while stayed almost the same in EX rats. In summary, chronic treatment with exenatide or metformin could lead to similar reductions in body weight and food intake in high-fat diet induce obese rats, meanwhile, intragastric glucose induced endogenous GLP-1 secretion are elevated after both treatments and the underlying mechanisms are not identical. The unraveling of the story may provide new agents targeting on incretin effects.

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270-LB

Effects of a CaSR Agonist on Body Weight, Glucose Metabolism, and Gastrointestinal Peptides

KAMAL A. AL-BARAZANJI, YAPING J. LIU, JUDI A. MCNULTY, STEVE M. SPARKS, THOMAS J. RIMELE, CLAUDIA N. GENERAUX, ANDREW YOUNG, LIHONG Z. CHEN, *Research Triangle Park, NC, Durham, NC*

The Calcium Sensing Receptor (CaSR), widely expressed in the gastrointestinal (GI) tract, senses Ca^{++} and other substances, including amino acids. It is considered part of the GI chemosensory system, and may play a role in metabolic regulation. We evaluated the effects of GSK3004774, a luminally-retained, potent, CaSR agonist in rodent models of obesity and diabetes. In obese C57BL/6 mice fed a 45% high-fat diet, a 15-day treatment of GSK3004774 resulted in a weight loss of 7.5 ± 1.8% compared to vehicle ($p<0.05$). The weight loss, predominantly from fat (-1.85 ± 0.5 g vs. vehicle 0.5 ± 0.34 g, $p<0.05$) was associated with a 12% reduction in cumulative food intake ($p<0.05$ vs. vehicle). It was not associated with increased plasma GIP, GLP-1 and PYY concentrations, an observation confirmed in normal Sprague Dawley rats during a food challenge test. GSK3004774 did, however, increase CCK/gastrin secretion. GSK3004774 had no effects on body weight and glycemic control in Zucker Diabetic Fatty rats. In conclusion, activation of the CaSR in the GI tract could be a potential approach to treatment of obesity. Further studies are needed to determine the site/s and mechanism/s of action, and whether effects in rodents translate to human obesity.

271-LB

PPAR-gamma Agonist Pioglitazone Ameliorates Pulmonary Arterial Hypertension in High Fat Diet-induced Animal

ANY ELISA SCHMIDT GONCALVES, ALEXANDRE G. DE OLIVEIRA, BRUNO CARVALHO, JULIANA VECINA, RODRIGO MARIN, MARIO SAAD, *Campinas, Brazil*

Pulmonary arterial hypertension (PAH) is a progressive disease of poor prognosis characterized by vasoconstriction of pulmonary arteries (PA) and proliferation of pulmonary vascular endothelial and smooth muscle cells. There is emerging evidence that many key genes involved in PAH development are targets of the insulin-sensitizing transcription factor PPARγ, and that pharmacological PPARγ activation would lead to their beneficial induction or repression and subsequent antiproliferative, anti-inflammatory, proapoptotic, and direct vasodilatory effects in the vasculature.

Based on previous data, the aims of this study were:

- Establish an animal model of insulin resistance induced by high fat diet and explore the development of PAH;
- Evaluate PPARγ expression in pulmonary artery of obese animals and determine if PPARγ agonist drugs pioglitazone can reverse PAH.

Male C57BL/6 mice were further randomized to receive Pioglitazone (20 mg/kg/day) in a reversal protocol (after 8 month of HF diet and PAH induction and treating for 4 weeks) by gavage.

Echocardiography (40-MHz transducer) was simultaneously performed and pulmonary acceleration time (PAT) and ejection time (ET) were measured by pulsed-wave Doppler of pulmonary artery flow. Also, it was determined, by Western blotting, the tissue expression and phosphorylation levels of PPARγ, JNK and ERK1/2 in artery, lung and right ventricle of control, obese and treated mice.

Our data show that Pioglitazone is able to minimize PAH effects in obese mice model through increasing of PPARγ expression and decreasing ERK1/2 activity. Thus, PPARγ and ERK1/2 are important mediators of PAH and obesity, since they are related to imbalance on vascular proliferation and can be potential target for the therapy of these medical conditions.

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OBESITY—HUMAN

272-LB

Evidence that Hypothalamic Gliosis in Humans is Associated with Obesity, Insulin Resistance, and Low Physical Activity

ELLEN A. SCHUR, SUSAN J. MELHORN, KATHRYN BERKSETH, MARY F. WEBB, VIDHI TYAGI, SEOK-KYUN OH, KEN MARAVILLA, *Seattle, WA*

The mediobasal hypothalamus (MBH) includes the arcuate nucleus (ARC), a region critical for the regulation of energy and glucose homeostasis. In rodents, high-fat diet induces obesity and a 'reactive gliosis' (expansion of microglia and astrocyte populations) in the ARC. We hypothesized that quantitative magnetic resonance imaging (MRI) could detect radiologic evidence of MBH gliosis that would be associated with obesity in humans. We measured T2 relaxation time in the MBH and in 2 reference regions (the amygdala and putamen) in 15 normal weight, never obese and 19 obese subjects. Using a nested design, all 33 subjects were ranked by left (L) MBH mean T2 relaxation time (based on prior research). The 11 cases within the highest tertile of L MBH T2 relaxation time (i.e., strongest radiologic evidence for gliosis) were compared to 11 controls in the bottom tertile. Sex, age, and T2 relaxation time in reference regions did not differ between cases and controls. The proportion of obese subjects was significantly higher among cases (82 vs. 36%; P=0.03) with a mean BMI among cases of 34.1 kg/m2 (controls=27.7 kg/m2, P=0.07). Higher BMI was linearly associated with longer L MBH T2 relaxation time ($P<0.05$). Fasting insulin levels and HOMA-IR were also positively associated ($P<0.05$) with L MBH T2 relaxation time, independent of sex, but not BMI. Cases self-reported significantly lower physical activity (P=0.01) and physical activity was negatively correlated with L MBH T2 relaxation time (P=0.01). MBH gliosis in humans, as assessed by quantitative MRI, was associated with obesity and insulin resistance. As in animal models, physical activity may be protective.

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273-LB

RNA Sequencing Reveals Distinct Gene Changes in the Subcutaneous Adipose Tissue of Morbidly Obese Insulin-Sensitive and Insulin-Resistant Humans

X. JULIA XU, MAGALI SOUMILLON, TARJEI MIKKELSEN, WALTER PORIES, LYNIS DOHM, NEIL B. RUDERMAN, *Boston, MA, Cambridge, MA, Greenville, NC*

Although obesity and insulin resistance (IR) often coexist, ~ 25% of severely obese individuals (BMI > 40) are insulin sensitive (IS), as assessed by hyperinsulinemic-euglycemic clamps or the homeostasis model of assessment (HOMA). Intriguingly, compared to the IR group, the IS patients are less likely to develop cardiovascular disease and other obesity-associated co-morbidities including type 2 diabetes. We have previously demonstrated that AMP-activated protein kinase (AMPK) activity is lower, and oxidative stress higher in the abdominal subcutaneous and visceral adipose tissue of IR than BMI-matched IS individuals. However, PCR array studies reveal limited and inconsistent gene changes in the subcutaneous adipose tissue.

In the present study, we utilized a novel RNA sequencing technique to characterize the differences in gene expression. Total RNA extracted from subcutaneous fat of 14 IS and 30 IR BMI-matched patients were profiled using a poly(A)+ 3' digital gene expression RNA-Sequencing protocol. The data revealed 39 sets of genes with elevated expression in the IR samples and 28 sets elevated in the IS samples ($p < 0.001$). Among the changes, the adipose tissue of IR group had elevated expression of inflammation and extracellular matrix remodeling pathway genes, whereas those from IS individuals showed higher expression of genes related to mitochondrial function and oxidative metabolism. To the best of our knowledge, this is the first study that provides a comprehensive transcriptome blueprint in human adipose tissue. Findings from this study will enable us to identify novel molecular targets/pathways that distinguish IS and IR obesity. Moreover, because subcutaneous adipose tissue is accessible to us following bariatric surgery (as oppose to visceral fat), our ability to detect clear-cut differences in gene expression in the subcutaneous fat will enable us to investigate how IS and IR patients respond to bariatric surgery.

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274-LB

Effects of Bariatric Surgery on C Fiber and Cardiac Autonomic Function in Obese Patients With and Without Diabetes

CAROLINA M. CASELLINI, HENRI K. PARSON, KIM HODGES, JOSHUA F. EDWARDS, DAVID C. LIEB, STEPHEN D. WOHLGEMUTH, AARON I. VINIK, *Norfolk, VA*

Sudoscan™ measures peripheral C fiber function as electrochemical skin conductance (ESC) of hands and feet. The aim of this study was to evaluate the impact of bariatric surgery on ESC in obese diabetic and non-diabetic subjects. Patients were evaluated at baseline, 1, 4, 12 and 24 weeks after vertical sleeve gastrectomy (VSG) or Roux-en-Y gastric bypass (RYGB). All subjects were assessed with Sudoscan™ of hands and feet, quantitative cardiac autonomic function tests (QAFT), quantitative sensory tests (QST) for pressure, cold and warm perception thresholds and sural nerve conduction studies. This is a preliminary report on the first 25 patients who have completed 12-week follow-up.

ESC of hands and feet improved significantly (MANOVA) by 12 weeks (Table 1). Weight, body mass index and percent (%) body fat also improved significantly. On linear regression analysis ESC of feet correlated significantly with % body fat ($p<0.01$) but not with other measures of metabolic function. QAFT also improved by week 12, but not other measures of somatic nerve function.

This preliminary report demonstrates rapid improvement of C fiber function in hands and feet after bariatric surgery that correlates with reduced % body fat. This is the first study to demonstrate the utility of Sudoscan™ as a measure of C fiber function responses to intervention.

Table 1:

	Baseline	1 week	4 weeks	12 weeks	P*
Feet ESC	60.84	59.39	60.67	67.12	<0.05
Hands ESC	57.06	48.67	48.67	59.90	<0.01
BMI	48.14	45.16	42.91	39.68	<0.0001
%Body Fat	44.52	43.61	41.37	38.55	<0.0001
Weight (lbs)	301.10	282.67	268.59	245.08	<0.0001
DB sdNN	51.21	50.43	44.93	63.29	NS
DB rmsSD	33.29	39.57	30.07	42.29	NS

**Multivariate analysis of repeated measures ANOVA (MANOVA) BMI=body mass index; DB sdNN=deep breathing sample difference of the beat to beat (NN) variability, ESC=electrochemical skin conductance, DB rmsSD=deep breathing root mean square of the difference of successive R-R intervals*

Supported By: Impeto Medical

275-LB

Increased Adipocyte Mitochondrial Respiration in Insulin-Resistant vs. Insulin-Sensitive Obese Subjects

ANJA BOEHM, ANDRAS FRANKO, HANS-ULRICH HAERING, MARTIN HRABE DE ANGELIS, HARALD STAIGER, *Tübingen, Germany, Neuherberg, Germany*

Among obese subjects, metabolically healthy and unhealthy obesity (MHO/MUHO) exists, but underlying pathomechanisms are not well understood yet. Mitochondrial dysfunction in obesity and diabetes is known, potential therapies augmenting energy expenditure are promising ideas currently under discussion. Aim of this study was to characterize the mitochondrial respiration capacity in subcutaneous (sc) human adipocytes from insulin-resistant (IR) vs. comparatively insulin-sensitive (IS) morbidly obese subjects; thus, providing hints for novel pathomechanisms. Primary sc preadipocytes from 4 IR vs. 4 IS non-diabetic Caucasians (BMI >40kg/m2), matched for gender, age, BMI, and percentage of body fat were in vitro differentiated to adipocytes. Cellular respiration was measured (day 0 and 21 of differentiation) by an XF24 Seahorse Analyzer. Data were protein-normalized. Stimulation of lipolysis was done by forskolin (FSK)-treatment. Statistics was done with a two-sided t-test. Mitochondrial respiration was 4-fold higher in adipocytes vs. preadipocytes, p=0.01. No difference regarding the respiration between IR and IS was found in preadipocytes. In adipocytes, several differences were detected: I) basal respiration was higher in IR vs. IS (5.12±0.79 vs. 3.18±0.81; p=0.0002). II) Maximal respiration and spare respiratory capacity was not different among the groups. III) Proton leak was higher in IR vs. IS (2.08±0.75 vs. 0.97±0.4; p=0.0396), while non-mitochondrial respiration was not affected. IV)ATP production was higher in IR vs. IS (2.04±0.64 vs. 0.84±0.22; p=0.0124; n=4). V) There was no difference in mitochondrial coupling between the groups. VI) Stimulation of lipolysis with FSK showed a significant increase (2.12-fold; p=0.0002) in basal respiration in IR as well as in IS. In conclusion, our results point to an increased mitochondrial respiration in adipocytes from IR vs. IS, perhaps reflecting a compensatory state in MUHO.

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276-LB

Circulating Branched-Chain Amino Acids and Irisin Level in Morbid Obese Individual with Type 2 Diabetes (T2DM) after Roux-en-y Gastric Bypass (RYGB)

PRAPIMPORN CHATTRANUKULCHAI SHANTAVASINKUL, ALESSANDRO MOR, LEONOR CORSINO, ALFONSO TORQUATI, *Durham, NC*

Elevation of circulating branched-chain amino acids (BCAA) has been associated with insulin resistance. RYGB has been shown to improve insulin sensitivity which partly mediated by decreasing of BCAA level. Irisin, recently identified myokine, causes browning white adipose tissue and increasing thermogenesis. The benefit of irisin has been proposed to be a potential novel treatment for obesity and T2DM. This prospective controlled trial aimed to determine the association of BCAA and irisin level before and 12-month after RYGB comparing to the diabetes support education (DSE).

A total of 58 morbidly obese individuals with T2DM underwent RYGB (n = 29) or DSE (n =29) and followed up for 12 months. Body composition analysis, serum levels of BCAA and irisin were measured before and after intervention.

At 12-month follow-up, patients who underwent RYGB had a significant weight loss ($p<0.05$), fat mass ($p<0.05$), and fat free mass ($p<0.05$). The irisin and BCAA level were also significantly lower in RYGB group ($p<0.05$). At baseline, the level of irisin were significantly associated with serum total BCAA (r 0.30, $p<0.05$), valine (r 0.32, $p<0.05$), leucine/isoleucine(r 0.26, $p<0.05$). After RYGB, the reduction of irisin level was positively associated with the changes of total BCAA ($r = 0.47$, $p < 0.05$), valine ($r = 0.47$, $p < 0.05$) leucine/isoleucine levels ($r = 0.42$, $p < 0.05$), the association was exist after controlling for BMI change, total lean mass change and age ($p <0.05$).

RYGB significantly improve insulin sensitivity. To the best of our knowledge, this is the first study that demonstrates not only the association of circulating irisin and BCAA level in morbidly obese individuals with T2DM but also the association of the reduction of irisin and the change of BCAA level after RYGB. Further studies are needed to explore whether irisin is associated with BCAA metabolism and its role in improvement of glucose homeostasis in morbidly obese individual after RYGB.

277-LB

Effect of Acyl Ghrelin Infusion on Glucose Disposal and Production in Obese and Lean Humans

ROBYN A. TAMBOLI, JOSEPH ANTOUN, EMILY A. ECKERT, PAM MARKS-SHULMAN, KAREEM JABBOUR, IRENE D. FEURER, NAJI N. ABUMRAD, *Nashville, TN*

Ghrelin is an orexigenic peptide produced primarily in stomach. Fasting ghrelin levels are lower in the obese. Ghrelin infusion was shown to worsen insulin sensitivity in lean humans, but there is no information about is effect in the obese, which is the objective of this study.

Eight obese and nine lean participants underwent an infusion of acyl ghrelin (1 pmol kg^{-1} min^{-1}) or saline in random order on consecutive days. Hyperinsulinemic-euglycemic clamps with glucose tracer infusions were performed each day with ghrelin or saline infusions. Data are presented as median (interquartile range), and comparisons were made with nonparametric tests.

Fasting acyl ghrelin levels (pg/ml) were lower in the obese than the lean [360 (184-581) vs. 770 (569-968), P = 0.006]. Acyl ghrelin infusion resulted in similar basal plasma acyl ghrelin in the obese and lean [3498 (2886-4483) vs. 2955 (2558-3666), P=0.2]. During the clamp, the obese had higher plasma acyl ghrelin than the lean [4249 (3138-4872) vs. 2586 (1984-3062), P=0.002). This translated into significantly higher clearance rates of plasma acyl ghrelin (~50%) in the obese compared to lean, which did not change with insulin infusion. Peripheral glucose uptake was significantly reduced with ghrelin infusion in both the lean and obese; however, the obese had a greater percent reduction compared to the lean [44% vs. 24%, P=0.001). Hepatic glucose production was not altered by ghrelin infusion in either group ($P \geq 0.35$).

The lower plasma acyl ghrelin in the obese appear to be due to increased clearance from the plasma compartment. At high physiological levels, acyl ghrelin worsens peripheral insulin sensitivity in both lean and obese; however, this effect appears to be more exaggerated in the obese. Hence, we hypothesize that lower plasma ghrelin levels in the obese might be protective against further worsening of the peripheral insulin resistance commonly present in the obese.

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278-LB

WITHDRAWN

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WITHDRAWN

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Short-term Changes in Lipopolysaccharide and Lipopolysaccharide-Binding Protein Levels after Two Different Bariatric Surgery Procedures in Normoglycemic and Diabetic Morbidly Obese Patients

MERCEDES CLEMENTE-POSTIGO, MARIA DEL MAR ROCA-RODRIGUEZ, FERNANDO CARDONA, FRANCISCO J. TINAHONES, *Málaga, Spain*

Bariatric surgery mostly implies metabolic improvements within few days from intervention, but the underlying mechanism is not understood and may differ depending on the bariatric procedure. Lipopolysaccharides (LPS) from the gut microbiota have been proposed as a triggering factor for the inflammatory state in obesity related with the development of insulin resistance and diabetes. Roux-en-Y gastric bypass leads to LPS decrease in the medium-term. Thus, the aim of this study was to analyze LPS and LPS-binding protein (LBP) in both normoglycemic (NG) and prediabetic-diabetic (P/D) morbidly obese patients in the short-term after two different bariatric surgery procedures.

50 morbidly obese patients underwent bariatric surgery: 24 sleeve gastrectomy (SG) and 26 biliopancreatic diversion of Scopinaro (BPD). Patients

were classified according their glycemic status in NG and P/D patients. LPS and LBP levels and biochemical and anthropometric variables were determined before and at days 15 and 90 after bariatric surgery.

A significant LPS reduction was only seen in P/D patients at 90d after SG. LBP levels rose at 15d after BPD but at 90d returned to baseline in NG and P/D patients. At 90d after SG, LBP levels significantly decreased compared to baseline in NG and P/D patients. LBP levels correlated significantly and positively with anthropometric variables and with triglycerides, insulin, HOMA-IR and CRP levels, and negatively with adiponectin levels.

Short-term LPS decrease after bariatric surgery depends on the surgery procedure as well as on the previous glycemic status of the patients. LBP is closely related to anthropometrical and biochemical parameters in morbidly obese patients undergone bariatric surgery.

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281-LB

Dopaminergic Effects on Brown Adipose Tissue

LONNEKE BAHLER, HEIN J. VERBERNE, MAARTEN R. SOETERS, JOOST HOEKSTRA, FRITS HOLLEMAN, *Amsterdam, Netherlands*

Bromocriptine is a centrally acting dopamine receptor agonist that improves insulin sensitivity in obese subjects. Yet, no explanation has been found for this effect of bromocriptine. Brown adipose tissue (BAT), a tissue that converts calories into heat, might be involved in this process. Since the central sympathetic nervous system is the primary activator of BAT, we hypothesized that dopamine plays a role in the activation of BAT. Therefore, the aim of this study was to investigate the influence of bromocriptine on BAT activity in 8 lean (BMI 23[21-25] kg/m2), healthy Caucasian males (20.9[19-23] years).

All subjects were studied before and after using bromocriptine (1st week 1,25mg/day, 2nd week 2,5mg/day) in a climate room at 21°C after an overnight fast. On these 2 study visits we measured metabolic BAT activity, defined as maximal standardized uptake value (SUVmax), using 18F-Fluorodeoxyglucose Positron Emission Tomography CT scans. Furthermore we investigated glucose metabolism with a 7 point oral glucose tolerance test, energy expenditure (EE) using indirect calorimetry, weight and body temperature. Subjects recorded their eating behavior in the 4 days before the study visits.

The use of bromocriptine did not significantly alter metabolic BAT activity (SUVmax before 11.97[4.3-15.8]; after 10.3[2.7-18.2]), EE (before 2103 Kcal/day [1340-2486]; after 1915 [1784-2437]), body temperature (before 36.0 °C [35.6-36.4]; after 36.2 [36.0-36.7]) or weight (80 kg[72.1-82.2]; after 80 [72.1-81.8]). Unexpectedly, subjects became significantly less insulin sensitive after bromocriptine use. The area under the curve for glucose increased (before 652 [539-752]; after 857 [772-992] (p=0.02)). But the area under the curve for insulin also increased (before 27x103 [26x103-37x103]; after 44x103 [41x103-65x103] (p=0.03)). There were no changes in diet between the 2 measurements that could explain the change in insulin sensitivity.

We conclude that bromocriptine does not activate BAT and does not increase EE in lean, healthy males.

282-LB

Effect of an Accelerometer, Multidisciplinary Intervention, or Combined Approach on Body Composition and Weight Loss in Overweight and Obese Patients

TRAVIS COMBEST, ELIZABETH TANKOVICH, MICHELLE MARDOCK, ASHA JAIN, ROBERT GOLDBERG, *Bethesda, MD*

The increasing prevalence of overweight and obesity demonstrates the need for effective and accessible weight loss interventions. There is currently limited clinical evidence to support the effectiveness of new technology-based weight loss interventions. The purpose of this study is to compare the effect of three weight loss interventions: Self-monitoring using accelerometers (ACC), multidisciplinary intervention weight loss counseling (MDI) or a combined approach (CB) on weight loss and body fat over a three month period.

Participants were randomly assigned to one of three interventions. Weight and percent body fat were measured using direct segmental multi-frequency bioelectrical impedance (DSM-BIA) at baseline,one, two, and three months. Forty-two patients (33 females, 9 males), mean age 51.8 ± 10.3 years, mean baseline weight 210.0 ± 45.9lbs, mean baseline body fat % 39.5 ± 7.2% at Walter Reed National Military Medical Center have completed this randomized controlled weight loss study.

Preliminary results suggest the change in weight over time at the 3 month time point was greatest for the CB group, with a median 3.5% weight loss (interquartile range: 0.8 to 6.2%), p=0.034. The MDI group had a weight loss of 2.1% (IQR: 1.5 to 2.5%, p=0.063) and the ACC group had a median weight loss of 1.0 % (IQR: 1.9% loss to 0.3% gain, p=0.31). The body fat % change at 3 months was also greatest for the CB group with a median 5.3% loss (IQR: 2.6 to 7.9%, p=0.016). The ACC group lost 4.9% (IQR: 2.1 to 8.0%, p=0.063) and the MDI group lost 1.4% (2.9% loss to 1.0% gain, p=0.69).

Practical Implications: Having interventions that help in decreasing weight and obesity would help aide in diabetes management, decrease disease risk and increase quality of life.

Disclaimer: The views expressed in this presentation are those of the author and do not reflect the official policy of the Department of Defense or U.S. Government.

283-LB

Correlation between HTR and SERT Genes Polymorphisms and Eating Disorders in Human Obesity

MARINA OLEGOVNA GALIEVA, EKATERINA ANATOLEVNA TROSHINA, MARINA GENNADEVNA AKSENOVA, NATALYA VALENTINOVNA MAZURINA, PAVEL ALEXANDROVICH VORONENKO, ELENA ALEXANDROVICH BIRYUKOVA, *Moscow, Russian Federation*

The aimed study was to examine the association eating disorders and gene polymorphism of the serotonin system.

Seven hundred sixty-five people of both genders (320 men and 445 women) were included in the study with overweight, grade 1 and 2 obesity (BMI ≥ 25 kg/m2 and ≤ 39,9 kg/m2). Women in their turn were divided into gynoid (n = 131) and android (n = 314) fat depots. Three genes polymorphisms of the serotonin system - the serotonin transporter (SERT (5HTTLPR)), serotonin receptor type 2A (HTR2A (-1438G / A)) and serotonin receptor type 2C (HTR2C (Ser23Cys)) were examine by RT-PCR. All patients were assessed for eating disorder psychopathology (externalities, restrictive and emotiogenic) by DEBQ questionnaire.

No association between the studied polymorphisms in genes and types of eating disorders in the group of men and women with gynoid type of obesity, was revealed. AG and GG genotypes HTR2A gene in women with android fat depots were associated with high scores on a scale of restrictive type of eating disorder (19,7 and 19,8 vs. 16,1 genotype AA), (Anova, p <0,01), and genotype AA - with high scores on a scale emotiogenic type of eating disorder (18,1 vs. 13,6 genotype AG), (Anova, p = 0,04). Genotype Ser / Cys HTR2C gene was associated with high scores in a scale of externalities type of eating disorder (21,2 vs. 17,4 genotype Cys/Cys), (Anova, p = 0,02). Scores of emotiogenic type scale of eating disorder was higher in the group of women with SS genotype SERT gene compared with LL genotype (17,1 vs. 13,7), but these results were not statistically significant (p = 0,06). Linear regression analysis revealed a negative correlation of expression of restrictive eating disorder whith BMI for genotypes GG gene HTR2A (K = -0,33, p <0,05).

The study of serotonin system genes' polymorphisms showed a correlation of eating disorders only in the subgroup of women with android fat depots - the lowest possible score in a restrictive eating disorder scale was significantly associated with a high BMI for genotypes GG gene HTR2A.

ISLET BIOLOGY—APOPTOSIS

284-LB

A Calcium-dependent Protease As a Potential Therapeutic Target for Wolfram Syndrome, a Prototype of Endoplasmic Reticulum–associated Diabetes

SIMIN LU, KOHSUKE KANEKURA, CHRISTINE M. OSLOWSKI, RITA MARTINEZ, MAYU YAMAZAKI-INOUE, MASASHI TOYODA, AMBER NEILSON, PATRICK BLANNER, CRIS BROWN, JONATHON WASSON, BESS A. MARSHALL, TAMARA HERSHEY, AKIHIRO UMEZAWA, PETER A. GREER, FUMIHIKO URANO, *St. Louis, MO, Boston, MA, Tokyo, Japan, Kingston, ON, Canada*

Endoplasmic reticulum (ER) is an emerging target for human chronic diseases, and Wolfram syndrome characterized by diabetes and neurodegeneration is a prototype of human ER disease. Here we show that the calpain protease is a link between the two Wolfram syndrome genes and death of neurons and β cells. Calpain activation is mediated by calcium leakage from the ER, which is enhanced by the loss of function of the Wolfram syndrome 1 gene. We show that the Wolfram syndrome 2 gene product (WFS2) associates with and regulates calpain 2. Elevated activation of calpain 2, seen with WFS2 knockdown, correlates with increased death in neurons and β cells; whereas suppression of calpain 2, seen with over-expression of WFS2, protects these cells from death. Evidence of calpain hyperactivity is observed in a mouse model of Wolfram syndrome as well as in neural progenitor cells derived from induced pluripotent stem cells of patients with Wolfram syndrome. Our results demonstrate that the pathway leading to calpain 2 activation provides potential therapeutic targets for Wolfram syndrome and other ER-associated diseases.

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For author disclosure information, see page LB91.

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Glucagon-like Peptide-1 Specifically Ablates Functionally Deficient Insulin Cells in Mouse Islets in Vivo

GLADYS TEITELMAN, YELENA GUZ, MAMDOUH KEDEES, *Brooklyn, NY*

In the present study, we sought to determine whether Glucagon-like peptide-1(GLP-1) modified the beta cell composition of islets. Two lines of bigenic mice were generated by crossing mice containing a transgene comprised of the rat insulin promoter (RIP) linked to Cre recombinase-estrogen receptor (RIP-CreER mice) with strains containing a floxed reporter gene encoding for either Human Placental Alkaline Phosphatase (PLAP, RIPCreER-ZAP mice) or Enhanced Yellow Fluorescent Protein (EYFP, RIPCreER-EYFP mice). Injection of Tamoxifen (TM) induces Cre activity, resulting in the expression of the reporter gene (EYFP or PLAP). Only cells that contain an active RIP-CreER transgene at the time of TM injection will express the reporter protein and transmit it to their progeny.

Injection of TM to normoglycemic 2 month old RIPCreER- EYFP mice resulted in expression of EYFP in 46.6 ± 2.1% (3 mice and a total of 8681IN+ cells scored) in 6 month bigenic mice. To prevent the cleavage of GLP-1 in vivo, an inhibitor (MK0626, Merck) of the enzyme dipeptidyl-peptidase (DPP4i) was administered to 5 month old RIPCreER-EYFP mice for two months. The DPP4i therapy induced a decrease in the percentage of IN+EYFP+ to 17.5± 1.73 (3 mice and a total of 9474 IN+ cells scored). GLP-1 mediates this action of the DPP4i since daily injection (10 nmol/kg daily) of the GLP-1 analog exendin 4 (ex-4) to 4 months RIPCreER-PLAP mice for two weeks dramatically reduced the percentage of IN+PLAP+ cells (2.83± 0.7; 5323 IN+ cells scored). Administration of GLP-1, but not of the DPP4i, resulted in a significant decrease in the beta cell mass in bigenic mice but not in similarly treated CD-1 mice. Neither ex-4 nor the DPP4i affected the rate of beta cell proliferation. Expression of the RIP-Cre transgene can induce glucose intolerance (J. Biol.Chem. 281:2649-2653) due to toxic effects of Cre expression. Taken together, our results reveal a novel function of GLP-1, which is to ablate functionally deficient beta cells in islets in vivo.

286-LB

Cannabinoids Regulate Bcl-2 and Cyclin D2 Expression in Pancreatic Beta Cells

JIHYE KIM, DA EUN JEONG, WOOK KIM, *Suwon, Republic of Korea*

We previously reported that cannabinoid 1 receptors (CB1Rs) are expressed in pancreatic β cells, where they induce cell death by directly inhibiting insulin receptor activation. Here we report that anti-apoptotic protein Bcl-2 and cell cycle regulator Cyclin D2 are involved in cannabinoid-induced pancreatic β-cell death and growth arrest. Treatment of MIN6 pancreatic β-cells with a synthetic CB1R agonist WIN55, 212-2 leads to decrease in the expression of Bcl-2 and Cyclin D2, in turn inducing caspase-3-dependent apoptosis and an arrest of the cells in the G0/G1 phase of the cell cycle. Consistently, pharmacological and genetic blockade of CB1Rs leads to reduced blood glucose and increased β-cell survival and proliferation after injury due to increased levels of Bcl-2 and Cyclin D2. These findings provide evidence for involvement of Bcl-2 and Cyclin D2 in the regulation of β-cell survival and growth and will serve as a basis for developing new therapeutic interventions to enhance β-cell function/growth in diabetes.

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ISLET BIOLOGY—BETA CELL—DEVELOPMENT AND POSTNATAL GROWTH

287-LB

Sox4 Cooperates with Neurogenin3 to Regulate Endocrine Pancreas Formation in the Mouse

ERIC E. XU, NICOLE A.J. KRENTZ, SARA TAN, SAM Z. CHOW, MEI TANG, CUILAN NIAN, VERONIQUE LEFEBVRE, FRANCIS C. LYNN, *Vancouver, BC, Canada, Cleveland, OH*

The Sry/HMG box (Sox) family of transcription factors is essential for normal endocrine cell formation and Sox9, the best-studied member of this family, is required for endocrine cell specification. Despite the longstanding knowledge that many other Sox family members are expressed during pancreas development, a role for these factors in establishment of β-cell fate remains to be determined. In order to assess how Sox4 regulates β-cell formation, we utilized pancreas (Pdx1-Cre; Sox4flox/flox) and endocrine (Neurog3-Cre; Sox4flox/flox) specific Sox4 null mice. Loss of Sox4 in the pancreatic anlage led to a significant 70% reduction of endocrine cells at embryonic day (E)18.5. Further analyses of this mutant at E15.5 demonstrated that Neurogenin3 (Neurog3)-expressing cells were 50% reduced in number. Using a new cell model, we demonstrated that Sox4 cooperated with Neurog3 to amplify Neurog3 expression in the endocrine progenitor cells. Loss of Sox4 in the Neurog3-Cre-expressing endocrine progenitors also resulted in significant 60-75% reductions in mature endocrine cells without differences in proliferation, apoptosis or Neurog3 expression. Expression profiling and cell culture models, demonstrated that Sox4 cooperates with Neurog3 to directly transactivate both Pax4 and Neurod1 in the nascent endocrine cell progenitors. Finally, we demonstrate that loss of Sox4 in endocrine progenitors does not lead to differentiation down an alternate cell fate but a dramatic appearance of chromogranin positive, hormone negative cells. In summary, Sox4 is essential for normal pancreatic endocrine cell differentiation both concomitant with, and downstream of Neurog3. These studies may allow refinement of stem cell differentiation protocols in order to generate large numbers of beta cells that could be used to treat those with diabetes.

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288-LB

Pdx1-mediated Islet Cell Replication Is Enhanced Through Regulation of the miR17~92 microRNA Cluster

JONATHAN M. HALDEMAN, JEANETTE BARAN-GALE, DANHONG LU, THOMAS C. BECKER, PRAVEEN SETHUPATHY, CHRISTOPHER B. NEWGARD, HANS E. HOHMEIER, *Durham, NC, Chapel Hill, NC*

A major goal of diabetes research is to uncover pathways that increase pancreatic islet β-cell mass by promoting β-cell replication while preserving function. Our lab has discovered that overexpression of the β-cell transcription factors Pdx1 or Nkx6.1 in rat islets is sufficient to drive β-cell replication while maintaining function. Furthermore, only Pdx1-mediated replication is blocked by Cdk4 inhibition, demonstrating that these factors act through separate pathways. In this study, we sought to determine whether miRNAs differentially regulated by Pdx1 or Nkx6.1 contribute to the ability of either factor to drive β-cell replication.

Here we show that Pdx1, but not Nkx6.1, overexpression in rat islets causes a ~2-fold increase in the miR-17~92 miRNA cluster, which has been previously implicated in promoting replication in other cell types. Chemical inhibition of the canonical miR-17~92 regulator, Myc, does not blunt Pdx1-induced miR-17~92 expression, suggesting that the observed effect of Pdx1 on miR-17~92 expression is not mediated through Myc. Analysis of published Pdx1 ChIP-seq data from both mouse and human islets reveal Pdx1 binding at the miR-17~92 promoter, which indicates that Pdx1 may be a direct trans-activator of the miR-17~92 locus. We performed computational simulations to predict the regulatory impact of each known miRNA on the Pdx1 gene network in both mouse and human. Interestingly, we found that miR-17, miR-19, and miR-92 from this cluster represent 3 of the 10 miRNAs with the highest Pdx1 network interaction scores. In support of this prediction, we found that inhibition of miR-17~92 cluster members significantly diminishes Pdx1-mediated rat islet cell replication by ~35%. In summary, these findings implicate a novel β-cell specific Pdx1/miR-17 circuit in the regulation of β-cell proliferation.

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289-LB

Parturition Events Terminate Endocrine Neogenesis

MASAKI MIURA, TAKESHI MIYATSUKA, TAKA-AKI MATSUOKA, YOSHIO FUJITANI, MICHAEL S. GERMAN, HIROTAKA WATADA, *Tokyo, Japan, Suita, Japan, San Francisco, CA*

Pancreatic endocrine cell neogenesis can be evaluated by quantifying the number of cells expressing the endocrine progenitor marker neurogenin 3 (Neurog3). Neurog3-expressing cells are observed adjacent to the ductal structure in the embryonic pancreas, but few cells staining for Neurog3 persist after birth. Although this perinatal decline in Neurog3 is well recognized, its exact timing and mechanism are uncertain. Using Neurog3-Timer mice that express the green/red florescent "Timer" protein specifically in endocrine progenitors, we quantified the number of endocrine progenitors by flow cytometry, and found that endocrine neogenesis abruptly declined over the 24 period between embryonic day 18.5 (E18.5) and postnatal day 0.5 (P0.5). We hypothesized that signals associated with parturition control endocrine neogenesis, and tested whether inducing delayed delivery by progesterone administration in pregnant mice impacts the timing of the extinction of Neurog3 expression. Comparing E19.5 embryos with P0.5 newborn pups born at E19 revealed a preservation of Neurog3 expressing cells in the E19.5 embryos (0.80%) compared to P0.5 pups (0.21%), even though both groups were 19.5 days post coitus (dpc). Quantitative RT-PCR revealed that the P0.5 newborn pups also expressed much lower Neurog3 mRNA than E19.5 embryos. In contrast, pancreata from pups delivered one day early at 18.5 dpc due to induction with RU486, a progesterone receptor antagonist, had significantly smaller numbers of endocrine progenitors than normal E18.5 embryos. Moreover, Insulin-Timer mice that express the "Timer" protein specifically in insulin-producing cells revealed significant reduction of beta cell neogenesis

in P0.5 pups compared to E19.5 embryos. These data demonstrate that signals associated with parturition tightly control pancreatic endocrine neogenesis including β cell neogenesis.

290-LB

Beta-Cell Expansion Is Governed by Intrinsic Replication "Speed Limit," Even in Response to Extreme Metabolic Stimuli

AARON R. COX, CAROL J. LAM, MATTHEW M. RANKIN, KOURTNEY KING, CHANGHONG LI, JAKE A. KUSHNER, *Houston, TX, Philadelphia, PA*

Obesity is a potent stimulus for β-cell expansion and represents a powerful tool to examine the capacity for β-cell regeneration. However, current models are unreliable or alter fetal β-cell development. We created a model of acute extreme obesity in young mice via whole body inducible gene deletion of the leptin receptor. Our goal was to determine if acute extreme obesity stimulates β-cell expansion, and to resolve the lineage mechanism and kinetics of β-cell regeneration.

We induced whole body leptin receptor (UBC-Cre^{ERT2}; LepR$^{loxp/loxp}$) gene deletion and sacrificed 3 or 5 weeks later for quantification of β-cell mass. A subgroup of mice received Canagliflozin, an inhibitor of renal glucose reabsorption, or PD 0332991, an inhibitor of the cell cycle regulator, Cdk4.

Whole body inducible LepR deficiency resulted in massive obesity. Surprisingly, acute LepR deficient mice only exhibited mild glucose intolerance and never developed frank diabetes, in sharp contrast with the phenotype of db/db mice. Acute LepR knockout mice compensate for insulin resistance by massively expanding β-cells (3-fold within 5 weeks). We carried out sequential labeling with thymidine analogs and observed that LepR deficiency only stimulated β-cells to expand by self-renewal, with no evidence of contribution by highly replicative β-cell progenitors. Notably, this extreme stimulus for β-cell proliferation was unable to bypass the replication refractory period of β-cells. Further, acute LepR deficiency induced β-cell proliferation occurs in a glucose independent manner (largely unaltered by Canagliflozin-mediated lowering of ambient blood glucose) that requires Cdk4 activation (sensitive to PD 0332991).

In conclusion, acute disruption of LepR signaling results in massive obesity and a remarkable increase in β-cell mass. However, even extreme β-cell expansion is governed by an intrinsic replication "speed limit" that restricts the generation of new β-cells.

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291-LB

Reprogramming of Adult Pancreatic Exocrine Cells to Beta-like Cells

LUC BAEYENS, MICHAEL S. GERMAN, HARRY HEIMBERG, *San Francisco, CA, Brussels, Belgium*

The current cell replacement therapy as a means of treating patients suffering from type I diabetes is severely hampered by a lack of available donor material. Cellular reprogramming of pancreatic non-endocrine cells may provide an attractive approach and could potentially present advancement in regenerative medicine.

We recently provided proof of concept by showing that chronic hyperglycemia in adult mice can be alleviated through the administration of Epidermal Growth Factor (EGF) and Ciliary Neurotrophic Factor (CNTF), by the conversion of terminally differentiated acinar cells to beta cells. The regenerative process requires Stat3 activation and depends on the expression of Neurogenin 3 (Ngn3) in acinar cells.

As rodent acinar cells exhibit a remarkable plasticity in vitro as they can transdifferentiate to duct-like cells, hepatocyte-like cells and, following growth factor-induced activation of MAPK and STAT3 signaling, to beta-like cells, we evaluated whether exocrine cells isolated from adult human pancreas are similarly responsive to pro-endocrine stimuli.

Human exocrine cells were transduced directly after isolation with lentiviruses expressing MAPK^{CA} and STAT3^{CA} and cultured as monolayers or as 3D structures in matrix, with or without free-floating pre-culture.

Simultaneous expression of activated STAT3 and MAPK in human exocrine cells activated the expression of the embryonic master switch for endocrine differentiation Ngn3 in transduced exocrine cells. When the exocrine cells were kept in suspension followed by 3D culture a significant increase in the number of beta-like cells was observed. Genetic lineage tracing identified human acinar cells as the source of Ngn3- and insulin-expressing cells.

Our data provide evidence that exocrine cells from human pancreas can be reprogrammed to beta-like cells. Given the large number of exocrine cells, this approach may present a novel strategy to improve cell therapy in type 1 diabetes.

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292-LB

In Vitro Direct Reprogramming of Sox9 Positive Progenitor Cells of the Human Bile Duct towards a Beta-Cell Fate: Progress towards Making Beta Cells for Autologous Cell Therapy in Type 1 Diabetic Patients

ANANNYA BANGA, JAMES R. DUTTON, *Minneapolis, MN*

We have previously demonstrated that the gene combination Pdx1, Ngn3 and MafA separated by 2A peptide sequences using an adenoviral vector (Ad-PNM), can uniquely reprogram a cell population in the mouse liver into insulin secreting ducts and persistently restore glucose homeostasis in diabetic mice. We identified the reprogrammed progenitor population as SOX9- expressing cells residing in the mouse intra-hepatic biliary tract. SOX9 positive cells serve as progenitor cells in mammalian intestine, pancreas and liver and our in vivo rodent reprograming experiments suggest they may provide a suitable target cell population for in-vitro reprogramming to generate beta cells for human cell replacement therapy.

Immunohistochemistry analysis of human liver sections revealed SOX9 expressing cells in the bile ducts form a distinct population of epithelial cells, also expressing ECAD and EpCAM, a putative marker for liver stem cells. When isolated from digested patient liver samples, the bile duct epithelial cells formed aggregated clusters upon culturing in low attachment plates. Subsequent plating on adherent dishes with or without collagen allowed the bile duct cell aggregates to attach and be separated from residual hepatocytes and red blood cells. When infected with Ad-PNM in vitro, the aggregates were seen to express insulin three days after infection along with expression of other beta cell markers. We are now investigating the extent of reprograming towards a beta cell phenotype with respect to normal human islets.

Thus, SOX9 positive cells from human bile ducts provide a new approach for direct, in vitro reprogramming for making beta cells and holds enormous possibilities for generating autologous human beta cells for transplantation therapy, thereby overcoming the constraints of using ES or iPS cells.

Supported By: NIH

293-LB

Exposure to Exendin-4 In Utero Results in Diabetes

KRISHNA PRASADAN, ILJANA GAFFAR, JOHN WIERSCH, XIANGWEI XIAO, CHIYO SHIOTA, PING GUO, GEORGE K. GITTES, *Pittsburgh, PA*

The long-acting glucagon-like peptide 1 (GLP-1) agonist, exendin-4, has insulinotrophic properties in vitro. Previous studies have demonstrated that postnatal injections of exendin-4 into mice with intrauterine growth retardation, a model of type 2 diabetes, prevented the development of adult hepatic insulin resistance. There is, however, little data concerning the effects of gestational exendin-4 exposure on the postnatal mouse. Our preliminary data show that exendin-4 injection in utero at gestational day 12 or gestational day 15 using an ultrasound guided micro injection system induced precocious endocrine development evidenced by increased beta-cell proliferation and islet hyperplasia in the neonatal pancreata of wild type mice. However, expansion of endocrine cells was severely impaired in exendin-4 treated embryos by postnatal day 8. Subsequently, embryos exposed to exendin-4 in utero developed diabetes by 8 weeks of age. We found that the severity of the diabetic phenotype is dependent on the age of in utero exposure to exendin-4. Despite an enhanced early endocrine differentiation in the neonatal pancreas following in utero exendin-4 treatment, we saw a blunted postnatal endocrine proliferation and the development of insulin resistance which resulted in diabetes in the adult mice.

294-LB

A New Method to Mark Live Proliferating Human Pancreatic β-Cells

ILANA R. POLLACK, KAREN TAKANE, JOSE FRANCISCO LOPEZ ACOSTA, RAFAEL FENUTRIA, NAGESHA GUTHALU, ADOLFO GARCIA-OCANA, RUPANGI VASAVADA, *New York, NY*

A critical goal in the treatment of diabetes is to find ways to induce proliferation in adult human β-cells. Understanding the molecular differences between proliferating β-cells and their senescent counterparts is essential to finding ways to stimulate β-cell proliferation. To do this, it is key to be able to mark, sort and isolate live proliferating β-cells for molecular analysis. Toward this end, we have developed an adenoviral vector (Ad-PrIf) that can simultaneously mark live cells that are insulin-producing and dividing. The vector contains fluorescent reporters, ZsGreen1 downstream of a rat insulin promoter, and mCherry downstream of a cell division cycle protein 2 (cdc2) homolog promoter. Live cell imaging in mouse and human islet cells transduced with Ad-PrIf shows ZsGreen1 expression 48h post-infection. Costaining of fixed cells for insulin and Zgreen1 demonstrates that ZsGreen1 expression is specific to insulin-producing cells. We have previously shown that Ad-CyclinE/cdk2 induces human β-cell proliferation. Human islet cell cultures co-infected

with Ad-PrIf and Ad-CyclinE/cdk2 have increased number of mCherry-positive cells by 72h relative to Ad-PrIf and Ad-LacZ co-infected cells. Together, this suggests that the cdc2 promoter driving mCherry in Ad-PrIf, is activated in dividing human islet cells. This is confirmed by colocalization of mCherry and phospho-histone H3, an endogenous proliferation marker, by immunostaining of fixed cells. Thus, Ad-PrIf vector can mark live proliferating human pancreatic β-cells in vitro. This vector is currently being modified by adding a Cre-lox component in order to permanently mark proliferating β-cells, allowing us to determine if an increase in human β-cell proliferation actually results in an increase in cell number.

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295-LB

Exendin-4 Enhances Endocrine Differentiation and Redirects Acinar Progenitors to an Endocrine Fate

ILJANA GAFFAR, KRISHNA PRASADAN, JOHN WIERSCH, XIANGWEI XIAO, CHIYO SHIOTA, PING GUO, FARZAD ESNI, GEORGE K. GITTES, *Pittsburgh, PA*

While insulinotropic peptides, such as glucagon-like peptide-1 (GLP-1), have been shown to increase PDX1 expression in pancreas cells in mice and enhance endocrine differentiation of human islet-like cell clusters in vitro, little is known about its effect in vivo on the developing pancreas. To further investigate the effect of GLP-1 in the mouse embryo, we injected exendin-4 (Ex-4), a long-acting GLP-1 analog, into the amniotic fluid at embryonic day 12 or 15 using an ultrasound-guided microinjection system. On embryonic day 17 or on the day of birth, the pancreas was harvested. Immunohistochemical staining revealed a significantly increased endocrine cell area in the treated embryos. Proliferation studies using BrdU showed an increase in the number of dividing cells in treated embryos. Next, to identify the genes associated with the expansion of endocrine cells, we isolated and sorted lineage tagged insulin-positive cells from embryonic day 18 MIP-GFP embryos after receiving exendin-4 in utero. Real-time PCR analysis showed an enhanced expression of several genes including cyclin D1, cyclin D2, SMAD7 and GCGR.

Concurrent with the expansion of endocrine cells, we saw a decrease in the acinar cell population in Ex-4 treated embryos. To determine if the increase in endocrine cells was at the expense of acinar progenitors, we lineage tagged early acinar progenitor cells using a tomato reporter mouse crossed with a cre-recombinase driven by the Mist1 promoter mouse. Based on our labeling efficiency, up to 24% of endocrine cells may have derived from progenitor cells previously directed towards an acinar fate.

In this study, we demonstrate the expansion of endocrine cells in the embryonic mouse pancreas after in utero Ex-4 treatment. While some of the expansion is due to increased proliferation of endocrine cells and their progenitors, a proportion of endocrine cells are derived from progenitors previously directed towards acinar differentiation.

296-LB

Determining whether Rodent β Cell Mitogens Also Stimulate Human β Cell Proliferation

KRISTIE I. AAMODT, JUDY BROWN, RADHIKA ARAMANDLA, NATHALIE FIASCHI-TAESCH, ANDREW F. STEWART, MARCELA BRISSOVA, ALVIN C. POWERS, *Nashville, TN, New York, NY*

Numerous compounds stimulate rodent β cell proliferation; however, translating these findings to human β cells remains a challenge. To examine human β cell proliferation in response to such compounds, we developed an *in vitro* medium-throughput, semi-automated method of quantifying human β cell proliferation using normal human islets. Dispersed human islets were plated onto collagen-coated 384-well plates, treated for 72 hours with compounds reported to stimulate rodent β cell proliferation, then fixed and labeled directly in the well for the β cell markers insulin and Pdx1, and the proliferation marker Ki67. Imaging was automated using a Leica fluorescence microscope and the LAS AF MATRIX M3 Developer Suite to obtain a single image for each well encompassing the entire area of the well at 20x magnification. Images were analyzed using Imaris 7.6 software with spots and surfaces functions, and this quantification procedure was validated by comparing it against results from manual cell counts (CV<10%). Transduction of dispersed human islet cells with a combination of adenoviruses encoding cyclin D3 or cdk6 was used as a positive control to ensure that the human β cells were capable of entering the cell cycle. All human islets had a robust insulin secretory response to glucose using a dynamic cell perifusion system. Human islet cells from three donors (average age = 50 years, range 40-57; average BMI = 32.9, range 25.4-37.9) were treated with prolactin, platelet-derived growth factor A, GABA, or serotonin at physiologic (5mM) and high (11mM) glucose levels and 1300-11,000 β cells were counted per treatment per donor. Cells transduced with cyclin D3 and cdk6 viruses had increased Ki67+ β cells (14%) compared to baseline levels (0.20%). However, none of these compounds increased Ki67+ β cells at either physiologic or high glucose. This method will allow testing of potential mitogens on human β cell proliferation.

297-LB

Endocrine Progenitor Cells in the Adult Human Pancreas

DANIELLE GOMEZ, MICHAEL SHAMBLOTT, MARCI O'DRISCOLL, *Tampa, FL*

Type 1 diabetes (T1D) is caused by autoimmune destruction of pancreatic β cells. Understanding the regulatory mechanisms controlling pancreatic endocrine differentiation has far reaching implications for treatment of T1D. A balance between endocrine progenitor cell recruitment, maintenance and differentiation result in islet mass sufficient to maintain normal glucose levels. One approach to cell-based treatment of T1D is to expand the endocrine progenitor cell pool in the pancreas then direct their development towards β cell fate. This requires a thorough understanding of the mechanisms that restrict progenitor cells from adopting a mature endocrine cell fate under normal circumstances, yet allow recruitment and islet regeneration when necessary. The identification and characterization of endocrine progenitor cells in the adult pancreas is essential.

Neurogenin 3 (NGN3) is necessary and sufficient for endocrine differentiation during murine pancreatic development. Approximately 2-10% of cells in normal adult pancreas express NGN3. Expression of NGN3 and NEUROD1, a proximal target of NGN3, increases following culture. The percentage of NGN3+ cells can be increased by pharmacologic inhibition of Notch signaling and inhibition of proteasome degradation. Viable NGN3+ cells can be isolated from human exocrine tissue using the cell surface marker CD133. In suspension culture, a subpopulation of CD133+ cells undergoes clonal proliferation and forms spherical aggregates containing cells that coexpress insulin C-peptide (CPEP), chromogranin A (CgA) and pancreatic and duodenal homeobox 1 (PDX1), as well as cells coexpressing glucagon and CgA. When CD133+ cells are cultured in hydrogel and nanofiber scaffolds, the percentage of CPEP-expressing cells increases >100-fold, compared to suspension culture, and release CPEP in a glucose-responsive manner. CD133+/NGN3+ cells from adult human pancreatic tissue recapitulate aspects of endocrine development and may offer an innovative therapy for the treatment of T1D.

298-LB

Type 1 and Type 2 Diabetes: Long-Lost Relatives

JOON HA, ARTHUR SHERMAN, *Bethesda, MD*

It is widely, though not universally, believed that type 2 diabetes (T2D) results from failure to compensate adequately for insulin resistance. We have previously developed a mathematical model for a rodent model of diet-induced diabetes, the female Zucker Diabetic Fatty rat, in which compensation depends on glucose- and secretion workload-dependent increases in beta-cell mass and function (Ha et al, Diabetes 62(Suppl. 1):A557 2013). We now explore whether the same model structure, with quantitative adjustments, applies to human diabetes. We find that accounting for increased body mass and blood volume (300-fold) and slowed responses of mass (100-fold for adults) and function (25-fold) is sufficient to reproduce human trajectories of T2D. As for the rodents, the model shows that insulin resistance leads to T2D only if there are pre-existing, otherwise silent, defects in mass or function. We also incorporate data from the literature on rates of beta-cell replication in children from infancy to age 20 and apply it to the onset of type 1 diabetes (T1D). We find that progression to T1D is slows with age in parallel with the slowing of replication rate, implying that slow replication is actually protective. This is possible because cell death rate also slows. The model also naturally simulates the honeymoon period of 6 - 9 months when insulin therapy is introduced shortly after crossing the diabetic threshold. The improvement is due to enhanced beta-cell function but is short-lived because mass continues to decline. Honeymoon duration also increases with age due to slowing of replication. In summary we find that T1D and T2D, despite many critical differences in the environment faced by the beta cells, share a common core of beta-cell biology.

299-LB

Uncovering Conserved Beta-Cell Transcriptome of Type 2 Diabetes by Meta-analysis of Microarray Data

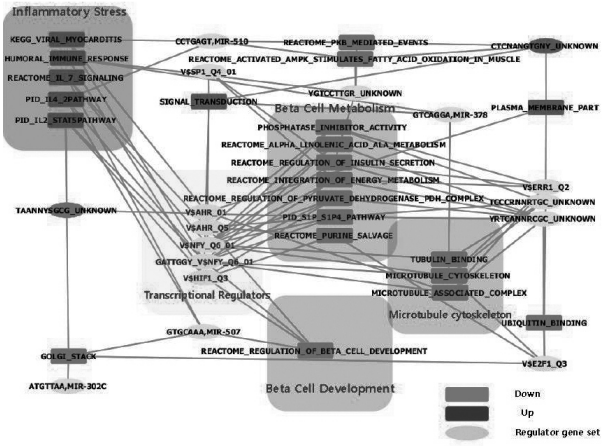
JUNG HUN OHN, DAEHEE HWANG, EUN-GYOUNG HONG, *Chuncheon, Republic of Korea, Daegu, Republic of Korea*

Pancreatic beta cell dysfunction is an early manifestation during progression to diabetes. Transcriptional profiling studies of beta cells from subjects with diabetes have revealed various genes or pathways of beta cell dysfunction. We aimed to uncover conserved beta cell transcriptional signature in diabetes by meta-analyzing microarray datasets and find regulators.

Microarray data of three independent transcriptional profiling studies of beta cells from diabetes patients (GSE20966, GSE25724, and GSE38642)

were obtained from the public database, Gene Expression Omnibus (GEO). Integrative meta-analysis was performed to extract consistently altered gene sets out of the 10,294 curated mSigDB gene sets.

Cytokine metabolism and immunologic response pathways were up-regulated, while beta cell development, energy metabolism, and microtubule associated gene sets were down-regulated consistently in all three datasets. Analysis of the network topology of transcription factor target gene sets and biological pathway/gene ontology gene sets suggests that HIF1A, aryl hydrocarbon receptor, and Nuclear Factor Y may be core regulators that account for repressed beta cell development and metabolism of diabetes patients exposed to chronic metabolic and inflammatory stress (figure).



300-LB

Characterization and Isolation of Embryo Stem Cell-like Cells in Adult Human Pancreas

SONG LEE, SONG-CHEOL KIM, SEONGHEE JEONG, HANA PARK, *Seoul, Republic of Korea*

For diabetes treatment, many scientists have been researching regeneration or differentiation to insulin-producing cells using stem/progenitor cells. However, the stem/progenitor cells are extremely rare existence and stem cell expressing location is not yet clearly demonstrated in human pancreatic tissue. Therefore we have identified embryo stem cell-like cells derived from adult human pancreas.

Enriched human exocrine cells are obtained after COBE purification of islet isolation. For islet-depleted pancreatic exocrine cells culture, endocrine cells were sorted out with PSA-NCAM antibody using magnetic-activated cell sorting and purified CA19-9 positive pancreatic ductal cells or non-purified cells were cultured for 6 days. We observed morphology changes and RNA expression pattern of embryo stem cell markers. Non-purified crud duct cells attached easily and epithelial-like cells extended grow up quickly from primary attached cells but purified ductal cells were showed insufficient growth. Expression of classic stem cell markers: Oct4, c-Myc, Klf4, Nanog, Sox2 and SSEA4 mRNAs was found in crude duct and purified duct cell fraction. However, these stem cell markers was not detected or weakly expressed in PSA-NCAM negative and CA19-9 negative cell fraction. To identification of stem cells present location, we SSEA4 positive cell selected from enriched exocrine cell fraction. Classic stem cell mRNA markers were only expressed in SSEA4 positive cells and SSEA4 positive cells was detected in pancreatic duct cell by immunocytochemistry. We characterized and isolated of SSEA4 positive embryo stem cell-like cells in pancreatic duct and hypothesize that these cells differentiate to insulin- producing cells in adult human pancreas.

ISLET BIOLOGY—BETA CELL—STIMULUS-SECRETION COUPLING AND METABOLISM

301-LB

The Furan Fatty Acid Metabolite CMPF Is Elevated in Diabetes and Induces β-Cell Dysfunction

KACEY J. PRENTICE, LEMIEUX LUU, EMMA M. ALLISTER, YING LIU, LUCY S. JUN, KYLE W. SLOOP, ALEXANDRE B. HARDY, LI WEI, WEIPING JIA, I. GEORGE FANTUS, DOUGLAS H. SWEET, GARY SWEENEY, RAVI RETNAKARAN, FEIHAN F. DAI, MICHAEL B. WHEELER, *Toronto, ON, Canada, Indianapolis, IN, Shanghai, China, Richmond, VA*

Both gestational (GDM) and type 2 diabetes (T2D) result from failure of the β cells to adapt to increased metabolic demands, however, the cause of GDM and the extremely high rate of progression to type-2 diabetes remain unknown. Using global metabolomics profiling, we show that the furan fatty acid metabolite 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) is elevated in the plasma of humans with GDM, as well as impaired glucose tolerant and T2D patients. In mice, diabetic levels of plasma CMPF induced glucose intolerance, impaired glucose-stimulated insulin secretion, and decreased glucose utilization. Mechanistically, we show that CMPF acts directly on the β cell and is metabolized to cause impaired mitochondrial function, decreased glucose-induced ATP accumulation, and induction of oxidative stress. Elevated reactive oxygen species levels resulted in dysregulation of key transcription factors PDX1 and FOXO1, and ultimately reduced insulin biosynthesis. Treatment with the antioxidant N-acetylcysteine prevented the CMPF-induced effects. Further, we determined that CMPF enters the β cell through organic anion transporter 3 (OAT3), and that pharmacological or genetic impairment of this transporter was also able to prevent CMPF-induced β cell dysfunction. Thus, CMPF provides a link between β cell dysfunction and GDM/T2D that could be targeted therapeutically.

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302-LB

Loss of Responsive Beta Cells Is the Major Secretory Deficit in the db/db Animal Model of Type 2 Diabetes

OANH H. DO, PETER THORN, *Brisbane, Australia*

It is now understood that a reduction in insulin secretion is an important characteristic of type 2 diabetes. However, the nature of this secretory defect remains unclear. Here, we have developed a 2-photon assay to measure individual insulin granule fusion events from cells within intact islets. In response to 15mmol/l glucose, db/db islets secreted ~77% less insulin compared to +/+ islets. Consistent with previous findings, the db/db islets had slower and smaller calcium responses to glucose and a decrease in syntaxin 1A expression. Finally, the calcium ionophore, ionomycin induced insulin secretion in +/+ islets but not in db/db, showing there is a defect in granule fusion. Consistent with the reduced glucose-induced insulin secretion, our 2-photon assay showed an ~80% reduction in exocytic fusion events. Image analysis determined that this overall loss of insulin granule fusion was described by a 73% loss of responding cells and a 50% decline in exocytic events in the remaining, responsive cells. Our assay also measured granule lifetime and post-fusion fluorescence intensity, and found no significant differences in responses between db/db and +/+ islets. However, in a modification of the assay, pH sensitive dye was used to identify kiss-and-run exocytic events and showed that in the remaining db/db exocytic responses, there was a higher proportion of kiss-and-run exocytosis compared to +/+ islets (11.6% vs. 6.6%, $p<0.05$). This change in the behavior of a very small number of granule fusion events is interesting but the predominant characteristic of the db/db islets is the loss of full fusion. We conclude that the major cause of the reduction of insulin secretion in db/db islets is the loss of responding beta cells.

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303-LB

Investigating Intra-islet Interactions between Pancreatic Cells

MARGARET WATTS, OFER KIMCHI, ARTHUR SHERMAN, *Bethesda, MD, Princeton, NJ*

Secretion of the pancreatic hormones insulin, glucagon, and somatostatin depends on both intrinsic responses from each cell type and modulation by paracrine secretion from the other cell types. We have combined existing mathematical models for electrical activity in response to glucose of alpha- and beta-cells with a new model for delta-cells to create an islet model with secretion of the three hormones into the interstitial space. As a first test, we reproduce the pulsatile secretion of glucagon, which is anti-synchronous with insulin, and somatostatin, which is synchronous with insulin (Hellman et al. Endocrinology 150(12):5534) in high glucose (20 mM). As widely accepted, we assumed that insulin inhibits glucagon secretion in alpha-cells while somatostatin inhibits both insulin and glucagon secretion. We assume that somatostatin acts on both alpha- and beta-cells by activating GIRK channels, and that insulin activates K(ATP) channels in alpha-cells. The model indicates that, in order to synchronize beta- and delta-cells, somatostatin secretion must be stimulated by beta-cells, possibly mediated by GABA. The paracrine effects of insulin, direct and through somatostatin, play a key role in taming the heterogeneity of the alpha- and delta-cells, notably suppressing any alpha-cells that inappropriately secrete glucagon. The model reproduces the glucose dependence of glucagon and somatostatin secretion, with or without inhibitors of K(ATP) channels and SERCA pumps (Vieira et al. Diabetologia 50(2):370). It is consistent with the effects of somatostatin knockout mice (Cheng-Xue et al. Diabetes 62(5):1612) and confirms that, while somatostatin lowers the tone of insulin and glucagon secretion, it does not determine the response to glucose.

Finally, if insulin secretion is reduced to simulate diabetic islets, then glucagon oscillations are lost and glucagon secretion is increased. This may explain the hyperglucagonemia that exacerbates the hyperglycemia of diabetes.

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304-LB

Identification of Zinc Transporters Responsible for Zinc Influx into β Cells

YING LIU, LOUISA HO, ALEXANDRE HARDY, MING ZHANG, ALPANA BHATTACHARJEE, FAY DAI, MICHAEL WHEELER, *Toronto, ON, Canada*

Zinc ions play an essential role in the regulation of pancreatic cellular functions, which include insulin synthesis, insulin secretion, anti-oxidative and anti-apoptotic processes, linked to both T1D and T2D. Our lab has previously shown the critical role of ZnT8, a member of zinc efflux transporter family, in insulin synthesis and secretion. However, very little is known regarding how zinc enters beta cells. We are the first to examine the zinc influx transporter (ZIP) transcriptome in pancreatic islets and show consistent high expression levels of ZIP6 and ZIP7 genes (Slc39a6 & Slc39a7) across human islets, mouse islets and MIN6 mouse pancreatic β cells. We also show that the cytosolic zinc content in pancreatic β cells is tightly associated with the expression levels of ZIP6 and ZIP7 under both basal and glucose stimulated conditions, confirming their important role in regulating cellular zinc homeostasis. Disrupted cellular zinc homeostasis, caused by down-regulation of ZIP6 and ZIP7 expression, impairs insulin secretion in response to both glucose and membrane depolarization, with no changes in total insulin content in MIN6 cells. More importantly, we also show interactions between ZIP6, ZIP7 and the GLP-1 receptor in MIN6 cells, and the disruption of this interaction diminishes GLP-1 enhanced glucose stimulated insulin secretion. And this insulin secretion impairment is related to zinc related oxidative stress and apoptosis. Our data suggests that ZIP6 and ZIP7 are two important zinc influx transporters in pancreatic β cells, and alterations in their expression levels may contribute to β cell dysfunction (insulin secretion) in diabetes via cellular zinc homeostasis and GLP-1's insulin secretagogue action.

305-LB

A Novel Pathway for Regulation of Insulin Secretion by Fractalkine and CX3CR1 System

YUN SOK LEE, HIDETAKA MORINAGA, JANE J. KIM, WILLIAM LAGAKOS, SUSAN TAYLOR, MALIK KESHWANI, GUY PERKINS, HUI DONG, AYSE G. KAYALI, IAN R. SWEET, JERROLD M. OLEFSKY, *La Jolla, CA, Seattle, WA*

Fractalkine (FKN) (CX3CL1) and its receptor CX3CR1 mediate cell-to-cell interactions in different tissues. Here, we demonstrate that the FKN/CX3CR1 system represents a novel regulatory mechanism for pancreatic islet beta cell function and insulin secretion. CX3CR1 KO mice exhibit glucose intolerance with normal insulin sensitivity, due to a marked beta cell defect in glucose and GLP1-stimulated insulin secretion. The defect in insulin secretion was also observed in vitro in isolated islets from CX3CR1 KO mice. In vivo administration of FKN improved glucose tolerance with an increase in insulin secretion. In vitro treatment of islets with FKN increased intracellular Ca2+ level and potentiated insulin secretion. The KO islets exhibited reduced expression of a set of genes which are necessary for the fully functional, differentiated beta cell state, whereas, treatment of WT islets with FKN leads to increased expression of these genes. Lastly, expression of FKN in islets was decreased by aging and HFD/obesity, suggesting that decreased fractalkine/CX3CR1 signaling could be a mechanism underlying beta cell dysfunction in type 2 diabetes.

306-LB

Beta Cells Respond to Hyperglycemia by Altering the Surface Expression of K(ATP) Channels

LESLIE S. SATIN, JOON HA, ERIC GLYNN, BENJAMIN M. THOMPSON, MATTHEW J. MERRINS, SURYAKIRAN VADREVU, ARTHUR SHERMAN, *Ann Arbor, MI, Bethesda, MD*

An open question in the etiology of type 2 diabetes is the relative importance of beta-cell mass and function in compensating for insulin resistance. In previous work (Ha et al, Diabetes 62(Suppl. 1):A557 2013) we proposed that functional adaptation precedes mass adaptation and predicted reduced K(ATP) channel surface expression in response to hyperglycemia. The purpose of this study was to test this hypothesis. We exposed mouse islets to high (11.1. mM) or low (2.8 mM) glucose overnight in vitro and then assayed glucose-dependent oscillations of cytosolic free calcium using fura-2 fluorescence and islet patch clamping to measure membrane potential. Chronic high glucose left-shifted the glucose thresholds of both calcium and electrical oscillations, whereas low glucose caused a right shift. To test whether these shifts were caused by reduced gKATP, we applied voltage ramps to beta cells within intact islets. The conductance changes observed reflected changes in K(ATP) surface expression, not ATP sensitivity, suggesting that adaptation is mediated by alterations in channel trafficking to the plasma membrane. Insulin secretion measured using static incubation was shifted in parallel with changes in calcium, electrical activity and gKATP. To test the involvement of insulin in the control of gKATP we co-applied the K(ATP) channel opener diazoxide (Dz) with 11 mM glucose overnight. Dz, which inhibits insulin secretion, caused a more profound left shift vs. 11 mM glucose alone, consistent with an effect of insulin to increase gKATP. This suggests that insulin inhibits its own secretion unless overruled by rises in glucose. To test whether AMPK might link channel trafficking and metabolism, we included the AMPK activator AICAR with high glucose/DZ overnight, and found this reduced the size of the left shift in islet glucose sensitivity. We conclude that beta cells have a novel mechanism for adaptation to varying metabolic challenges by altering the number of K(ATP) channels on the cell surface.

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307-LB

A Novel Pathway of Glucodetoxification in Pancreatic β-Cells Linked to Glycerol Release

YVES MUGABO, SHANGANG ZHAO, JOSE IGLESIAS, SARI GEZZAR, ANFAL ALMASS, DONGWEI ZHANG, JULIEN LAMONTAGNE, MARCO PINEDA, ERIK JOLY, MURTHY MADIRAJU, MARC PRENTKI, *Montreal, QC, Canada*

Chronic excess supply of glucose and fatty acids to β-cells can be toxic and lead to apoptosis and depletion of insulin stores. It is important to identify the detoxification mechanisms inherent in β-cells to escape fuel surfeit toxicity. We found that fuel detoxification in β-cells involves glycerolipid/ fatty acid cycle, storage of glucose and fatty acid carbons as triglycerides and glycogen and release of glucose-derived metabolites. During glucose metabolism, glycerol and fatty acids are thought to be released from the β-cell exclusively due to accelerated triglyceride lipolysis that is linked with insulin secretion as orlistat completely inhibits glucose stimulated insulin secretion (GSIS) and fatty acid release. We find that while GSIS response and glucose oxidation in rat islets reach plateau by 16 mmol/l glucose, glycerol release increases up to 25 mmol/l glucose and, paradoxically, is unaffected by orlistat above 10 mmol/l glucose. This revealed that at high glucose, glycerol is produced by mechanisms other than lipolysis. We found that β-cells harbor a specific glycerol-3-phosphatase (G3Pase) that participates in glycerol release from glucose-derived carbons, bypassing oxidation. The presence of a specific G3Pase in mammalian tissues was not known and our results show that this enzyme helps in glucodetoxification, protects β-cells from metabolic stress and influence GSIS. Thus overexpression of this enzyme increases glycerol release, reduces GSIS and protects INS832/13 β-cells from glucotoxicity while RNAi-knockdown has opposite effects. In conclusion, we have identified a novel enzyme that participates in β-cell glucodetoxification and GSIS by facilitating direct production of glycerol from glucose-derived glycerol-3-phosphate.

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308-LB

A Reliable and Sensitive Chemiluminiscent Enzyme Immunoassay to Accurately Measure C-peptide Levels in Human Samples

CHRIS WISHERD, JULIE MELITO, TIM MCKENDRY, COLLIN SHAW, STACY DION, JULIE DONALDSON, TAL MURTHY, MARTIN BLANKFARD, *Salem, NH*

Measurement of C-peptide, a 31 amino acid peptide, is being used to further understand diabetes mellitus, hypoglycemia and insulinoma. C-peptide is a byproduct formed in the process involving a series of enzymatic cleavages of preproinsulin and proinsulin, with proinsulin being the immediate precursor of insulin and C-peptide. C-peptide and insulin are known to be released in equimolar amounts from beta cells of pancreas. Since the half-life of C-peptide is about 30 minutes compared to insulin which is only about 3 minutes, measuring C-peptide may be more attractive for indirectly estimating glucose stimulated insulin secretion, understanding beta cell function and/or identifying beta cell functional mass. Furthermore, measurement of insulin and C-peptide together may provide valuable information for the evaluation of hypoglycemia and insulinoma. Lastly, the ability to quantify exogenous or xenotransplated human C-peptide without cross-reaction with endogenous c-peptide is of interest to many. Evidently, measuring C-peptide in serum samples requires a robust, sensitive and reliable assay with a broad dynamic range. In this study, we discuss the development and results of a chemiluminescent enzyme immunoassay to measure C-peptide in human samples. Our results indicate this new assay is capable of measuring <3 pg/mL (1pmol/L) while also offering a broad dynamic range of 3 to 9000 pg/mL, allowing the ability to measure TIDM hypoinsulinemic samples as well as TIIDM fed hyperinsulinemic samples in a single assay without the need for downstream dilution. Samples spiked with 3 levels of C-peptide recover at averages of 94%, 95% and 94% at the low,

mid and high spikes, respectively. Furthermore, we observed an inter and intra assay variation of <10% and minimal or no cross reactivity with human insulin/proinsulin and C-peptide from other species. The assay eliminates need for sample dilution, saves time and reagent cost, leads to potential savings for screening labs.

309-LB

Comparing Effects of Circulating Nonesterified Fatty Acids on Alpha and Beta Cell Responses Following Carbohydrate-rich, Mixed, and Fat-rich Liquid Meals between Normal Glucose Tolerant South Asians and Caucasians

RUPA AHLUWALIA, FILIP K. KNOP, TINA VILSBØLL, LAKSHMINARAYAN RANGANATH, JURIS J. MEIER, JITEN VORA, *Liverpool, United Kingdom, Hellerup, Denmark, Bochum, Germany*

Non-esterified fatty acids (NEFAs) stimulate endogenous insulin secretion along with mediating insulin resistance and pancreatic beta cell dysfunction. They are also known to influence postprandial incretin hormone responses. Raised fasting NEFA levels and impaired insulin-mediated plasma NEFA suppression during oral glucose tolerance test, are often seen in South Asians. Role of incretin hormones in NEFA dynamics coupled with insulin resistance in South Asians, is less well understood.

We aimed to compare fasting and postprandial levels of circulating NEFAs following meals of varying compositions, respectively, in normal glucose tolerant (NGT) South Asians and Caucasians.

Eleven NGT South Asian (5 women; mean±SEM age: 35±4 years; BMI: 24.7±1.0 kg/m^2; fasting plasma glucose (FPG): 4.7±0.2 mM) and 15 age, gender and BMI-matched Caucasians (8 women; age: 32±3 years; BMI: 25.1±1.0 kg/m^2; FPG: 4.6±0.1 mM) underwent three isocaloric liquid meals (~500 kcal) of varying compositions (carbohydrate-rich (CHO), mixed (MIX) and fat-rich (FAT)).

Both fasting NEFA and insulin levels were higher in South Asians vs. Caucasians (NEFA: 0.60±0.02 vs. o.47± 0.02 mM, p 0.003; Insulin: 11.02±0.9 vs.7.3±0.4 mU/l, p<0.0001) Insulin responses (area under the curve (AUC)) were higher in South Asians vs. Caucasians (CHO: 27,631±5901 vs. 10,352±900 mU/l×min, *P*<0.0001; MIX: 15,548±3295 vs. 8,064±873 mU/l×min, *P*=0.02; FAT: 7,228±1,092 vs. 4,027±438 mU/l ×min, *P*=0.006). Postprandial NEFA responses (AUC) were lower in South Asians vs. Caucasians (CHO: 3.8±1.5 vs. 5.5±2.1 mM×min, *P*=0.002; MIX: 7.5±1.5 vs. 10.0±1.5 mM×min, *P*=0.2; FAT: 18.64±2.1 vs. 20.53±2.2 mM×min, *P*=0.5).

NGT South Asians compared to Caucasians, demonstrate altered postprandial NEFA levels in the presence of higher insulin responses. Role of incretin hormones in these pertubations remain to be explored.

310-LB

Isolation and Identification of Mesenchymal Stem Cell–derived Adult Human Pancreas

SONG LEE, SEONGHEE JEONG, HANA PARK, SONG-CHEOL KIM, *Seoul, Republic of Korea*

Mesenchymal stem cells (MSCs), derived from bone marrow, adipose tissue and most connective tissues have been recognized as a promising source for cell therapy. MSCs have been detected in human pancreatic endocrine and exocrine tissue cultures, have resided in the pancreas and have been derived from chronic diabetes patients expressing c-peptide and insulin. These cells have generated a great deal of interest because of their potential uses in regenerative medicine and tissue engineering.

In this study, we isolated MSCs from adult human pancreas of partially pancreatectomized patients, whether isolated MSC-like cells from discarded pancreata after pancreatectomy may be able to use to stem cell based therapy. The pancreata was digested by collagenase using Ricordi chamer circulation system and obtained enriched exocrine fraction after COBE gradient. To remove the endocrine cells, enriched exocrine cell fraction incubated with microbead conjugated PSA-NCAM, endocrine cell surface marker, antibody for 1h at 4°C and sorted out using magnetic-activated cell sorting. Pancreatic duct cells also sorted with CA19-9 antibody in enriched exocrine fraction. Purified exocrine cells are cultured 6 days in RPMI 1640 media supplemented with 10% FBS. We observed growing cells morphological changes and analysis MSCs classic surface markers such as CD73, CD90, CD105 by Fluorescence-activated cell sorting. The MSCs-like morphological changes were detected in culture 4 day and all surface markers positive cells > 90% detected in culture 6 day.

These results indicate human adult pancreata is a new source of MSC might be affects therapy of patient with type 1 diabetes in clinical, because isolated MSCs from living donor is expected to extensive capacity to proliferation, self-renewal and differentiation into insulin producing cells.

ISLET BIOLOGY—SIGNAL TRANSDUCTION

311-LB

Activation of mTOR is Essential for Pancreatic Islet a cell Hyperplasia Induced by Glucagon Receptor Blockade

DAVID TSAO, TERRENCE PARK, MITSUKO LYNN YAMAMOTO, ERICK KINDT, TIM NICHOLS, ALISON FORGIE, JOHN LIN, *South San Francisco, CA, La Jolla, CA*

Glucagon signaling increases hepatic glucose output and leads to a rise in circulating glucose. Thus blocking the glucagon receptor (Gcgr) is beneficial in regulating glucose homeostasis in animal models of diabetes and also shows promising results in clinical trials for patients with type 2 diabetes. However, a consequence of blocking the glucagon receptor is islet α cell hyperplasia, which is a potential safety concern for the development of future treatments targeting this receptor pathway. The molecular and cellular mechanisms leading to this induced α cell phenotype remain unknown. Using mice on a high fat diet to induce diabetes, we show that a novel monoclonal antibody, which blocks the glucagon receptor, improves glucose homeostasis and leads to α cell hyperplasia. We also found that antibody treatment leads to a decrease in liver amino acid catabolism genes and an increase in plasma amino acid levels, similar to that seen in other models deficient in glucagon signaling. Since mTOR signaling is dependent on the availability of nutrients such as amino acids, and is involved in growth and proliferation, we measured mTOR activation in mice. We found that mTOR is hyper-activated in pancreatic islets compared to other tissues in antibody-treated mice. We then co-treated mice with the glucagon receptor blocking antibody and the mTOR inhibitor, rapamycin. Antibody-treated mice that were also dosed with rapamycin showed a significant decrease in α cell number compared to mice treated with antibody alone, and similar levels to non-treated mice, demonstrating α cell hyperplasia resulting from blocking glucagon signaling is dependent on mTOR activation.

312-LB

Beta-arrestin 2 Recruitment and Biased Agonism at the Free Fatty Acid Receptor GPR40

ARTURO MANCINI, GYSLAINE BERTRAND, ÉRIC CARPENTIER, JULIEN GHISLAIN, KEVIN VIVOT, MICHEL BOUVIER, VINCENT POITOUT, *Montreal, QC, Canada, Montpellier, France*

GPR40 is a G protein-coupled receptor (GPCR) for free fatty acids primarily expressed in pancreatic beta cells. Pharmacological activation of GPR40 is a potential strategy to increase insulin secretion in type 2 diabetes (T2D). Yet, current knowledge of GPR40 pharmacology remains limited. GPR40 mainly signals via the heterotrimeric G protein Gq/11. However, it is now evident that GPCRs can also engage functionally distinct G protein-independent signaling via beta-arrestins (bArr) 1 and 2. Further, G protein- and bArr-based signaling can be differentially modulated by different ligands, thus eliciting ligand-specific responses ("biased agonism"). Whether GPR40 i) engages bArr-dependent signaling, and ii) is subject to biased agonism is not known. Using BRET-based biosensors for real-time monitoring of cell signaling in living cells, we detected a direct, ligand-induced GPR40:bArr2 interaction, with the synthetic GPR40 agonist TAK875 being 2.01 ± 0.18-fold more effective than palmitate (PA) in recruiting bArr2 (p<0.001, n=4-7). Conversely, TAK875 acts as a partial agonist of Gq/11-dependent GPR40 signaling (0.56 ± 0.06- and 0.47 ± 0.05-fold vs. PA for Gq/11 activation (p=0.012, n=3-4) and cytosolic [Ca2+] (p=0.0012, n=12-14), respectively). Importantly, TAK875-, but not PA-induced insulin secretion is attenuated in bArr2 -/- mouse islets (-31.3 ± 6.1% vs. WT; p<0.001, n=5-8), thus providing functional validation of our bArr2 biosensor data and establishing bArr2 as a novel mediator of GPR40 insulinotropic signaling. Taken together, these data reveal for the first time that in addition to coupling to Gq/11, GPR40 is functionally linked to a bArr2-mediated signaling axis. Further, our findings identify ligand-specific signaling signatures downstream of GPR40. These observations expose a level of previously unrecognized complexity for GPR40 signal transduction and may guide the development of pathway-selective GPR40 agonists showing improved clinical efficacy and safety in T2D.

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313-LB

Transforming Growth Factor β Signaling Molecules and Phosphorylated Mitogen-activated Protein Kinase Are Upregulated in Workload-Induced Islet Cell Proliferation

ILJANA GAFFAR, XIANGWEI XIAO, YOUSEF EL-GOHARY, JOHN WIERSCH, KRISHNA PRASADAN, CHIYO SHIOTA, PING GUO, GEORGE K. GITTES, *Pittsburgh, PA*

Increasing the insulin-producing β-cell mass could be a cure for diabetes. Rodent studies have shown that β-cell replication predominantly accounts for any β-cell mass increase, however, the underlying molecular basis for this replication remains to be elucidated. Transforming Growth Factor β (TGFβ) superfamily signaling pathways are essential for proper pancreas development, and also affect β-cell replication and function. When a TGFβ ligand binds to the TGFβ type II receptor, the downstream effects result in the formation of a SMAD2, SMAD3, and SMAD4 complex, the nuclear translocation of which regulates target gene transcription. Additionally, SMAD7 can inhibit TGFβ superfamily signaling.

We performed partial pancreatectomy (PPX), to induce β-cell proliferation, or sham-operation on wild-type and β-cell specific SMAD2 knock-out (SMAD2β) mice. BrdU drinking water was provided to the mice immediately after the procedure to label proliferating cells. Islets were isolated for western blotting and quantitative PCR.

We found a significant increase in SMAD7 levels and a modest increase in SMAD2 levels in islets after PPX, suggesting an attenuation of TGFβ signaling. β-cell proliferation increased more in SMAD2β mice than in wild-type mice after PPX, suggesting that further downregulation of TGFβ signaling may increase β-cell replication. The levels of TGFβ receptors and TGFβ ligands in islet cells were unchanged after PPX, suggesting that the changes in SMADs/TGFβ signaling after PPX may be transduced through non-TGFβ ligands. We saw an upregulation of epidermal growth factor receptor and phosphorylated mitogen-activated protein kinase suggesting a role for this pathway in islet proliferation.

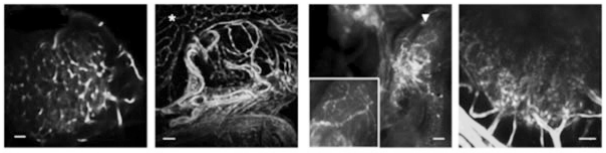
Our data highlights an important role of TGFβ signaling plays in pancreatic islet proliferation after PPX, and that islet cell proliferation is coordinated by the interplay of different signaling pathways.

314-LB

Promoting Beta-Cell Regeneration in Vascularized Tissue

JENNIFER B. MOSS, LARRY G. MOSS, *Durham, NC*

Deficits of human islets for research and transplantation create a need for engineered tissues that will recapitulate complex *in vivo* environments. The development of vascularized islet models would advance efforts to discover therapeutics required for alleviating diabetes. After a conditional beta cell knockout, the regenerating zebrafish pancreas is capable of restoring beta cell growth and function within two weeks (Figure: GFP+ vasculature and mCherry+ beta cells in adult zebrafish imaged at regeneration days 0, 3, 7 and 14). Using this facile model for probing signaling pathways important for beta cell regrowth and function, a small molecule inhibitor of the PTEN pathway has been found to enhance beta cell regeneration and partially rescue mTOR activity. To translate these findings into a vascularized tissue culture model, engineered human islet hydrogels that promote beta cell expansion along blood vessels generated *in vitro* are being screened for small molecule inducers of beta cell proliferation to simulate genuine physiological endpoints.



315-LB

Effect of High Glucose and High Fat on β Cell Proliferation and Cell Death in Type 2 Diabetes

RICHA AGGARWAL, NI ZENG, BANGYAN STILES, *Los Angeles, CA*

Pancreatic β cells, which are insulin producing cells localized in the islets of Langerhans, are responsible for maintaining glucose homeostasis and thus play an important role in diabetes therapy. Type II diabetic patients usually have high levels of glucose and free fatty acids (FFAs) and exhibit reduced β cell mass. Previous studies have indicated that both glucose and FFAs can have either pro- or anti-proliferative effects on β cells depending upon the exposure time, but the underlying molecular mechanisms remain unclear. The objective of my study is to understand how FFAs influence islet mass under both short-term and long-term exposure. My preliminary data indicates increased islet mass and β cell proliferation in mice fed with high fat diet (HFD) for 14 days (short-term treatment). Islets isolated from these mice show increased expression of cell cycle regulator Cyclin D1 and decreased protein levels of cell cycle inhibitor p16, suggesting that these two factors may mediate the pro-proliferating effects of short-term high fat diet. Consistent with that, in a β cell line cultured in vitro, Cyclin D1 was up-regulated and p16 down-regulated upon short-term palmitic acid exposure, further confirming the important roles of cell cycle regulators in β cells' response to FFA. Together, my results show that short-term exposure of β cells to FFAs causes increase in both islet mass and β cell proliferation through cell cycle regulatory protein such as Cyclin D1 and p16.

ISLET BIOLOGY—SIGNAL TRANSDUCTION

316-LB

PERK EIF2a Kinase Regulates ER Chaperones to Control the Balance between Proinsulin Secretion and Degradation in Pancreatic Beta Cells

CARRIE R. LEWIS, RONG WANG, BARBARA C. MCGRATH, DOUGLAS R. CAVENER, *University Park, PA*

PERK (EIF2AK3) deficiency results in permanent neonatal diabetes in humans and mice. The most striking cellular abnormality in PERK deficiency is a massive accumulation of proinsulin in the endoplasmic reticulum (ER) of the pancreatic beta cells, which we denoted as Impacted ER phenotype. Two hypotheses have been proposed to explain the Impacted ER phenotype: derepression of protein synthesis leading to over-synthesis of proinsulin versus failure to regulate proinsulin quality control and trafficking. We have disproven the protein synthesis derepression hypothesis by showing that the Impacted ER phenotype persists even when protein synthesis is partially repressed by treatment with a low dosage of the protein synthesis inhibitor anisomycin. We now have new evidence to support the hypothesis that PERK controls the balance between anterograde trafficking leading to secretion and ER-associated degradation (ERAD). The loss of this control results in the Impacted ER phenotype. PERK apparently mediates this control of ER functions by regulating the expression of ER chaperones including ERp72 and GRP78/BiP. To test the hypothesis that the balance between anterograde trafficking and degradation is determined by the balance of ER chaperones, we have manipulated the expression levels of the ER chaperones to assess how this impacts the fate of proinsulin along the secretory pathway in normal beta cells and contributes to the Impacted ER phenotype in PERK-depleted cells. We speculate that PERK functions to modulate proinsulin quality control and trafficking in response to metabolic demand for insulin, which is communicated to beta cells by glucose and other insulin secretagogues.

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ABSTRACT AUTHOR INDEX

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Aillon, Daniel V.	*Employee*: Pinnacle Technology.
Akhan, Muharrem	Disclosed no conflict of interest.
Aksenova, Marina G.	Disclosed no conflict of interest.
Al-Barazanji, Kamal A.	Disclosed no conflict of interest.
Allister, Emma M.	Disclosed no conflict of interest.
Alluis, Bertrand	*Employee*: Adocia; *Stock/Shareholder*: Adocia.
Almaca, Joana	Disclosed no conflict of interest.
Al-Mass, Anfal	Disclosed no conflict of interest.
Alsina-Fernandez, Jorge	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Altintas, Mehmet M.	Disclosed no conflict of interest.
Ambrosi, Thomas	Disclosed no conflict of interest.
An, Ding	*Employee*: Ember Therapeutics; *Stock/Shareholder*: Ember Therapeutics.
An, JaeJin	Disclosed no conflict of interest.
An, Jee Hyun	Disclosed no conflict of interest.
Anandh Babu, Pon Velayutham	Disclosed no conflict of interest.
An-Chang, Cheng	Disclosed no conflict of interest.
Andama, Benjamin	Disclosed no conflict of interest.
Andersen, Grit	Disclosed no conflict of interest.
Andersen, Henning	*Employee*: Novo Nordisk A/S; *Stock/Shareholder*: Novo Nordisk A/S.
Andersen, Henrik Ullits	*Employee*: Novo Nordisk A/S.
Anderson, Stacey	*Consultant*: Senseonics; *Research Support*: Dexcom, Inc., Medtronic, Roche Pharmaceuticals.
Andrew, Toby	Disclosed no conflict of interest.
Andrews, Steve	Disclosed no conflict of interest.
Ang, Wei	Disclosed no conflict of interest.
Anjum, B.	Disclosed no conflict of interest.
Annabi, Firas A.	Disclosed no conflict of interest.
Antoun, Joseph	Disclosed no conflict of interest.
Anzaldo-Campos, Maria Cecilia	Disclosed no conflict of interest.
Aouadi, Myriam	Disclosed no conflict of interest.
Araki, Atsushi	*Advisory Panel*: Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company; *Research Support*: Diaichi Sankyo, Takeda Pharmaceutical Company, Ltd.
Araki, Eiichi	Disclosed no conflict of interest.
Aramandla, Radhika	Disclosed no conflict of interest.
Araneta, Maria Rosario G.	Disclosed no conflict of interest.
Arbit, Ehud	*Consultant*: Oramed Pharmaceuticals.
Aronson, Ronnie	*Advisory Panel*: Medtronic; *Consultant*: Eli Lilly and Company, Medtronic, Novo Nordisk A/S, Sanofi; *Research Support*: Medtronic.
Arosemena, Leopoldo	Disclosed no conflict of interest.
Arslan, Erol	Disclosed no conflict of interest.
Arthurs, Blake	Disclosed no conflict of interest.
Atabai, Kamran	Disclosed no conflict of interest.
Atisso, Charles	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Attané, Camille	Disclosed no conflict of interest.
Ba-Essa, Ebtesam M.	Disclosed no conflict of interest.
Baba, Mendel	Disclosed no conflict of interest.
Bachovin, William	Disclosed no conflict of interest.
Bachstetter, Adam	Disclosed no conflict of interest.
Baeyens, Luc	Disclosed no conflict of interest.
Bahler, Lonneke	Disclosed no conflict of interest.
Bahn, Gideon	Disclosed no conflict of interest.
Bai, Juli	Disclosed no conflict of interest.
Bai, Yang	Disclosed no conflict of interest.
Baik, Sei Hyun	Disclosed no conflict of interest.
Bailey, Timothy S.	Disclosed no conflict of interest.
Bajaj, Mandeep	*Consultant*: Genentech; *Research Support*: Amylin Pharmaceuticals, Inc., AstraZeneca/Bristol-Meyers Squibb, Boehringer Ingelheim Pharmaceuticals, Inc.; *Speaker's Bureau*: Sanofi, Takeda Pharmaceuticals U.S.A., Inc.
Bakke, Siril S.	Disclosed no conflict of interest.
Ballesteros, Juana	Disclosed no conflict of interest.
Balo, Andy	Disclosed no conflict of interest.
Balta, Sevket	Disclosed no conflict of interest.
Banga, Anannya	Disclosed no conflict of interest.
Banks, Phillip	*Employee*: Lexicon Pharmaceuticals, Inc.; *Stock/Shareholder*: Lexicon Pharmaceuticals, Inc.
Baran-Gale, Jeanette	Disclosed no conflict of interest.
Barclay, Alan	*Research Support*: Roche Diagnostics Australia Pty Ltd.
Barlow, Gillian M.	Disclosed no conflict of interest.
Baron, Michelle	*Employee*: Intarcia Therapeutics.
Barquiel, Beatriz	Disclosed no conflict of interest.
Barret, Brian S.	*Employee*: Pinnacle Technology.
Barrett, Amy	Disclosed no conflict of interest.
Basu, Ananda	Disclosed no conflict of interest.
Basu, Rita	Disclosed no conflict of interest.
Baumeier, Christian	Disclosed no conflict of interest.
Beam, Craig	Disclosed no conflict of interest.
Beaulieu, Marie-Dominique	Disclosed no conflict of interest.
Becker, Thomas C.	Disclosed no conflict of interest.
Bedini, Jose Luis	Disclosed no conflict of interest.
Belton, Anne	*Advisory Panel*: Abbott Diabetes Care, Boehringer Ingelheim GmbH & Co. KG, Sanofi on programs for the International Diabetes Federation; *Consultant*: Lifescan Canada.
Bena, James F.	Disclosed no conflict of interest.
Benard, Nathalie	*Employee*: Merck Sharp & Dohme Limited.
Benatti, Rafaela O.	Disclosed no conflict of interest.
Bendahan, David	Disclosed no conflict of interest.
Benedini, Stefano	Disclosed no conflict of interest.
Benware, Sheila	*Employee*: Pacific Diabetes Technologies, Inc.
Bergenstal, Richard M.	*Advisory Panel*: Abbott Diabetes Care, Amylin Pharmaceuticals, Inc., Bayer Health Care, LLC, Becton, Dickinson and Company, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb/AstraZeneca, Calibra Medical, Inc., Dexcom, Inc., Eli Lilly and Company, Halozyme Therapeutics, Hygieia, Inc., Johnson & Johnson, Medtronic, Merck, Novo Nordisk Inc., Roche Pharmaceuticals, Sanofi, Takeda Pharmaceutical Company, Ltd.; *Research Support*: Abbott Diabetes Care, Amylin Pharmaceuticals, Inc., Bayer Health Care, LLC, Becton, Dickinson and Company, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb/AstraZeneca, Calibra Medical, Inc., Dexcom, Inc., Eli Lilly and Company, Halozyme Therapeutics, Hygieia, Inc., Johnson & Johnson, Medtronic, Merck, Novo Nordisk Inc., Roche Pharmaceuticals, Sanofi, Takeda Pharmaceutical Company, Ltd.
Berger, Matthew	Disclosed no conflict of interest.
Berglund, Eric D.	Disclosed no conflict of interest.
Bergman, Richard	Disclosed no conflict of interest.
Berkseth, Kathryn	Disclosed no conflict of interest.
Bersot, Ross	Disclosed no conflict of interest.
Bertrand, Gyslaine	Disclosed no conflict of interest.
Bevier, Wendy	Disclosed no conflict of interest.
Bezy, Olivier	Disclosed no conflict of interest.
Bhanot, Sanjay	*Employee*: Isis Pharmaceuticals; *Stock/Shareholder*: Isis Pharmaceuticals.
Bhatt, Deepak L.	*Research Support*: Amarin, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eisai, Inc., Ethicon,

AUTHOR	RELATIONSHIP/COMPANY
	Medtronic, Roche Pharmaceuticals, Sanofi, The Medicines Company.
Bhattacharjee, Alpana	Disclosed no conflict of interest.
Bhattacharyya, Sumit	Disclosed no conflict of interest.
Billimek, John	Disclosed no conflict of interest.
Birkenfeld, Andreas L.	Disclosed no conflict of interest.
Biryukova, Elena Alexandrovich	Disclosed no conflict of interest.
Blankfard, Martin	Disclosed no conflict of interest.
Blanner, Patrick	Disclosed no conflict of interest.
Blasi, Eileen	*Employee*: Pfizer, Inc.
Blenis, John	Disclosed no conflict of interest.
Blonde, Lawrence	*Consultant*: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eisai, Inc., GlaxoSmithKline, Janssen Pharmaceuticals, Merck, Novo Nordisk Inc., Quest Diagnostics, Sanofi; *Other Relationship*: AACE; *Research Support*: Eli Lilly and Company, Novo Nordisk Inc., Sanofi; *Speaker's Bureau*: Amylin Pharmaceuticals, Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Janssen Pharmaceuticals, Merck, Novo Nordisk Inc., Sanofi.
Blum, Janice	Disclosed no conflict of interest.
Blumer, Ian	*Advisory Panel*: Bayer Health Care, LLC, BD Medical Diabetes Care, Eli Lilly and Company, GSK, Janssen Pharmaceuticals, Medtronic, Novo Nordisk Inc., Roche Pharmaceuticals, Sanofi, Takeda Pharmaceuticals U.S.A., Inc.; *Speaker's Bureau*: Animas Corporation, Merck.
Bocian, Carla	Disclosed no conflict of interest.
Bode, Bruce W.	*Consultant*: Halozyme Therapeutics, Medtronic, Novo Nordisk Inc., Sanofi; *Speaker's Bureau*: Eli Lilly and Company, Medtronic, Novo Nordisk Inc., Sanofi.
Boehm, Anja	Disclosed no conflict of interest.
Boh, Eileen T.	Disclosed no conflict of interest.
Bokvist, Krister	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company, Novo Nordisk A/S.
Bokvist, Krister B.	*Employee*: Eli Lilly and Company.
Bolli, Geremia B.	*Advisory Panel*: Sanofi; *Consultant*: Novartis Pharmaceuticals Corporation; *Speaker's Bureau*: Eli Lilly and Company.
Bolus, W.R.	Disclosed no conflict of interest.
Bomans, Myriam	*Employee*: Beta-cell NV.
Bonnefond, Amélie	Disclosed no conflict of interest.
Borges, Fernanda O.	Disclosed no conflict of interest.
Bornfeldt, Karin E.	Disclosed no conflict of interest.
Borthakur, Alip	Disclosed no conflict of interest.
Bosch, Fatima	Disclosed no conflict of interest.
Boston, Ray C.	Disclosed no conflict of interest.
Boucher, Jeremie	Disclosed no conflict of interest.
Bound, Michelle J.	Disclosed no conflict of interest.
Bouvier, Michel	*Speaker's Bureau*: Bristol-Myers Squibb Company, Eli Lilly and Company, Roche Pharmaceuticals, Vertex Pharmaceuticals, Inc.
Bowden, Donald W.	Disclosed no conflict of interest.
Bowyer, Vicky	Disclosed no conflict of interest.
Boyce, Tawny W.	Disclosed no conflict of interest.
Boyko, Edward J.	Disclosed no conflict of interest.
Bradfield, Jonathan P.	Disclosed no conflict of interest.
Brady, Hugh	Disclosed no conflict of interest.
Bray, George A.	Disclosed no conflict of interest.
Breen, Matthew	*Employee*: Pacific Diabetes Technologies, Inc.
Brekke, Lee	*Employee*: Optum.
Brelsfoard, Jennifer	Disclosed no conflict of interest.
Brethauer, Stacy A.	Disclosed no conflict of interest.
Breton, Marc D.	*Advisory Panel*: Bayer Health Care, LLC; *Research Support*: Abbott Diabetes Care, Animas Corporation, Becton, Dickinson and Company, Dexcom, Inc., Lifescan Animas, Inc., Sanofi, Tandem Diabetes Care; *Speaker's Bureau*: Abbott Diabetes Care, Roche Pharmaceuticals, Sanofi.
Bridges, Nancy D.	Disclosed no conflict of interest.
Brissova, Marcela	Disclosed no conflict of interest.
Brodovicz, Kimberly G.	*Employee*: Merck; *Stock/Shareholder*: Merck.
Broedl, Uli C.	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Brønden, Andreas	Disclosed no conflict of interest.
Brooks, Belinda	Disclosed no conflict of interest.
Brosnan, M.J.	Disclosed no conflict of interest.
Brown, Adam S.	Disclosed no conflict of interest.
Brown, Alastair J.	Disclosed no conflict of interest.
Brown, Cris	Disclosed no conflict of interest.
Brown, Judy	Disclosed no conflict of interest.
Brown, Mark	Disclosed no conflict of interest.
Brown, Rebecca J.	Disclosed no conflict of interest.
Brown, Sue A.	*Research Support*: Dexcom, Inc., Lifescan Animas, Inc., Medtronic, Roche Pharmaceuticals.
Brown, Tara	Disclosed no conflict of interest.
Browne, Jessica L.	*Research Support*: Roche Diagnostics Australia Pty Ltd.
Brudi, Philippe	*Employee*: Merck.
Brusko, Cynthia S.	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Bruttomesso, Daniela	Disclosed no conflict of interest.
Bu, Yagmin	Disclosed no conflict of interest.
Buchanan, Thomas A.	Disclosed no conflict of interest.
Bui, Nancy	Disclosed no conflict of interest.
Burciu, Camelia	Disclosed no conflict of interest.
Buse, John B.	*Consultant*: Amylin Pharmaceuticals, Inc., Andromeda Biotech, Ltd., AstraZeneca Pharmaceuticals LP, Biodel, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Catabasis, Cebix, Inc., Diartis Pharmaceuticals, Eli Lilly and Company, Exsulin, GI Dynamics, Halozyme Therapeutics, Hoffman La Roche, Johnson & Johnson, Lexicon Pharmaceuticals, Inc., LipoScience, Medtronic MiniMed, Inc., Merck, Metabolon, Inc., Novan, Novo Nordisk Inc., Orexigen Therapeutics, Inc., Osiris Therapeutics, Inc., Pfizer, Inc., Sanofi, Tolerx, Inc., Transitions Therapeutics, Inc., Transpharma.
Buyken, Anette E.	Disclosed no conflict of interest.
Buysman, Erin	*Employee*: Optum.
Caccavello, Russell	Disclosed no conflict of interest.
Cahn, Avivit	*Advisory Panel*: Boehringer Ingelheim Pharmaceuticals, Inc., Novartis Pharma AG, Novo Nordisk Inc.; *Speaker's Bureau*: AstraZeneca/Bristol-Meyers Squibb, Teva Pharmaceuticals.
Cai, Lu	Disclosed no conflict of interest.
Caicedo, Alejandro	Disclosed no conflict of interest.
Cakar, Mustafa	Disclosed no conflict of interest.
Caldwell, Bryan D.	*Consultant*: Valeant.
Calle, Roberto A.	*Employee*: Pfizer, Inc.
Calloway-Jones, Jessica	Disclosed no conflict of interest.
Calvo, Sean R.	*Consultant*: Merck.
Canney, Lori	*Employee*: Biodel, Inc.; *Stock/Shareholder*: Biodel, Inc.
Cao, Charlie	*Employee*: Takeda Global Research & Development Center, Inc.
Capehorn, Matthew	*Advisory Panel*: Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company, Merck Sharp & Dohme Limited, Novo Nordisk A/S; *Research Support*: Cambridge Weight Plan, Lighter Life, Novo Nordisk A/S; *Speaker's Bureau*: Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company, Merck Sharp & Dohme Limited; *Stock/Shareholder*: RIO Weight Management Ltd, RIO Weight Management Ltd (*Spouse/Partner*).
Capezio, Luisa	*Employee*: Roche Diagnostics Australia Pty Ltd.
Cardani, Rosanna	Disclosed no conflict of interest.
Cardona, Fernando	Disclosed no conflict of interest.
Cardona, Saumeth	Disclosed no conflict of interest.
Cargill, Robert	*Board Member*: Pacific Diabetes Technologies, Inc; *Employee*: Pacific Diabetes Technologies, Inc; *Stock/Shareholder*: Pacific Diabetes Technologies, Inc.
Carpentier, Éric	Disclosed no conflict of interest.
Carr, Jeffrey	Disclosed no conflict of interest.
Carstensen, Bendix	*Employee*: Steno Diabetes Center A/S; *Stock/Shareholder*: Novo Nordisk A/S.
Carstensen, Lisbeth	Disclosed no conflict of interest.
Cartland, Sian	Disclosed no conflict of interest.
Carvalho, Jasmine	Disclosed no conflict of interest.
Casellas, Alba	Disclosed no conflict of interest.
Casellini, Carolina M.	Disclosed no conflict of interest.
Castaneda, Javier	*Employee*: Medtronic.
Castorino, Kristin	*Research Support*: Dexcom, Inc., Lifescan Animas, Inc., Novo Nordisk Inc., Sanofi.
Cavallerano, Jerry D.	Disclosed no conflict of interest.
Cavanagh, Erika	Disclosed no conflict of interest.
Cavener, Douglas R.	Disclosed no conflict of interest.
Caywood, Rachel	Disclosed no conflict of interest.
Cersosimo, Eugenio	*Advisory Panel*: Janssen Pharmaceuticals, Takeda Pharmaceutical Company, Ltd.; *Speaker's Bureau*: Bristol-Myers Squibb/AstraZeneca, Janssen Pharmaceuticals, Takeda Pharmaceutical Company, Ltd.
Chailurkit, La-or	Disclosed no conflict of interest.
Chan, Lawrence	Disclosed no conflict of interest.
chandra, Sandeep	Disclosed no conflict of interest.
Chang, Anna	Disclosed no conflict of interest.
Chang, Fang-Mei	Disclosed no conflict of interest.
Chang, Healani	Disclosed no conflict of interest.

AUTHOR	RELATIONSHIP/COMPANY
Chang, Richard C.	Disclosed no conflict of interest.
Chang, Ryan	Disclosed no conflict of interest.
Chanut-Vogel, Celine	*Employee*: Merck Sharp & Dohme Limited.
Chao, Maria	Disclosed no conflict of interest.
Chaparro-Riggers, Javier	*Employee*: Pfizer, Inc.
Charpentier, Guillaume	*Advisory Panel*: Boehringer Ingelheim Pharmaceuticals, Inc., Johnson & Johnson, Roche Pharmaceuticals; *Board Member*: Eli Lilly and Company, Medtronic, Novo Nordisk A/S, Takeda Pharmaceutical Company, Ltd.; *Consultant*: Sanofi; *Research Support*: Novartis Pharma AG.
Charron-Prochownik, Denise C.	Disclosed no conflict of interest.
Chasan, Joeol	Disclosed no conflict of interest.
Chaudhry, Zunaira Z.	Disclosed no conflict of interest.
Chen, Danny	*Employee*: Pfizer, Inc.
Chen, Hong-Chi	Disclosed no conflict of interest.
Chen, Hongyu	Disclosed no conflict of interest.
Chen, Kai	Disclosed no conflict of interest.
Chen, Li	Disclosed no conflict of interest.
Chen, Lihong Z.	Disclosed no conflict of interest.
Chen, Liwei	Disclosed no conflict of interest.
Chen, Xiang	Disclosed no conflict of interest.
Chen, Xiaoping	Disclosed no conflict of interest.
Chen, Yanyun	*Employee*: Eli Lilly and Company.
Chen, Zhanghua	Disclosed no conflict of interest.
Cheng, Jie	Disclosed no conflict of interest.
Cheng, Wei	*Employee*: Isis Pharmaceuticals; *Stock/Shareholder*: Isis Pharmaceuticals.
Cheng, Xi	*Employee*: Sanofi.
Cheng, Zhong	Disclosed no conflict of interest.
Chernavvsky, Daniel R.	Disclosed no conflict of interest.
Cherney, David Z.	*Advisory Panel*: Boehringer Ingelheim GmbH & Co. KG, Janssen Pharmaceuticals; *Consultant*: Boehringer Ingelheim GmbH & Co. KG, janssen; *Research Support*: Boehringer Ingelheim GmbH & Co. KG.
Cheruku, Patali S.	Disclosed no conflict of interest.
Chiasson, Jean-Louis	Disclosed no conflict of interest.
Chiu, Amy Pei-Ling	Disclosed no conflict of interest.
Cho, Kae Won	Disclosed no conflict of interest.
Cho, Nam Han	Disclosed no conflict of interest.
Cho, Yoon Hi	Disclosed no conflict of interest.
Choi, Dong Seop	Disclosed no conflict of interest.
Choi, Haysook	Disclosed no conflict of interest.
Choi, In Young	Disclosed no conflict of interest.
Choi, Jessica J.	Disclosed no conflict of interest.
Choi, Kyung Mook	Disclosed no conflict of interest.
Choi, Myung-Sook	Disclosed no conflict of interest.
Choudhary, Sanjeev	Disclosed no conflict of interest.
Choue, Ryowon	Disclosed no conflict of interest.
Chouinard, My	*Employee*: Ember Therapeutics; *Stock/Shareholder*: Ember Therapeutics.
Chow, Sam Z.	Disclosed no conflict of interest.
Christensen, Britt	Disclosed no conflict of interest.
Christensen, Mikkel	Disclosed no conflict of interest.
Christian, Rose	*Employee*: Bristol-Myers Squibb Company.
Christiansen, Jens S.	Disclosed no conflict of interest.
Christiansen, Mark	Disclosed no conflict of interest.
Chu, James	*Consultant*: Sanofi; *Research Support*: Novo Nordisk Inc.; *Speaker's Bureau*: AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Sanofi.
Chua, Kathleen Shari	Disclosed no conflict of interest.
Chung, ChenChih	Disclosed no conflict of interest.
Chung, Wendy K.	Disclosed no conflict of interest.
Cissokho, Sophie	*Consultant*: Sanofi.
Clark, Douglas	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Clarke, William R.	Disclosed no conflict of interest.
Clemente-Postigo, Mercedes	Disclosed no conflict of interest.
Cline, Gary W.	Disclosed no conflict of interest.
Close, Kelly L.	Disclosed no conflict of interest.
Cobelli, Claudio	*Research Support*: Dexcom, Inc., Insulet Corporation, Roche Pharmaceuticals.
Cochran, Elaine K.	Disclosed no conflict of interest.
Codella, Roberto	Disclosed no conflict of interest.
Coderre, Lise	Disclosed no conflict of interest.
Cohen, Jessica L.	Disclosed no conflict of interest.
Cohen, Ohad	*Advisory Panel*: Medtronic; *Consultant*: Eli Lilly and Company, Medtronic, Sanofi; *Research Support*: Eli Lilly and Company, Medtronic, Novo Nordisk A/S, Sanofi.
Coleman, Lenore T.	Disclosed no conflict of interest.
Colombo, Roberto	Disclosed no conflict of interest.
Combest, Travis	Disclosed no conflict of interest.
Commissariat, Persis V.	Disclosed no conflict of interest.
Conger, Elizabeth A.	Disclosed no conflict of interest.
Conget, Ignacio	*Advisory Panel*: Medtronic; *Consultant*: Bayer Health Care, LLC, Eli Lilly and Company, GSK, Medtronic, MSD, Novartis Pharma AG, Novo Nordisk A/S, Sanofi; *Research Support*: Medtronic.
Congreve, Miles	Disclosed no conflict of interest.
Conley, John	*Stock/Shareholder*: Pacific Diabetes Technologies, Inc.
Contreras, Sonia	Disclosed no conflict of interest.
Cook, William	*Employee*: AstraZeneca Pharmaceuticals LP.
Corsino, Leonor	Disclosed no conflict of interest.
Coskun, Tamer	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Côté, José	Disclosed no conflict of interest.
Cousminer, Diana L.	Disclosed no conflict of interest.
Couture, Réjean	Disclosed no conflict of interest.
Cox, Aaron R.	Disclosed no conflict of interest.
Cox, Amanda J.	Disclosed no conflict of interest.
Cox, Nancy J.	Disclosed no conflict of interest.
Craig, Maria E.	Disclosed no conflict of interest.
Cree-Green, Melanie	Disclosed no conflict of interest.
Crowe, Susanne	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Crown, William	*Employee*: Optum.
Cruz Lopez, Miguel	Disclosed no conflict of interest.
Cuddihy, Robert	*Employee*: Sanofi, United Health Group-Optum (*Spouse/Partner*); *Stock/Shareholder*: United Health Group-Optum (*Spouse/Partner*).
Cummins, Martin J.	Disclosed no conflict of interest.
Cummins, Robert	*Employee*: Eli Lilly and Company.
Curtis, Bradley H.	*Employee*: Eli Lilly and Company, Eli Lilly and Company (*Spouse/Partner*); *Stock/Shareholder*: Eli Lilly and Company, Eli Lilly and Company (*Spouse/Partner*).
Czech, Michael P.	Disclosed no conflict of interest.
Czech, Mike	Disclosed no conflict of interest.
Cziraky, Mark	*Employee*: HealthCore.
Dai, Fay	Disclosed no conflict of interest.
Dai, Feihan F.	Disclosed no conflict of interest.
Dai, Ge	*Employee*: Merck; *Stock/Shareholder*: Merck.
D'Alessio, David	Disclosed no conflict of interest.
Dalla Man, Chiara	Disclosed no conflict of interest.
Dallongeville, Jean	Disclosed no conflict of interest.
Daneman, Denis	Disclosed no conflict of interest.
Dang, Lei	Disclosed no conflict of interest.
Dasanayake, Isuru S.	Disclosed no conflict of interest.
Dassau, Eyal	*Research Support*: Animas Corporation, Dexcom, Inc., Insulet Corporation, Lifescan Animas, Inc.
Dauriz, Marco	Disclosed no conflict of interest.
Davis, Quentin	*Other Relationship*: LKC.
Davis, Timothy M.	Disclosed no conflict of interest.
Davis, Wendy A.	Disclosed no conflict of interest.
De Bruin, Tjerk	*Employee*: AstraZeneca Pharmaceuticals LP; *Stock/Shareholder*: AstraZeneca Pharmaceuticals LP.
De La Cruz-Munoz, Nestor	Disclosed no conflict of interest.
De Portu, Simona	*Employee*: Medtronic.
De Pouvourville, Gerard	Disclosed no conflict of interest.
De Ribeiro, Ana Julia V.	Disclosed no conflict of interest.
De Souza, Errol	*Board Member*: Biodel, Inc.; *Employee*: Biodel, Inc.; *Stock/Shareholder*: Biodel, Inc.
Deacon, Carolyn	*Consultant*: Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb/AstraZeneca, Eli Lilly and Company, Merck, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc.; *Employee*: Merck (*Spouse/Partner*); *Stock/Shareholder*: Merck (*Spouse/Partner*).
DeBoer, Mark	Disclosed no conflict of interest.
Debussche, Xavier	Disclosed no conflict of interest.
Deda, Livia	Disclosed no conflict of interest.
Deed, Gary	*Research Support*: Roche Diagnostics Australia Pty Ltd.
Deer, James	Disclosed no conflict of interest.
Deeter, Lance	Disclosed no conflict of interest.
DeFronzo, Ralph	*Advisory Panel*: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim GmbH & Co. KG, Bristol-Myers Squibb Company, Lexicon Pharmaceuticals, Inc., Novo Nordisk Inc.; *Research Support*: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Janssen Pharmaceuticals, Takeda Pharmaceutical Company, Ltd.; *Speaker's Bureau*: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Novo Nordisk Inc.
Dehn, Clayton A.	*Employee*: Celerion.
Del Favero, Simone	Disclosed no conflict of interest.
DeMelo, Emilia N.	Disclosed no conflict of interest.
Demil, Nacima	*Employee*: Sanofi.
Deng, Yingfeng	Disclosed no conflict of interest.

AUTHOR	RELATIONSHIP/COMPANY
D'Eon, Stephanie A.	Disclosed no conflict of interest.
Des Rosiers, Christine	Disclosed no conflict of interest.
Desai, Tejal	Disclosed no conflict of interest.
Despa, Florin	Disclosed no conflict of interest.
Dhaneshwar, Abha	Disclosed no conflict of interest.
Di Bartolo, Belinda	Disclosed no conflict of interest.
Diker-Cohen, Talia	Disclosed no conflict of interest.
DiMeglio, Linda	Disclosed no conflict of interest.
Dimitrov, Todor	*Employee*: Ember Therapeutics.
Ding, Eric L.	Disclosed no conflict of interest.
Ding, Ming	Disclosed no conflict of interest.
Dion, Stacy	Disclosed no conflict of interest.
Distelmaier, Klaus	Disclosed no conflict of interest.
Do, Oanh H.	Disclosed no conflict of interest.
Doerr, Eric D.	Disclosed no conflict of interest.
Doherty, Daniel A.	Disclosed no conflict of interest.
Dohm, Lynis	Disclosed no conflict of interest.
Dolan, Lawrence M.	Disclosed no conflict of interest.
Donaghue, Kim C.	Disclosed no conflict of interest.
Donaldson, Julie	Disclosed no conflict of interest.
Dong, Hui	Disclosed no conflict of interest.
Dong, Jessica P.	Disclosed no conflict of interest.
Dong, Lily Q.	Disclosed no conflict of interest.
Dong, Zhi	Disclosed no conflict of interest.
Dore, David D.	*Research Support*: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline, Merck, Novo Nordisk Inc.
Down, Susan	*Advisory Panel*: Abbott Diabetes Care, AstraZeneca/ Bristol-Meyers Squibb, Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company, Johnson & Johnson, Novo Nordisk A/S, Sanofi; *Board Member*: Forum for Injection Technique; *Speaker's Bureau*: OmniaMed, SB Communications.
Downs, John R.	Disclosed no conflict of interest.
Doyle III, Francis J.	*Research Support*: Animas Corporation, Dexcom, Inc.
D'Souza, Karen M.	Disclosed no conflict of interest.
Du, Xiaosong	Disclosed no conflict of interest.
dubal, Puja	Disclosed no conflict of interest.
Dube, Simmi	Disclosed no conflict of interest.
Dubin, Jeffrey S.	Disclosed no conflict of interest.
Ducar, Dallas	Disclosed no conflict of interest.
Duff, Jenny	Disclosed no conflict of interest.
Dungan, Kathleen M.	*Advisory Panel*: Eli Lilly and Company; *Research Support*: Merck, Novo Nordisk Inc.
Dunger, David B.	Disclosed no conflict of interest.
Dupuis, Josée	Disclosed no conflict of interest.
Durgan, Christopher	Disclosed no conflict of interest.
Dutton, James R.	Disclosed no conflict of interest.
Eby, Elizabeth	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Eckert, Emily A.	Disclosed no conflict of interest.
Edelman, Steven	*Advisory Panel*: Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company; *Speaker's Bureau*: Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company.
Edwards, Joshua F.	Disclosed no conflict of interest.
Eggerman, Thomas L.	Disclosed no conflict of interest.
Egli, Dieter	Disclosed no conflict of interest.
El Ouaamari, Abdelfattah	Disclosed no conflict of interest.
El-Gohary, Yousef	Disclosed no conflict of interest.
Elia, Yesmino	Disclosed no conflict of interest.
Elias, Ivet	Disclosed no conflict of interest.
Elmquist, Joel K.	Disclosed no conflict of interest.
El-Sayed, Yasser	*Research Support*: Dexcom, Inc.
Engel, Samuel S.	*Employee*: Merck; *Stock/Shareholder*: Merck.
Erlandsen, Mogens	Disclosed no conflict of interest.
Eschwège, Eveline	*Advisory Panel*: Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Roche Pharmaceuticals; *Other Relationship*: Haute Autorité de santé.
Esni, Farzad	Disclosed no conflict of interest.
Espinasse, Melanie	*Employee*: Sanofi.
Eurich, Dean T.	Disclosed no conflict of interest.
Evans, Mark	*Employee*: Pfizer, Inc.
Evans-Molina, Carmella	Disclosed no conflict of interest.
Eynatten, Maximilian	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Fahmy, Tarek	Disclosed no conflict of interest.
Fahrbach, Jessie L.	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Faleo, Gaetano	Disclosed no conflict of interest.
Famulla, Susanne	Disclosed no conflict of interest.
Fan, Chun-Po S.	*Research Support*: Merck.
Fantus, I. George	Disclosed no conflict of interest.
Farb, Thomas B.	*Employee*: Eli Lilly and Company.
Farhy, Leon S.	Disclosed no conflict of interest.

AUTHOR	RELATIONSHIP/COMPANY
Feener, Edward	Disclosed no conflict of interest.
Feigl, Andrea B.	Disclosed no conflict of interest.
Feng, Yuan Z.	Disclosed no conflict of interest.
Fenutria, Rafael	Disclosed no conflict of interest.
Ferdynus, Cyril	Disclosed no conflict of interest.
Ferrando, Arny A.	Disclosed no conflict of interest.
Ferrannini, Ele	*Advisory Panel*: Boehringer Ingelheim GmbH & Co. KG, Merck Sharp & Dohme Limited; *Consultant*: GlaxoSmithKline, Sanofi; *Research Support*: Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company.
Ferrannini, Giulia	Disclosed no conflict of interest.
Ferré, Tura	Disclosed no conflict of interest.
Feuer, William	Disclosed no conflict of interest.
Feurer, Irene D.	Disclosed no conflict of interest.
Fiaschi-Taesch, Nathalie	Disclosed no conflict of interest.
Ficorilli, James V.	*Employee*: Eli Lilly and Company.
Fischer, Annelie	Disclosed no conflict of interest.
Fisher, Edwin B.	Disclosed no conflict of interest.
Fisher, Lawrence	*Consultant*: Roche Pharmaceuticals.
Fitch, Thomas	*Employee*: Eli Lilly and Company.
Fleming, Thomas H.	Disclosed no conflict of interest.
Florez, Jose C.	Disclosed no conflict of interest.
Foley, Laurie	Disclosed no conflict of interest.
Folias, Alexandra	Disclosed no conflict of interest.
Fonseca, Vivian	Disclosed no conflict of interest.
Forck, Nelli	Disclosed no conflict of interest.
Forgie, Alison	*Employee*: Pfizer, Inc.
Forst, Thomas	*Advisory Panel*: Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb/AstraZeneca, Eli Lilly and Company, Sanofi; *Research Support*: Boehringer Ingelheim Pharmaceuticals, Inc., Novartis Pharma AG, Sanofi; *Speaker's Bureau*: Berlin Chemie AG, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb/AstraZeneca, Eli Lilly and Company, Novartis Pharma AG, Novo Nordisk Inc., Sanofi.
Forster, Jeri	Disclosed no conflict of interest.
Franckhauser, Sylvie	Disclosed no conflict of interest.
Franco, Daniel A.	Disclosed no conflict of interest.
Franko, Andras	Disclosed no conflict of interest.
Fransen, Stephen	Disclosed no conflict of interest.
Freathy, Rachel M.	Disclosed no conflict of interest.
Frederich, Robert	*Employee*: Bristol-Myers Squibb Company.
Freedman, Barry I.	Disclosed no conflict of interest.
Friis, Søren	Disclosed no conflict of interest.
Froguel, Philippe	Disclosed no conflict of interest.
Fryburg, David	*Stock/Shareholder*: Pfizer, Inc.
Fuchs, Camil	*Research Support*: Oramed Pharmaceuticals.
Fujimoto, Wilfred Y.	Disclosed no conflict of interest.
Fujitani, Yoshio	Disclosed no conflict of interest.
Fukuda, Kazuki	Disclosed no conflict of interest.
Fukuda, Makoto	Disclosed no conflict of interest.
Fushimi, Nobutoshi	Disclosed no conflict of interest.
Gaboury, Louis	Disclosed no conflict of interest.
Gaffar, Iljana	Disclosed no conflict of interest.
Gaidosh, Gabriel	Disclosed no conflict of interest.
Galieva, Marina O.	Disclosed no conflict of interest.
Galloway, Stuart D.	Disclosed no conflict of interest.
Galvan, Yudy	Disclosed no conflict of interest.
Gamerman, Victoria	*Employee*: Boehringer Ingelheim Pharmaceuticals, Inc.
Gan, Kexin	Disclosed no conflict of interest.
Gan, W.J.	Disclosed no conflict of interest.
Ganguli, Rohan	Disclosed no conflict of interest.
Gao, Linlin	Disclosed no conflict of interest.
Gao, Ying	Disclosed no conflict of interest.
Gao, Yuan	Disclosed no conflict of interest.
Garcia Mena, Jaime	Disclosed no conflict of interest.
Garcia-Barjau, Herminia	Disclosed no conflict of interest.
GarciaMenendez, Lorena	Disclosed no conflict of interest.
Garcia-Ocana, Adolfo	Disclosed no conflict of interest.
Garg, Satish K.	*Advisory Panel*: Halozyme Therapeutics; *Research Support*: Cebix, Inc., Eli Lilly and Company, Halozyme Therapeutics, MannKind Corporation, Medtronic, Novo Nordisk Inc., Sanofi; *Speaker's Bureau*: Eisai, Inc., Johnson & Johnson, Medtronic, Novo Nordisk Inc., Roche Pharmaceuticals, Sanofi.
Gastaldelli, Amalia	Disclosed no conflict of interest.
Gau, Bih-Shya	Disclosed no conflict of interest.
Gaulton, Kyle J.	Disclosed no conflict of interest.
Gautier, Jean-Francois	*Board Member*: AstraZeneca/Bristol-Meyers Squibb, Eli Lilly and Company, Ipsen, Merck Sharp & Dohme Limited, Novo Nordisk A/S, Roche Pharmaceuticals; *Speaker's Bureau*: AstraZeneca/Bristol-Meyers

AUTHOR	RELATIONSHIP/COMPANY
	Squibb, Eli Lilly and Company, Ipsen, Merck Sharp & Dohme Limited, Novo Nordisk A/S, Roche Pharmaceuticals.
Gavin III, James R.	*Advisory Panel*: Janssen Research & Development; *Consultant*: Boehringer Ingelheim Pharmaceuticals, Inc.; *Speaker's Bureau*: Janssen Pharmaceuticals.
Geary, Richard	*Employee*: Isis Pharmaceuticals; *Stock/Shareholder*: Isis Pharmaceuticals.
Geiss, Linda S.	Disclosed no conflict of interest.
Generaux, Claudia N.	Disclosed no conflict of interest.
German, Michael S.	Disclosed no conflict of interest.
Geronimo-Carrillo, Rodolfo	Disclosed no conflict of interest.
Gerstein, Hertzel C.	*Advisory Panel*: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim GmbH & Co. KG, Bristol-Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline, Novo Nordisk A/S, Roche Pharmaceuticals, Sanofi; *Consultant*: Sanofi; *Research Support*: Eli Lilly and Company, Sanofi.
Gezzar, Sari	Disclosed no conflict of interest.
Ghanem, Hoda	Disclosed no conflict of interest.
Ghislain, Julien	Disclosed no conflict of interest.
Ghobrial, Oliver	*Employee*: Eli Lilly and Company.
Gilliland, Frank D.	Disclosed no conflict of interest.
Gittes, George K.	Disclosed no conflict of interest.
Glenn, Kimberly R.	Disclosed no conflict of interest.
Gloyn, Anna L.	Disclosed no conflict of interest.
Glynn, Eric	Disclosed no conflict of interest.
Go, Min Jin	Disclosed no conflict of interest.
Goldberg, Ira J.	Disclosed no conflict of interest.
Goldberg, Robert	Disclosed no conflict of interest.
Goldman, Dana	*Consultant*: Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Sanofi.
Goldman, Julie	Disclosed no conflict of interest.
Gomez, Danielle	Disclosed no conflict of interest.
Goncalves, Any Elisa S.	Disclosed no conflict of interest.
Gonder-Frederick, Linda	Disclosed no conflict of interest.
Gondhalekar, Ravi	Disclosed no conflict of interest.
Gong, Cynthia	Disclosed no conflict of interest.
Gong, Li	Disclosed no conflict of interest.
Gong, Yan	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
González González, José G.	*Research Support*: Eli Lilly and Company.
Gonzalez, Eva	Disclosed no conflict of interest.
Gonzalez, Jeffrey S.	Disclosed no conflict of interest.
Gonzalez, Noemi	Disclosed no conflict of interest.
Goodrich, Rebekah	Disclosed no conflict of interest.
Gorczynski, Paul	Disclosed no conflict of interest.
Gorden, Phillip	Disclosed no conflict of interest.
Gorrell, Mark D.	*Advisory Panel*: Novartis Pharmaceuticals Corporation.
Gourdy, Pierre	*Consultant*: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Eli Lilly and Company, Merck Sharp & Dohme Limited, Novo Nordisk A/S, Sanofi; *Research Support*: AstraZeneca Pharmaceuticals LP, Sanofi; *Speaker's Bureau*: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Eli Lilly and Company, Janssen Research & Development, Merck, Novo Nordisk A/S, Pierre Fabre, Sanofi.
Grabman, Jesse	Disclosed no conflict of interest.
Grabner, Michael	*Employee*: HealthCore.
Graham, James L.	Disclosed no conflict of interest.
Graham, Timothy	Disclosed no conflict of interest.
Grande, Cristina	Disclosed no conflict of interest.
Grandinetti, Andrew	Disclosed no conflict of interest.
Grant, Struan F.	Disclosed no conflict of interest.
Grarup, Niels	Disclosed no conflict of interest.
Greenfield, Sheldon	Disclosed no conflict of interest.
Greer, Peter A.	Disclosed no conflict of interest.
Gregg, Edward W.	Disclosed no conflict of interest.
Grigsby-Toussaint, Diana	Disclosed no conflict of interest.
Gudbjörnsdottir, Soffia	Disclosed no conflict of interest.
Guerrero, Angelica	Disclosed no conflict of interest.
Gugliucci, Alejandro	Disclosed no conflict of interest.
Guimaraes, Cristiano	Disclosed no conflict of interest.
Guindon, Lynette	Disclosed no conflict of interest.
Guinness, Mary	*Employee*: Biodel, Inc.
Guo, Lili	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Guo, Ping	Disclosed no conflict of interest.
Gupta, Vineet	Disclosed no conflict of interest.
Guthalu, Nagesha	Disclosed no conflict of interest.
Gutierrez, Absalon	Disclosed no conflict of interest.
Gutierrez, Dario A.	Disclosed no conflict of interest.
Guz, Yelena	Disclosed no conflict of interest.
Guzman-Corrales, Laura	Disclosed no conflict of interest.
Ha, Joon	Disclosed no conflict of interest.
Hach, Thomas	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Hachiya, Hiroki	Disclosed no conflict of interest.
Haenel, Heinz H.	Disclosed no conflict of interest.
Haering, Hans-Ulrich	Disclosed no conflict of interest.
Haffner, Steven M.	Disclosed no conflict of interest.
Hagen, Mary E.	Disclosed no conflict of interest.
Haldeman, Jonathan M.	Disclosed no conflict of interest.
Hamdouchi, Chafiq	*Employee*: Eli Lilly and Company.
Hammarstedt, Ann	Disclosed no conflict of interest.
Han, Bok-Ghee	Disclosed no conflict of interest.
Han, Bora	*Employee*: Pfizer, Inc.
Handley, Margaret A.	Disclosed no conflict of interest.
Hanley, Anthony J.	Disclosed no conflict of interest.
Hansen, Esben S.	Disclosed no conflict of interest.
Hansen, Lars	*Employee*: Bristol-Myers Squibb Company.
Hansen, Morten	Disclosed no conflict of interest.
Hansen, Troels K.	Disclosed no conflict of interest.
Hao, Cong	Disclosed no conflict of interest.
Haque, Ahrar	Disclosed no conflict of interest.
Har, Ronnie	Disclosed no conflict of interest.
Hara, Kazuo	Disclosed no conflict of interest.
Harding, Jessica	Disclosed no conflict of interest.
Hardy, Alexandre B.	Disclosed no conflict of interest.
Harith, Hanis	Disclosed no conflict of interest.
Harman, Sherman M.	Disclosed no conflict of interest.
Harmon, Hans P.	*Employee*: Pinnacle Technology.
Harris, Stewart B.	*Advisory Panel*: AstraZeneca/Bristol-Meyers Squibb, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Janssen Pharmaceuticals, Merck, Novo Nordisk Inc., Sanofi, Takeda Pharmaceutical Company, Ltd.; *Consultant*: Merck, Novo Nordisk Inc., Sanofi; *Research Support*: Merck, Novo Nordisk Inc., Sanofi; *Speaker's Bureau*: Eli Lilly and Company, Merck, Novo Nordisk Inc., Sanofi.
Harrison, Teresa N.	Disclosed no conflict of interest.
Hashimoto, Koshi	Disclosed no conflict of interest.
Hastings, Stephanie M.	Disclosed no conflict of interest.
Hasty, Alyssa H.	Disclosed no conflict of interest.
Hattersley, Andrew T.	Disclosed no conflict of interest.
Havel, Peter J.	Disclosed no conflict of interest.
Hayashi, Tomoshige	Disclosed no conflict of interest.
Hayata, Manabu	Disclosed no conflict of interest.
He, Sijia	Disclosed no conflict of interest.
He, Yujie	Disclosed no conflict of interest.
He, Zhiheng H.	Disclosed no conflict of interest.
Heeren, Jörg	Disclosed no conflict of interest.
Heimberg, Harry	Disclosed no conflict of interest.
Heise, Tim	*Advisory Panel*: Novo Nordisk A/S; *Research Support*: Adocia, Becton, Dickinson and Company, Biocon, Boehringer Ingelheim GmbH & Co. KG, Bristol-Myers Squibb Company, Dance Pharmaceuticals, Eli Lilly and Company, Evolva, Hoffman La Roche, Johnson & Johnson, Marvel, Novartis Pharma AG, Novo Nordisk A/S, Sanofi, Servier; *Speaker's Bureau*: Eli Lilly and Company, Novo Nordisk A/S.
Hellmann, Pattie	Disclosed no conflict of interest.
Helmrath, Michael	Disclosed no conflict of interest.
Henry, Robert R.	*Advisory Panel*: Amgen, Inc., AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Daiichi-Sankyo, Inc., Elcelyx Therapeutics, Inc., Eli Lilly and Company, Eli Lilly and Company, Intarcia Therapeutics, Inc., Medtronic, Merck, Novo Nordisk Inc., Roche Pharmaceuticals, Sanofi; *Research Support*: AstraZeneca/Bristol-Meyers Squibb, Eli Lilly and Company, Medtronic, Sanofi.
Heptulla, Rubina A.	Disclosed no conflict of interest.
Herder, Christian	Disclosed no conflict of interest.
Herman, Gregory	*Stock/Shareholder*: Pacific Diabetes Technologies, Inc.
Herman, Mark A.	Disclosed no conflict of interest.
Herman, William H.	Disclosed no conflict of interest.
Hernandez, Javier	Disclosed no conflict of interest.
Herold, Kevan C.	Disclosed no conflict of interest.
Herranz, Lucrecia	Disclosed no conflict of interest.
Herrmann, Kathrin	*Employee*: AstraZeneca Pharmaceuticals LP; *Research Support*: JDRF.
Hershey, Tamara	Disclosed no conflict of interest.
Hess, Sibylle	*Employee*: Sanofi.
Hesse, Deike	Disclosed no conflict of interest.
Hessler, Danielle	Disclosed no conflict of interest.

AUTHOR	RELATIONSHIP/COMPANY
Hill, Jeffrey M.	*Consultant*: Merck.
Hillman, Natalia	Disclosed no conflict of interest.
Hing, Stephen	Disclosed no conflict of interest.
Hinshaw, Ling	Disclosed no conflict of interest.
Hiort, Line Conradsen	*Employee*: Novo Nordisk A/S; *Stock/Shareholder*: Novo Nordisk A/S.
Hirose, Takahisa	*Advisory Panel*: Eli Lilly, Novo Nordisk, Sanofi; *Other Relationship*: Insulin dosing committee, Sanofi; *Research Support*: Astellas, Boehringer Ingelheim, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Johnson & Johnson, Kissei, MSD, Novartis, Novo Nordisk, Ono, Roche, Sanofi, Takeda, Tanabe-Mitsubishi, Terumo; *Speaker's Bureau*: Astellas, Boehringer Ingelheim, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Johnson & Johnson, Kissei, MSD, Novartis, Novo Nordisk, Ono, Roche, Sanofi, Takeda, Tanabe-Mitsubishi, Terumo.
Hirsch, Irl B.	*Consultant*: Abbott Diabetes Care, Roche Pharmaceuticals; *Research Support*: Halozyme Therapeutics, Sanofi.
Hirshberg, Boaz	*Employee*: AstraZeneca Pharmaceuticals LP.
Hjelmesæth, Jøran	Disclosed no conflict of interest.
Hnatshyn, Serhiy	*Employee*: Bristol-Myers Squibb Company.
Ho, Louisa	Disclosed no conflict of interest.
Hodges, Kim	Disclosed no conflict of interest.
Hoebaus, Clemens	Disclosed no conflict of interest.
Hoekstra, Joost	*Advisory Panel*: AstraZeneca/Bristol-Meyers Squibb.
Hohmeier, Hans E.	Disclosed no conflict of interest.
Holleman, Frits	*Advisory Panel*: Johnson & Johnson, Sanofi.
Holst, Jens J.	*Advisory Panel*: GlaxoSmithKline, Novo Nordisk Inc., Zealand Pharma A/S; *Consultant*: Novo Nordisk Inc.; *Research Support*: Merck, Novartis Pharmaceuticals Corporation.
Homan, Edwin	Disclosed no conflict of interest.
Home, Philip D.	*Advisory Panel*: AstraZeneca/Bristol-Meyers Squibb, GlaxoSmithKline, Janssen Pharmaceuticals, Johnson & Johnson, Merck Sharp & Dohme Limited, Novartis Pharmaceuticals Corporation, Roche Diagnostics, Roche Pharmaceuticals, Sanofi, SkyePharma, Takeda Pharmaceutical Company, Ltd.; *Research Support*: AstraZeneca/Bristol-Meyers Squibb, Eli Lilly and Company, GlaxoSmithKline, Novo Nordisk Inc., Sanofi; *Speaker's Bureau*: AstraZeneca/Bristol-Meyers Squibb, Eli Lilly and Company, Merck Sharp & Dohme Limited, Novo Nordisk Inc.
Homer, Kenneth	*Research Support*: Oramed Pharmaceuticals.
Hommel, Eva E.	*Advisory Panel*: Medtronic; *Employee*: Novo Nordisk A/S.
Hompesch, Marcus	*Employee*: Profil Institute for Clinical Research, Inc.; *Stock/Shareholder*: Profil Institute for Clinical Research, Inc.
Hong, Eun-Gyoung	Disclosed no conflict of interest.
Hong, Ho Cheol	Disclosed no conflict of interest.
Horikoshi, Momoko	Disclosed no conflict of interest.
Horowitz, Michael	*Advisory Panel*: AstraZeneca/Bristol-Meyers Squibb, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Merck, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Sanofi.
Hosoe, Hayato	Disclosed no conflict of interest.
Houle, Janie	Disclosed no conflict of interest.
Hövelmann, Ulrike	Disclosed no conflict of interest.
Høyem, Pernille H.	Disclosed no conflict of interest.
Hoyt, Scott	*Employee*: Merck; *Stock/Shareholder*: Merck.
Hrabe de Angelis, Martin	Disclosed no conflict of interest.
Hsu, Fang-Chi	Disclosed no conflict of interest.
Hsu, William C.	Disclosed no conflict of interest.
Hu, Charlie	*Employee*: Eli Lilly and Company.
Hu, Frank B.	Disclosed no conflict of interest.
Hu, Gang	Disclosed no conflict of interest.
Hu, Wenli	*Employee*: Sanofi.
Huang, Paul L.	Disclosed no conflict of interest.
Huang, Runging	Disclosed no conflict of interest.
Huang, Tao	Disclosed no conflict of interest.
Huang, Yuan	Disclosed no conflict of interest.
Humphries, Paul	Disclosed no conflict of interest.
Hunter, Tracy	*Employee*: Roche Diagnostics.
Hurd, Ralph E.	Disclosed no conflict of interest.
Hwang, Daehee	Disclosed no conflict of interest.
Hwang, Joo-Yeon	Disclosed no conflict of interest.
Hwang, Sang Youn	Disclosed no conflict of interest.
Hyde, Craig L.	Disclosed no conflict of interest.
Ibrahim, Mahmoud	Disclosed no conflict of interest.
Ibrahim, Yazeed M.	Disclosed no conflict of interest.
Iglesias, Jose	Disclosed no conflict of interest.
Ignaut, Debra A.	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Ilkayeva, Olga	Disclosed no conflict of interest.
Imam, Shahnawaz	Disclosed no conflict of interest.
Inagaki, Nobuya	*Consultant*: Kyoto University Graduate School of Medicine.
Inge, Thomas	*Research Support*: Ethicon EndoSurgery, Inc.
Inoue, Kohei	*Employee*: EPS Corporation; *Stock/Shareholder*: EPS Corporation.
Investigators for VADT	Disclosed no conflict of interest.
Inzucchi, Silvio E.	*Advisory Panel*: Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb/AstraZeneca, Janssen Pharmaceuticals, Merck; *Consultant*: Gilead Sciences, Inc., Novo Nordisk Inc.
Iqbal, Nayyar	*Employee*: Bristol-Myers Squibb Company.
Ito, Shun	Disclosed no conflict of interest.
Iwasaki, Masahiro	Disclosed no conflict of interest.
Jabbour, Kareem	Disclosed no conflict of interest.
Jaber, Linda A.	Disclosed no conflict of interest.
Jackson, Richard A.	Disclosed no conflict of interest.
Jacobs, Nehle	Disclosed no conflict of interest.
Jacobs-Tulleneers-Thevissen, Daniel	Disclosed no conflict of interest.
Jähnert, Markus	Disclosed no conflict of interest.
Jain, Asha	Disclosed no conflict of interest.
Jansson, John-Olov	Disclosed no conflict of interest.
Januszewski, Andrzej S.	Disclosed no conflict of interest.
Jaume, Juan	Disclosed no conflict of interest.
Jazayeri, Ali	Disclosed no conflict of interest.
Jenkins, Alicia J.	Disclosed no conflict of interest.
Jenkins, Todd	Disclosed no conflict of interest.
Jensen, Troels M.	Disclosed no conflict of interest.
Jeong, Da eun	Disclosed no conflict of interest.
Jeong, Seonghee	Disclosed no conflict of interest.
Jermendy, György	*Advisory Panel*: AstraZeneca Pharmaceuticals LP; *Speaker's Bureau*: AstraZeneca Pharmaceuticals LP.
Ji, Jinjin	Disclosed no conflict of interest.
Jia, Weiping	Disclosed no conflict of interest.
Jiang, Yi-Der	Disclosed no conflict of interest.
Jin, XiaoWei	Disclosed no conflict of interest.
Johansen, Odd Erik	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Johnson, David A.	*Employee*: Pinnacle Technology.
Johnson, Donna A.	*Employee*: Pinnacle Technology.
Johnson, Jeffrey	Disclosed no conflict of interest.
Johnson, Matthew L.	Disclosed no conflict of interest.
Johnston, Peter S.	*Employee*: Sanofi; *Stock/Shareholder*: Sanofi.
Joly, Erik	Disclosed no conflict of interest.
Jones, Grace Marie	Disclosed no conflict of interest.
Jones, Julia	Disclosed no conflict of interest.
Jones, Karen L.	Disclosed no conflict of interest.
Joost, Hans-Georg	Disclosed no conflict of interest.
Jor'dan, Azizah J.	Disclosed no conflict of interest.
Jørgensen, Marit E.	Disclosed no conflict of interest.
Josan, Sonal	Disclosed no conflict of interest.
Joshi, Peter K.	Disclosed no conflict of interest.
Jue, Thomas	Disclosed no conflict of interest.
Jun, Lucy S.	Disclosed no conflict of interest.
Jung, Hyejung	Disclosed no conflict of interest.
Jung, Sung-Youb	Disclosed no conflict of interest.
Jung, Un Ju	Disclosed no conflict of interest.
Jung, Won Hoon	Disclosed no conflict of interest.
Jurczak, Michael J.	Disclosed no conflict of interest.
Kadowaki, Takashi	Disclosed no conflict of interest.
Kaehr, Mark M.	Disclosed no conflict of interest.
Kahn, Barbara B.	Disclosed no conflict of interest.
Kahn, C. Ronald	Disclosed no conflict of interest.
Kahn, Richard	Disclosed no conflict of interest.
Kahn, Steven E.	Disclosed no conflict of interest.
Kaiser, Daniel	Disclosed no conflict of interest.
Kajno, Esi	Disclosed no conflict of interest.
Kakizoe, Yutaka	Disclosed no conflict of interest.
Kaku, Kohei	*Consultant*: Kawasaki Medical School.
Kamano, Jemima H.	Disclosed no conflict of interest.
Kamitz, Anne	Disclosed no conflict of interest.
Kampmann, Ulla	Disclosed no conflict of interest.
Kanameni, Srikanth	Disclosed no conflict of interest.
Kanaya, Alka	Disclosed no conflict of interest.
Kanekura, Kohsuke	Disclosed no conflict of interest.
Kang, Jahoon	Disclosed no conflict of interest.
Kang, Liya	Disclosed no conflict of interest.
Kang, Mi Ae	Disclosed no conflict of interest.
Kanwar, Yashpal	Disclosed no conflict of interest.
Kanzleiter, Timo	Disclosed no conflict of interest.
Kapitza, Christoph	*Other Relationship*: Sanofi; *Research Support*: Boehringer Ingelheim Pharmaceuticals, Inc., Dance Biopharm,

AUTHOR	RELATIONSHIP/COMPANY
	Inc., Eli Lilly and Company, Hoffman La Roche, Johnson & Johnson, Novartis Pharma AG, Novo Nordisk A/S, Noxxon, Sanofi, Servier.
Kaplan, Sherrie H.	Disclosed no conflict of interest.
Karounos, Dennis G.	*Research Support*: Eli Lilly and Company, NIH, Novo Nordisk Inc., VA Medical Center.
Kase, Eili T.	Disclosed no conflict of interest.
Kashyap, Sangeeta R.	Disclosed no conflict of interest.
Kaste, Renee	*Employee*: Boehringer Ingelheim Pharmaceuticals, Inc.
Katz, Lorraine	Disclosed no conflict of interest.
Kaufman, Derrick	Disclosed no conflict of interest.
Kavurma, Mary	Disclosed no conflict of interest.
Kawai, Hiromi	Disclosed no conflict of interest.
Kawalec, Jill S.	Disclosed no conflict of interest.
Kayali, Ayse G.	Disclosed no conflict of interest.
Kaye, Keith	Disclosed no conflict of interest.
Ke, Weijian	Disclosed no conflict of interest.
Ke, Xuehua	*Employee*: HealthCore.
Keane, Fiona	Disclosed no conflict of interest.
Kedees, Mamdouh	Disclosed no conflict of interest.
Keenan, Hillary A.	Disclosed no conflict of interest.
Kelsey, Megan M.	*Research Support*: Daiichi-Sankyo, Inc.
Kempf, Christian	Disclosed no conflict of interest.
Kennedy, Brian	Disclosed no conflict of interest.
Kenowitz, Joslyn	Disclosed no conflict of interest.
Kerwin, Bill	Disclosed no conflict of interest.
Keshwani, Malik	Disclosed no conflict of interest.
Keskimäki, Ilmo	Disclosed no conflict of interest.
Khalifeh-Soltani, Amin	Disclosed no conflict of interest.
Khanna, Vishesh	Disclosed no conflict of interest.
Khofri, Teresa	Disclosed no conflict of interest.
Khunti, Kamlesh	*Advisory Panel*: Eli Lilly and Company, Merck Sharp & Dohme Limited, Novo Nordisk Inc., Sanofi; *Consultant*: Eli Lilly and Company, Merck Sharp & Dohme Limited, Novartis Pharma AG, Novo Nordisk A/S, Sanofi; *Research Support*: Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company, Merck Sharp & Dohme Limited, Novartis Pharma AG, Novo Nordisk A/S, Pfizer, Inc., Sanofi.
Kibbey, Richard G.	Disclosed no conflict of interest.
Kidron, Miriam	*Employee*: Oramed Pharmaceuticals; *Stock/Shareholder*: Oramed Pharmaceuticals.
Kim, Bong-Jo	Disclosed no conflict of interest.
Kim, Dae Jin	Disclosed no conflict of interest.
Kim, Do Yeon	Disclosed no conflict of interest.
Kim, Hee Young	Disclosed no conflict of interest.
Kim, Hee-Youn	Disclosed no conflict of interest.
Kim, Hye Suk	Disclosed no conflict of interest.
Kim, Hyerang	Disclosed no conflict of interest.
Kim, Jane J.	Disclosed no conflict of interest.
kim, Jihye	Disclosed no conflict of interest.
Kim, Jin Young	Disclosed no conflict of interest.
Kim, Jongoh	Disclosed no conflict of interest.
Kim, Jung Kuk	Disclosed no conflict of interest.
Kim, Ki Young	Disclosed no conflict of interest.
Kim, Koon Soon	Disclosed no conflict of interest.
Kim, Kyeong Jin	Disclosed no conflict of interest.
Kim, Nam Hoon	Disclosed no conflict of interest.
Kim, Nan Hee	Disclosed no conflict of interest.
Kim, Sin Go	Disclosed no conflict of interest.
Kim, Sin Gon	Disclosed no conflict of interest.
Kim, Song-Cheol	Disclosed no conflict of interest.
Kim, Sun Hwa	Disclosed no conflict of interest.
Kim, Won Y.	Disclosed no conflict of interest.
Kim, Wook	Disclosed no conflict of interest.
Kim, Young Hoon	Disclosed no conflict of interest.
Kim, Young-Je	Disclosed no conflict of interest.
Kimchi, Ofer	Disclosed no conflict of interest.
Kindt, Erick	*Employee*: Pfizer, Inc.
King, George L.	*Research Support*: Boehringer Ingelheim Pharmaceuticals, Inc., Sanofi.
King, Kourtney	Disclosed no conflict of interest.
Kinzell, John H.	Disclosed no conflict of interest.
Kirby, Brenda	Disclosed no conflict of interest.
Kirk, Shelley	Disclosed no conflict of interest.
Kirwan, John P.	Disclosed no conflict of interest.
Kitamura, Kenichiro	Disclosed no conflict of interest.
Kluth, Oliver	Disclosed no conflict of interest.
Knop, Filip K.	*Advisory Panel*: Bristol-Myers Squibb/AstraZeneca, Eli Lilly and Company, Sanofi, Zealand Pharma A/S; *Consultant*: AstraZeneca/Bristol-Meyers Squibb, Gilead Sciences, Inc., Ono Pharmaceutical Co., Ltd., Zealand Pharma A/S; *Research Support*: Sanofi; *Speaker's Bureau*: AstraZeneca/Bristol-Meyers Squibb, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Gilead Sciences, Inc., Merck Sharp & Dohme Limited, Novo Nordisk A/S, Ono Pharmaceutical Co., Ltd., Sanofi, Zealand Pharma A/S.
Knott, Caitlin	Disclosed no conflict of interest.
Ko, Yu	Disclosed no conflict of interest.
Kobayashi, Satoru	Disclosed no conflict of interest.
Koehler, Walter	*Consultant*: Roche Diagnostics GmbH.
Kogut, Elizabeth	Disclosed no conflict of interest.
Koiwai, Kazuki	*Employee*: Nippon Boehringer Ingelheim Co., Ltd.
Koleck, Michèle	Disclosed no conflict of interest.
Kolterman, Orville G.	Disclosed no conflict of interest.
Kondo, Tatsuya	Disclosed no conflict of interest.
Kong, Xingxing	Disclosed no conflict of interest.
Konganti, Kranti	Disclosed no conflict of interest.
Kooijman, Marjolein N.	Disclosed no conflict of interest.
Koppensteiner, Renate	Disclosed no conflict of interest.
Koska, Juraj	Disclosed no conflict of interest.
Koumantakis, George	*Employee*: Roche Diagnostics Australia Pty Ltd.
Kovatchev, Boris P.	*Advisory Panel*: Animas Corporation, Sanofi; *Research Support*: Abbott Diabetes Care, Animas Corporation, Becton, Dickinson and Company, Dexcom, Inc., Lifescan Animas, Inc., Sanofi, Tandem Diabetes Care.
Kowitt, Sarah	Disclosed no conflict of interest.
Koyama, Masayoshi	*Employee*: Sanofi; *Stock/Shareholder*: Sanofi.
Kraemer, Maria	Disclosed no conflict of interest.
Kramer, Caroline K.	Disclosed no conflict of interest.
Krasner, Alan	*Employee*: Biodel, Inc.; *Stock/Shareholder*: Biodel, Inc.
Kreiner-Møller, Eskil	Disclosed no conflict of interest.
Krentz, Nicole A.	Disclosed no conflict of interest.
Kriegel, Christina	Disclosed no conflict of interest.
Kronshage, Birgit	Disclosed no conflict of interest.
Kroon, Evert	*Employee*: Viacyte.
Ku, Bon Jeong	Disclosed no conflict of interest.
Kudva, Yogish C.	*Consultant*: Dexcom, Inc.
Kulkarni, Rohit N.	Disclosed no conflict of interest.
Kunz, David	Disclosed no conflict of interest.
Kuroda, Shingo	*Employee*: Takeda Pharmaceutical Company, Ltd.
Kurose, Takeshi	Disclosed no conflict of interest.
Kurt, Omer	Disclosed no conflict of interest.
Kurtyka, Karen M.	*Other Relationship*: Merck.
Kushner, Jake A.	Disclosed no conflict of interest.
Kuwata, Hitoshi	Disclosed no conflict of interest.
Kwon, Oh-shin	Disclosed no conflict of interest.
Kwon, Se Chang	Disclosed no conflict of interest.
Lachey, Jenn	*Employee*: Ember Therapeutics; *Stock/Shareholder*: Ember Therapeutics.
Ladeira, Luciana	Disclosed no conflict of interest.
Lagakos, William	Disclosed no conflict of interest.
Lage, Maureen J.	*Consultant*: Eli Lilly and Company, Eli Lilly and Company (*Spouse/Partner*).
Lage, Ricardo	Disclosed no conflict of interest.
Laktabai, Jeremiah	Disclosed no conflict of interest.
Lam, Carol J.	Disclosed no conflict of interest.
Lambert, Jean	Disclosed no conflict of interest.
Lamontagne, Julien	Disclosed no conflict of interest.
Lane, Wendy S.	*Advisory Panel*: Halozyme Therapeutics, Novo Nordisk Inc.; *Research Support*: Novo Nordisk Inc.; *Speaker's Bureau*: Eli Lilly and Company, Novo Nordisk Inc.
Langefeld, Carl D.	Disclosed no conflict of interest.
Lanza, Ian	Disclosed no conflict of interest.
Lanzano, Patricia	Disclosed no conflict of interest.
Lapuerta, Pablo	*Employee*: Lexicon Pharmaceuticals, Inc.; *Stock/Shareholder*: Lexicon Pharmaceuticals, Inc.
Lau, Nathan	Disclosed no conflict of interest.
Lau, Winston	Disclosed no conflict of interest.
Laugesen, Esben	Disclosed no conflict of interest.
Lauritzen, Torsten	Disclosed no conflict of interest.
Lavin, Philip T.	*Research Support*: Capricor, ZS Pharma.
LeDuc, Charles A.	Disclosed no conflict of interest.
Lee, Douglas S.	*Employee*: Pfizer, Inc.
Lee, Eun-Ah	Disclosed no conflict of interest.
Lee, Hansongyi	Disclosed no conflict of interest.
Lee, Henry	Disclosed no conflict of interest.
Lee, Jennifer	Disclosed no conflict of interest.
Lee, Jisoo	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Lee, Jong Soo	Disclosed no conflict of interest.
Lee, Joyce Y.	Disclosed no conflict of interest.
Lee, Jun Choul	Disclosed no conflict of interest.
Lee, Scott W.	*Employee*: Medtronic MiniMed, Inc.
Lee, Shun Fu	Disclosed no conflict of interest.
Lee, Song	Disclosed no conflict of interest.

AUTHOR	RELATIONSHIP/COMPANY
Lee, Young-Mi	Disclosed no conflict of interest.
Lee, Yun Sok	*Other Relationship*: Takeda Pharmaceuticals U.S.A., Inc.
Lefebvre, Veronique	Disclosed no conflict of interest.
Lehman, Donna M.	Disclosed no conflict of interest.
Lehnert, Hendrik	Disclosed no conflict of interest.
Leibel, Rudolph L.	Disclosed no conflict of interest.
Leibowitz, Gil	Disclosed no conflict of interest.
Lemes, Simone F.	Disclosed no conflict of interest.
Leng, Ying	Disclosed no conflict of interest.
Leonetti, Donna L.	Disclosed no conflict of interest.
Leong, Aaron S.	Disclosed no conflict of interest.
Lepananon, Tanarat	Disclosed no conflict of interest.
Lespérance, François	Disclosed no conflict of interest.
Levin, Philip	*Advisory Panel*: Novo Nordisk Inc., Sanofi; *Consultant*: Novo Nordisk Inc., Sanofi; *Research Support*: Amylin Pharmaceuticals, Inc., Eli Lilly and Company, Novo Nordisk Inc., Roche Pharmaceuticals, Sanofi; *Speaker's Bureau*: Amylin Pharmaceuticals, Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eli Lilly and Company, Novo Nordisk Inc., Sanofi.
Lew, Yiijen	Disclosed no conflict of interest.
Lewin, Andrew	*Research Support*: AbbVie, Allergan, Inc., Amgen, Inc., Amylin Pharmaceuticals, Inc., Bavarian Nordic, Bayer Health Care, LLC, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Catabasis, Daiichi-Sankyo, Inc., Elcelyx Therapeutics, Inc., Eli Lilly and Company, Esperion, Gilead Sciences, Inc., Hanmi Pharmaceuticals, Hoffman La Roche, Idenix, Isis Pharmaceuticals, Janssen Pharmaceuticals, Merck, N-Gene, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Omthera, Pfizer, Inc., PhaseBio, Pronova, Sanofi, Sanofi Aventis, Theracos, TransTech.
Lewis, Carrie R.	Disclosed no conflict of interest.
Li, Changhong	Disclosed no conflict of interest.
Li, Hai	Disclosed no conflict of interest.
Li, Hong	Disclosed no conflict of interest.
Li, Liwu	Disclosed no conflict of interest.
Li, Mei	Disclosed no conflict of interest.
Li, Ming	*Employee*: Biodel, Inc.
Li, XueNing	Disclosed no conflict of interest.
Li, Yan	*Employee*: Bristol-Myers Squibb Company.
Li, Yanbing	Disclosed no conflict of interest.
Li, Yazhen	Disclosed no conflict of interest.
Li, YongGuo	Disclosed no conflict of interest.
Li, You You	Disclosed no conflict of interest.
Li, Yuanbin	Disclosed no conflict of interest.
Li, Zhiyi	*Research Support*: Merck.
Li, Zhuo	Disclosed no conflict of interest.
Liang, Qiangrong	Disclosed no conflict of interest.
Liao, Yi-Chun	Disclosed no conflict of interest.
Lieb, David C.	Disclosed no conflict of interest.
Lien, Angela Shin-Yu	Disclosed no conflict of interest.
Lim, Hyunjung	Disclosed no conflict of interest.
Lin, John	*Employee*: Pfizer, Inc.
Lin, Yung-Chieh	Disclosed no conflict of interest.
Lindi, Virpi	Disclosed no conflict of interest.
Ling, Zhidong	Disclosed no conflict of interest.
Lingaya, Mark Anthony	Disclosed no conflict of interest.
Linjawi, Sultan	*Advisory Panel*: Novo Nordisk A/S; *Speaker's Bureau*: AstraZeneca Pharmaceuticals LP, Novartis Pharma AG, Novo Nordisk A/S, Roche Pharmaceuticals.
Liu, Ching-Ti	Disclosed no conflict of interest.
Liu, Dacheng	*Employee*: Boehringer Ingelheim Pharmaceuticals, Inc.
Liu, Feng	Disclosed no conflict of interest.
Liu, Franklin	Disclosed no conflict of interest.
Liu, Juan	Disclosed no conflict of interest.
Liu, Liehua	Disclosed no conflict of interest.
Liu, Meilian	Disclosed no conflict of interest.
Liu, Selina L.	Disclosed no conflict of interest.
Liu, Shiwei	Disclosed no conflict of interest.
Liu, Tiemin	Disclosed no conflict of interest.
Liu, Yan	Disclosed no conflict of interest.
Liu, Yang	Disclosed no conflict of interest.
Liu, Yaping J.	Disclosed no conflict of interest.
Liu, Ying	Disclosed no conflict of interest.
Liu, Yong	Disclosed no conflict of interest.
Liu, Yujia	Disclosed no conflict of interest.
Ljung, Rickard	Disclosed no conflict of interest.
Lobbens, Stephane	Disclosed no conflict of interest.
Loike, John	Disclosed no conflict of interest.
Long, Yang	Disclosed no conflict of interest.

AUTHOR	RELATIONSHIP/COMPANY
Lopez-Sendon, Jose	*Advisory Panel*: AstraZeneca Pharmaceuticals LP; *Research Support*: Sanofi; *Speaker's Bureau*: AstraZeneca Pharmaceuticals LP.
Lorenzo, Carlos	Disclosed no conflict of interest.
Lu, Danhong	Disclosed no conflict of interest.
Lu, Simin	Disclosed no conflict of interest.
Lubura, Marko	Disclosed no conflict of interest.
Lumeng, Carey N.	Disclosed no conflict of interest.
Lund, Søren S.	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Luo, Yi	*Employee*: Bristol-Myers Squibb Company.
Lurmann, Frederick W.	Disclosed no conflict of interest.
Luu, Lemieux	Disclosed no conflict of interest.
Luzi, Livio	*Advisory Panel*: AstraZeneca Pharmaceuticals LP; *Speaker's Bureau*: Menarini, Novo Nordisk Inc., Sigma-Tau S.p.A.
Lv, You	Disclosed no conflict of interest.
Lyden, Maureen R.	*Consultant*: Roche Diagnostics.
Lynch, Christopher J.	Disclosed no conflict of interest.
Lynn, Francis C.	Disclosed no conflict of interest.
Ma, Jacey H.	Disclosed no conflict of interest.
Ma, Jin-ju	Disclosed no conflict of interest.
Maa, April	Disclosed no conflict of interest.
Mabery, Eric	Disclosed no conflict of interest.
MacDonald, Patrick E.	Disclosed no conflict of interest.
Mace, Oliver J.	Disclosed no conflict of interest.
Machleidt, Felix	Disclosed no conflict of interest.
Macnaughton, Lindsay S.	Disclosed no conflict of interest.
Madani, Suliya	*Employee*: Novo Nordisk A/S.
Madiraju, Anila K.	Disclosed no conflict of interest.
Madiraju, Murthy	Disclosed no conflict of interest.
Maezawa, Hideaki	*Employee*: Takeda Pharmaceutical Company, Ltd.
Magana-Castillo, Margarita	Disclosed no conflict of interest.
Magee, Michelle F.	*Consultant*: American College of Cardiology, Medscape, LLC, Sanofi; *Employee*: Food and Drug Administration (*Spouse/Partner*); *Research Support*: American Diabetes Association Core Research Award, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Cytochroma, Eli Lilly and Company; *Speaker's Bureau*: Sanofi.
Magge, Sheela N.	Disclosed no conflict of interest.
Magliano, Dianna J.	Disclosed no conflict of interest.
Mahdi, Abbas A.	Disclosed no conflict of interest.
Maheshwari, Anuj	Disclosed no conflict of interest.
Mahmud, Farid H.	Disclosed no conflict of interest.
Maiti, Pranab	*Research Support*: Jubilant BioSys.
Makarechi, Leila	Disclosed no conflict of interest.
Malik, Vasanti	Disclosed no conflict of interest.
Malin, Steven K.	Disclosed no conflict of interest.
Mallad, Ashwini	Disclosed no conflict of interest.
Malone, Daniel	Disclosed no conflict of interest.
Mancini, Arturo	Disclosed no conflict of interest.
Maniatis, Nikolas	Disclosed no conflict of interest.
Manning Fox, Jocelyn E.	Disclosed no conflict of interest.
Manor, Brad	Disclosed no conflict of interest.
Manyara, Simon	Disclosed no conflict of interest.
Maravilla, Ken	Disclosed no conflict of interest.
Mardock, Michelle	Disclosed no conflict of interest.
Marinelli, Marcella	Disclosed no conflict of interest.
Marks-Shulman, Pam	Disclosed no conflict of interest.
Maroccia, Magali	*Consultant*: Sanofi.
Marsh, Zachary	Disclosed no conflict of interest.
Marshall, Bess A.	Disclosed no conflict of interest.
Marshall, Fiona	Disclosed no conflict of interest.
Martin Carli, Jayne F.	Disclosed no conflict of interest.
Martin, Emily T.	Disclosed no conflict of interest.
Martin, John	Disclosed no conflict of interest.
Martin, Paula	*Employee*: AstraZeneca Pharmaceuticals LP.
Martinez, Luc	*Consultant*: Amgen, Inc., AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Ipsen, Mayoli Spindler, Novo Nordisk A/S, Pfizer, Inc.; *Speaker's Bureau*: Amgen, Inc., Ipsen, Mayoli Spindler, Novo Nordisk A/S, Servier.
Martinez, Rita	Disclosed no conflict of interest.
Martinez-Santibanez, Gabriel	Disclosed no conflict of interest.
Martinez-Serrano, Amalia	Disclosed no conflict of interest.
Masharani, Umesh	Disclosed no conflict of interest.
Mateo-Crisostomo, Yadira	Disclosed no conflict of interest.
Matfin, Glenn	*Advisory Panel*: Sanofi, Valeritas, LLC; *Consultant*: Eli Lilly and Company; *Research Support*: Eli Lilly and Company, Halozyme Therapeutics, Novo Nordisk Inc., Sanofi.
Mathur, Ruchi	Disclosed no conflict of interest.
Matsuhisa, Munehide	*Other Relationship*: Advisor for EDITION JP Studies, Sanofi.

AUTHOR	RELATIONSHIP/COMPANY
Matsumura, Takeshi	Disclosed no conflict of interest.
Matsuoka, Taka-aki	Disclosed no conflict of interest.
Matthews, David	Disclosed no conflict of interest.
Matzke, Daniela	Disclosed no conflict of interest.
Mavros, Panagiotis	*Employee*: Merck; *Stock/Shareholder*: Merck.
Mayer, Dirk	Disclosed no conflict of interest.
Mayer, John P.	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Mayer, Melissa	Disclosed no conflict of interest.
Mayo, Rachel	Disclosed no conflict of interest.
Mazurina, Natalya V.	Disclosed no conflict of interest.
Mazze, Roger	*Consultant*: Abbott Diabetes Care, Sanofi, Voluntis.
McAlister, Finlay A.	Disclosed no conflict of interest.
McCall, Anthony L.	Disclosed no conflict of interest.
McCarthy, Mark I.	Disclosed no conflict of interest.
McCaughan, Geoffrey	Disclosed no conflict of interest.
McCluskie, Kerryn	Disclosed no conflict of interest.
McDonald, Timothy J.	Disclosed no conflict of interest.
McDonough, Manuela	Disclosed no conflict of interest.
McElgunn, Zachary	Disclosed no conflict of interest.
McElwee, Molly	Disclosed no conflict of interest.
McEwen, Laura N.	Disclosed no conflict of interest.
McGlory, Chris S.	Disclosed no conflict of interest.
McGrath, Barbara C.	Disclosed no conflict of interest.
McGraw, Timothy E.	Disclosed no conflict of interest.
McKendry, Tim	Disclosed no conflict of interest.
McKleroy, William	Disclosed no conflict of interest.
McLennan, Susan	Disclosed no conflict of interest.
McMullen, William	Disclosed no conflict of interest.
McNeely, Marguerite J.	Disclosed no conflict of interest.
McNulty, Judi A.	Disclosed no conflict of interest.
McQueen, Matthew J.	*Research Support*: Boehringer Ingelheim Pharmaceuticals, Inc., Sanofi.
Mehta, Rucha J.	Disclosed no conflict of interest.
Mehta, Sanjeev N.	Disclosed no conflict of interest.
Meier, Juris J.	Disclosed no conflict of interest.
Meiffren, Grégory	*Employee*: Adocia; *Stock/Shareholder*: Adocia.
Meigs, James B.	Disclosed no conflict of interest.
Mejia Benitez, Maria Aurora	Disclosed no conflict of interest.
Melhorn, Susan J.	Disclosed no conflict of interest.
Melito, Julie	Disclosed no conflict of interest.
Mellbin, Linda	*Research Support*: Bayer, Merck, Sanofi, Swedish Diabetes Association, Swedish Heart Lung Foundation; *Speaker's Bureau*: AstraZeneca, Bayer-Schering, Eli Lilly, Merck, Novartis, Roche, Sanofi.
Melo, Arine M.	Disclosed no conflict of interest.
Menchaca-Diaz, Rufino	Disclosed no conflict of interest.
Mendrick, Edward	Disclosed no conflict of interest.
Menya, Diana	Disclosed no conflict of interest.
Meola, Giovanni	Disclosed no conflict of interest.
Merrins, Matthew J.	Disclosed no conflict of interest.
Mete, Mihriye	Disclosed no conflict of interest.
Meunier, Sophie	Disclosed no conflict of interest.
Meyers, Ikenna	Disclosed no conflict of interest.
Michalek, Joel	Disclosed no conflict of interest.
Michalon, Sonia	Disclosed no conflict of interest.
Migrino, Raymond	Disclosed no conflict of interest.
Mikkelsen, Anders F.	Disclosed no conflict of interest.
Mikkelsen, Tarjei	Disclosed no conflict of interest.
Mills, Tyler	Disclosed no conflict of interest.
Min, Fang-yuan	Disclosed no conflict of interest.
Mirmira, Raghavendra G.	Disclosed no conflict of interest.
Misha'l, Aly A.	Disclosed no conflict of interest.
Miura, Masaki	Disclosed no conflict of interest.
Miyasato, Yoshikazu	Disclosed no conflict of interest.
Miyatsuka, Takeshi	Disclosed no conflict of interest.
Mizumoto, Teruhiko	Disclosed no conflict of interest.
Moineddin, Rahim	Disclosed no conflict of interest.
Moisan, Christine	*Employee*: Merck Sharp & Dohme Limited.
Monk, Arlene	Disclosed no conflict of interest.
Montesano, Anna	Disclosed no conflict of interest.
Montserrat, Joan	Disclosed no conflict of interest.
Mor, Alessandro	Disclosed no conflict of interest.
Moraes-Vieira, Pedro M.	Disclosed no conflict of interest.
Morales, Walter	Disclosed no conflict of interest.
Moran, Colin N.	Disclosed no conflict of interest.
Morgan, Erin	*Employee*: Isis Pharmaceuticals; *Stock/Shareholder*: Isis Pharmaceuticals.
Mori, Akihiro	Disclosed no conflict of interest.
Mori, Masatomo	Disclosed no conflict of interest.
Morinaga, Hidetaka	Disclosed no conflict of interest.
Morris, Andrew P.	Disclosed no conflict of interest.
Morris, Kristin	*Employee*: Pacific Diabetes Technologies, Inc.
Morrow, Linda	*Employee*: Profil Institute for Clinical Research, Inc.; *Stock/Shareholder*: Profil Institute for Clinical Research, Inc.
Mosenzon, Ofri	*Advisory Panel*: Eli Lilly and Company, Novartis Pharma AG, Novo Nordisk Inc., Sanofi; *Research Support*: AstraZeneca/Bristol-Meyers Squibb; *Speaker's Bureau*: Eli Lilly and Company, Merck Sharp & Dohme Limited, Novartis Pharma AG, Novo Nordisk Inc., Sanofi.
Moss, Jennifer B.	Disclosed no conflict of interest.
Moss, Larry G.	Disclosed no conflict of interest.
Motran, Laura	Disclosed no conflict of interest.
Motté, Evi	Disclosed no conflict of interest.
Moura, Fabio	Disclosed no conflict of interest.
Mu, James	*Employee*: Merck; *Stock/Shareholder*: Merck.
Mu, S.M.	*Employee*: Merck Sharp & Dohme Limited.
Muchmore, Douglas B.	*Employee*: Halozyme Therapeutics; *Stock/Shareholder*: Halozyme Therapeutics, Halozyme Therapeutics (*Spouse/Partner*).
Muehlen-Bartmer, Isabel	*Employee*: Sanofi.
Mueller, Robert	Disclosed no conflict of interest.
Mugabo, Yves	Disclosed no conflict of interest.
Mukaneza, Yvette	Disclosed no conflict of interest.
Mulligan, Kathy	Disclosed no conflict of interest.
Mulvagh, Sharon L.	*Research Support*: Astellas Pharma U.S., Inc., Lantheus Medical Imaging.
Murthy, Tal	Disclosed no conflict of interest.
Müssig, Karsten	Disclosed no conflict of interest.
Nadeau, Kristen J.	Disclosed no conflict of interest.
Nagel, Friederike	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Nair, K. Sreekumaran	Disclosed no conflict of interest.
Nakamura, Katherine	Disclosed no conflict of interest.
Nakazawa, Masato	Disclosed no conflict of interest.
Nassar, Carine M.	Disclosed no conflict of interest.
Nauck, Michael	*Board Member*: Amylin Pharmaceuticals, Inc., Berlin Chemie AG, Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company, Hoffman La Roche, Intarcia Therapeutics, Inc., Janssen Pharmaceuticals, Merck Sharp & Dohme Limited, Novartis Pharma AG, Sanofi, Takeda Pharmaceutical Company, Ltd., Versartis, Inc.; *Consultant*: Amylin Pharmaceuticals, Inc., AstraZeneca Pharmaceuticals LP, Berlin Chemie AG, Boehringer Ingelheim GmbH & Co. KG, Bristol-Myers Squibb Company, Diartis Pharmaceuticals, Eli Lilly and Company, GlaxoSmithKline, Hoffman La Roche, MannKind Corporation, Merck Sharp & Dohme Limited, Novartis Pharma AG, Novo Nordisk A/S, Novo Nordisk Inc., Sanofi, Takeda Pharmaceutical Company, Ltd., Wyeth; *Research Support*: AstraZeneca Pharmaceuticals LP, Berlin Chemie AG, Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company, GlaxoSmithKline, Merck Sharp & Dohme Limited, Metacure, Novartis Pharma AG, Novo Nordisk A/S, Roche Pharmaceuticals, ToleRx.
Navabi, Kasra	Disclosed no conflict of interest.
Nawroth, Peter P.	Disclosed no conflict of interest.
Nayer, Ali	Disclosed no conflict of interest.
Naylor, Erik	*Employee*: Pinnacle Technology.
Neilson, Amber	Disclosed no conflict of interest.
Netto, Eduardo	Disclosed no conflict of interest.
Neutel, Joel	*Research Support*: Oramed Pharmaceuticals.
Newgard, Christopher B.	Disclosed no conflict of interest.
Newswanger, Brett J.	Disclosed no conflict of interest.
Nguy, Michael Q.	Disclosed no conflict of interest.
Nguyen, Huong	Disclosed no conflict of interest.
Nhola, Lara	Disclosed no conflict of interest.
Nian, Cuilan	Disclosed no conflict of interest.
Nichols, Tim	*Employee*: Pfizer, Inc.
Nicoloro, Sarah M.	Disclosed no conflict of interest.
Nikoliķ Natasa	Disclosed no conflict of interest.
Nishimura, Rimei	*Advisory Panel*: Astellas Pharma U.S., Inc., Kowa Pharmaceuticals; *Consultant*: Boehringer Ingelheim GmbH & Co. KG, Eli Lilly and Company; *Research Support*: Astellas Pharma U.S., Inc., Boehringer Ingelheim GmbH & Co. KG, Daiichi-Sankyo, Inc., Japan Diabetes Foundation; *Speaker's Bureau*: Astellas Pharma U.S., Inc., AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim GmbH & Co. KG, Daiichi-Sankyo, Inc., Eli Lilly and Company, Johnson & Johnson, Kissei Pharmaceutical Co., Ltd., Kowa Pharmaceuticals, Medtronic, Novo Nordisk Inc., Ono Pharmaceutical Co., Ltd., Sanofi, Takeda Pharmaceutical Company, Ltd., Tanabe-Mitsubishi.

AUTHOR	RELATIONSHIP/COMPANY
Nissen, Steven E.	*Consultant*: Novo Nordisk A/S.
Nolan, Charles E.	Disclosed no conflict of interest.
Nonogaki, Katsunori	Disclosed no conflict of interest.
Nosek, Leszek	Disclosed no conflict of interest.
Novak, Vera	Disclosed no conflict of interest.
Novoselova, Mariia	Disclosed no conflict of interest.
Nowotny, Bettina	Disclosed no conflict of interest.
Nowotny, Peter	Disclosed no conflict of interest.
Ntalla, Ioanna	Disclosed no conflict of interest.
Nunes, Anthony P.	*Employee*: OptumInsight; *Research Support*: Merck, Novo Nordisk Inc.
Nyitray, Crystal	Disclosed no conflict of interest.
Obrosova, Irina G.	Disclosed no conflict of interest.
O'Day, Diana R.	Disclosed no conflict of interest.
O'Driscoll, Marci	Disclosed no conflict of interest.
O'Farrell, Libbey	*Employee*: Eli Lilly and Company.
Ogbaa, Ike	*Employee*: Lexicon Pharmaceuticals, Inc.; *Stock/Shareholder*: Lexicon Pharmaceuticals, Inc.
Oh, Seok-Kyun	Disclosed no conflict of interest.
Ohashi, Noritsugu	Disclosed no conflict of interest.
Öhman, Peter	*Employee*: AstraZeneca Pharmaceuticals LP; *Stock/Shareholder*: AstraZeneca Pharmaceuticals LP.
Ohn, Jung Hun	Disclosed no conflict of interest.
Ohshima, Kihachi	Disclosed no conflict of interest.
Okada, Shuichi	Disclosed no conflict of interest.
Olefsky, Jerrold M.	*Other Relationship*: A patent royalty payment.
Olivas, Lourdes M.	Disclosed no conflict of interest.
Ongphiphadhanakul, Boonsong	Disclosed no conflict of interest.
Onishi, Yukiko	Disclosed no conflict of interest.
Onouchi, Hitoshi	*Employee*: Takeda Pharmaceutical Company, Ltd.
Opsteen, Christine	Disclosed no conflict of interest.
Oram, Richard A.	Disclosed no conflict of interest.
Oslowski, Christine M.	Disclosed no conflict of interest.
Pacini, Giovanni	Disclosed no conflict of interest.
Packham, David K.	Disclosed no conflict of interest.
Pallardo, Felipe	Disclosed no conflict of interest.
Pan, An	Disclosed no conflict of interest.
Pan, Qianqian	Disclosed no conflict of interest.
Pan, Zui	Disclosed no conflict of interest.
Paneerselan-Bharath, Leena	Disclosed no conflict of interest.
Parada, Humberto	Disclosed no conflict of interest.
Pardo, Scott	*Employee*: Bayer Healthcare.
Pare, Guillaume	*Advisory Panel*: Sanofi; *Research Support*: Sanofi.
Park Kim, Soohyun	Disclosed no conflict of interest.
Park, Byung Kil	Disclosed no conflict of interest.
Park, Hana	Disclosed no conflict of interest.
Park, Jae Mo	Disclosed no conflict of interest.
Park, Terrence	*Employee*: Pfizer, Inc.
Park, Tim	Disclosed no conflict of interest.
Park, Yong B.	Disclosed no conflict of interest.
Park, Yong Bok	Disclosed no conflict of interest.
Park, Young Jin	Disclosed no conflict of interest.
Parkin, Christopher	*Consultant*: Dexcom, Inc., Intuity Medical, Inc., Roche Diagnostics.
Parson, Henri K.	Disclosed no conflict of interest.
Pascual, Conrado	Disclosed no conflict of interest.
Pasquel, Francisco	Disclosed no conflict of interest.
Passos Oliveira, João Gabriel J.	Disclosed no conflict of interest.
Pastakia, Sonak	*Consultant*: Abbott Diabetes Care.
Patek, Stephen D.	*Research Support*: Edwards Scientific, Eli Lilly and Company; *Stock/Shareholder*: TypeZero Technologies LLC.
Patel, Hiren	Disclosed no conflict of interest.
Patel, Jayesh	Disclosed no conflict of interest.
Patel, Nishita	Disclosed no conflict of interest.
Patel, Rajesh T.	Disclosed no conflict of interest.
Patel, Sanjay	*Employee*: Boehringer Ingelheim Ltd.
Pearson, Ewan R.	Disclosed no conflict of interest.
Pedersen, David J.	Disclosed no conflict of interest.
Pehmoller, Christian	Disclosed no conflict of interest.
Pei, Yi	Disclosed no conflict of interest.
Penfornis, Alfred	*Board Member*: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Sanofi; *Other Relationship*: Abbott Diabetes Care, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Medtronic, Merck Sharp & Dohme Limited, Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Sanofi, Takeda Global Research & Development Center, Inc.; *Research Support*: Sanofi; *Speaker's Bureau*: Eli Lilly and Company, Medtronic, Merck Sharp & Dohme Limited, Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Sanofi.
Peng, Limin	Disclosed no conflict of interest.
Peng, Xianbu	*Employee*: Eli Lilly and Company.
Peralta, Jesus	Disclosed no conflict of interest.
Perkins, Bruce A.	*Research Support*: Boehringer Ingelheim GmbH & Co. KG.
Perkins, Guy	Disclosed no conflict of interest.
Pernic, Allison A.	Disclosed no conflict of interest.
Peroni, Odile D.	Disclosed no conflict of interest.
Perry, Rachel J.	Disclosed no conflict of interest.
Pesta, Dominik	Disclosed no conflict of interest.
Peter, Nelson	Disclosed no conflict of interest.
Peters, Anne L.	*Advisory Panel*: Abbott Diabetes Care, AstraZeneca/Bristol-Meyers Squibb, BD Medical Diabetes Care, Eli Lilly and Company, Janssen Pharmaceuticals, Medscape, LLC, Medtronic MiniMed, Inc., Novo Nordisk Inc., Sanofi; *Speaker's Bureau*: AstraZeneca/Bristol-Meyers Squibb, Novo Nordisk Inc.
Petersen, Bettina	*Employee*: Roche Diagnostics GmbH.
Petersen, Max C.	Disclosed no conflict of interest.
Petillo, Peter A.	*Employee*: Pinnacle Technology.
Petruschke, Thorsten	*Employee*: Bayer Healthcare.
Peyot, Marie-line	Disclosed no conflict of interest.
Peyrot, Mark	*Advisory Panel*: Novo Nordisk A/S; *Consultant*: Eli Lilly and Company, Novo Nordisk A/S, Tethys; *Other Relationship*: Novo Nordisk A/S; *Research Support*: Bristol-Myers Squibb Company, Genentech, Novo Nordisk A/S.
Pezos, Nektaria	Disclosed no conflict of interest.
Phan, Anh-Danh T.	Disclosed no conflict of interest.
Phanachet, Pariya	Disclosed no conflict of interest.
Philis-Tsimikas, Athena	Disclosed no conflict of interest.
Pichotta, Philip	*Employee*: Biodel, Inc.; *Stock/Shareholder*: Biodel, Inc.
Pillow, Ensa	Disclosed no conflict of interest.
Pimentel, Daniela A.	Disclosed no conflict of interest.
Pimentel, Mark	*Consultant*: Salix Pharmaceuticals, Inc; *Research Support*: Salix Pharmaceuticals, Inc.
Pineda, Marco	Disclosed no conflict of interest.
Pino, Maria	Disclosed no conflict of interest.
Pipeleers, Daniel	*Advisory Panel*: Viacyte.
Pitkänen, Niina	Disclosed no conflict of interest.
Pohl, Roderike	*Employee*: Biodel, Inc.
Poitout, Vincent	*Consultant*: Takeda Canada.
Pollack, Ilana R.	Disclosed no conflict of interest.
Polonsky, William H.	*Advisory Panel*: Novo Nordisk Inc., Roche Pharmaceuticals, Sanofi; *Consultant*: Abbott Diabetes Care, Boehringer Ingelheim GmbH & Co. KG, Dexcom, Novo Nordisk Inc., Roche Pharmaceuticals, Sanofi; *Research Support*: Dexcom, Sanofi.
Pories, Walter	Disclosed no conflict of interest.
Pothier, Claire E.	Disclosed no conflict of interest.
Poulsen, Per L.	Disclosed no conflict of interest.
Powell, David R.	*Employee*: Lexicon Pharmaceuticals, Inc.; *Stock/Shareholder*: Lexicon Pharmaceuticals, Inc.
Powers, Alvin C.	Disclosed no conflict of interest.
Powers, Margaret A.	*Advisory Panel*: Eli Lilly and Company; *Research Support*: Sanofi.
Pradhan, Geetali	Disclosed no conflict of interest.
Prakoso, Emilia	Disclosed no conflict of interest.
Prasadan, Krishna	Disclosed no conflict of interest.
Prentice, Kacey J.	Disclosed no conflict of interest.
Prentki, Marc	Disclosed no conflict of interest.
Prentki, Raphaël	Disclosed no conflict of interest.
Prestrelski, Steven J.	Disclosed no conflict of interest.
Price, David A.	Disclosed no conflict of interest.
Probstfield, Jeffrey	*Advisory Panel*: Sanofi; *Consultant*: Sanofi; *Research Support*: AstraZeneca, BristolMyersSquibb, Sanofi.
Prokopenko, Inga	Disclosed no conflict of interest.
Puchaiwattananon, Orawan	Disclosed no conflict of interest.
Pullinger, Clive	Disclosed no conflict of interest.
Qi, Lu	Disclosed no conflict of interest.
Qiu, Ying	*Employee*: Merck; *Stock/Shareholder*: Merck.
Quan, Judy	Disclosed no conflict of interest.
Quimbo, Ralph	*Employee*: HealthCore.
Qunibi, Wajeh Y.	*Research Support*: ZS Pharma.
Quon, Michael J.	*Speaker's Bureau*: Merck; *Stock/Shareholder*: Eli Lilly and Company, Novartis Pharmaceuticals Corporation, Pfizer, Inc., Roche Pharmaceuticals.
Rader, Daniel J.	Disclosed no conflict of interest.
Radican, Larry	*Employee*: Merck; *Stock/Shareholder*: Merck.
Raffield, Laura M.	Disclosed no conflict of interest.
Raghavan, Sridharan	Disclosed no conflict of interest.
Rahimi, Yasmeen	Disclosed no conflict of interest.
Rajpathak, Swapnil N.	Disclosed no conflict of interest.
Raleigh, Jim	Disclosed no conflict of interest.

AUTHOR	RELATIONSHIP/COMPANY
Ramalho, Ana Claudia R.	Disclosed no conflict of interest.
Ran, Nina	Disclosed no conflict of interest.
Ran, X.W.	Disclosed no conflict of interest.
Ranganath, Lakshminarayan	Disclosed no conflict of interest.
Rankin, Matthew M.	Disclosed no conflict of interest.
Ranson, Aymeric	*Employee*: Adocia; *Stock/Shareholder*: Adocia.
Rantz, Tim	Disclosed no conflict of interest.
Rao, Paturi V.	*Board Member*: DiabetOmics Diagnostics Pvt. Ltd. (*Spouse/Partner*); *Consultant*: Diabetes Care Center, Hyderabad (*Spouse/Partner*); *Employee*: NIMS University Hospital (government employee); *Research Support*: Indian Council of Medical Research, Novo Nordisk A/S, Research Society for the Study of Diabetes in India; *Stock/Shareholder*: DiabetOmics Inc., Beaverton OR, USA.
Rappaport, Jonathan	Disclosed no conflict of interest.
Rasmussen, Henrik S.	*Employee*: ZS Pharma, Inc.
Ratanawongsa, Neda	Disclosed no conflict of interest.
Rath, Michaela	Disclosed no conflict of interest.
Raymond, Ralph	Disclosed no conflict of interest.
Rayner, Christopher K.	*Research Support*: Eli Lilly and Company, Merck, Novartis Pharmaceuticals Corporation.
Raz, Itamar	*Advisory Panel*: AstraZeneca/Bristol-Meyers Squibb, Eli Lilly and Company, Medscape, LLC, Merck Sharp & Dohme Limited, Novo Nordisk Inc., Sanofi; *Consultant*: Andromeda Biotech, Ltd., AstraZeneca/Bristol-Meyers Squibb, Insuline Medical; *Speaker's Bureau*: AstraZeneca/Bristol-Meyers Squibb, Eli Lilly and Company, Johnson & Johnson, Merck Sharp & Dohme Limited, Novartis Pharma AG, Novo Nordisk Inc., Sanofi; *Stock/Shareholder*: Insuline Medical.
Reaven, Peter D.	*Consultant*: Amgen, Inc.; *Research Support*: Bristol-Myers Squibb/AstraZeneca, Novo Nordisk Inc.; *Speaker's Bureau*: Amylin/Eli Lilly.
Rees, Christen	*Employee*: Roche Diagnostics.
Register, Kenyon	Disclosed no conflict of interest.
Rehfeld, Jens F.	Disclosed no conflict of interest.
Reich, Heather N.	Disclosed no conflict of interest.
Reifel Miller, Anne	*Employee*: Eli Lilly and Company.
Reily, Michael	*Employee*: Bristol-Myers Squibb Company.
Renna, Laura	Disclosed no conflict of interest.
Renner, Travis	Disclosed no conflict of interest.
Retnakaran, Ravi	*Consultant*: Novo Nordisk Inc.; *Research Support*: Novo Nordisk Inc.
Reusch, Jane E.	Disclosed no conflict of interest.
Reyna, Sara M.	Disclosed no conflict of interest.
Reynolds, Kristi	Disclosed no conflict of interest.
Reznik, Yves	*Advisory Panel*: Abbott Diabetes Care, Eli Lilly and Company, Medtronic; *Research Support*: Eli Lilly and Company, Medtronic, Novo Nordisk A/S.
Rhee, Sang Dal	Disclosed no conflict of interest.
Ribera, Albert	Disclosed no conflict of interest.
Richter, Sara	Disclosed no conflict of interest.
Riddell, David	Disclosed no conflict of interest.
Ridderstråle, Martin	*Advisory Panel*: Medtronic; *Employee*: Novo Nordisk A/S.
Riddle, Matthew C.	*Advisory Panel*: Sanofi; *Consultant*: Amylin Pharmaceuticals, Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Elcelyx Therapeutics, Inc., Eli Lilly and Company, Sanofi, Valeritas, LLC; *Research Support*: Eli Lilly and Company, Sanofi.
Riegler, Erin	Disclosed no conflict of interest.
Rimele, Thomas J.	Disclosed no conflict of interest.
Ritzel, Robert	Disclosed no conflict of interest.
Rivard, Marie-Ève	Disclosed no conflict of interest.
Rivas-Acuna, Valentina	Disclosed no conflict of interest.
Robertson, R. Paul	Disclosed no conflict of interest.
Robshaw, Ashley	Disclosed no conflict of interest.
Roca, Carles	Disclosed no conflict of interest.
Roca-Rodriguez, Maria del Mar	Disclosed no conflict of interest.
Roden, Michael	Disclosed no conflict of interest.
Rodrigues, Brian	Disclosed no conflict of interest.
Rohde, Ulrich	Disclosed no conflict of interest.
Rojeski, Maria	*Employee*: Sanofi.
Romley, John	*Advisory Panel*: Bristol-Myers Squibb/AstraZeneca; *Consultant*: Bristol-Myers Squibb Company, Sanofi.
Rosenstock, Julio	*Advisory Panel*: Boehringer Ingelheim Pharmaceuticals, Inc., Daiichi-Sankyo, Inc., Eli Lilly and Company, GlaxoSmithKline, Halozyme Therapeutics, Intarcia Therapeutics, Inc., Janssen Pharmaceuticals, Lexicon Pharmaceuticals, Inc., MannKind Corporation, Merck, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Sanofi, Takeda Pharmaceuticals U.S.A., Inc.; *Research Support*: Amylin Pharmaceuticals, Inc., AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Daiichi-Sankyo, Inc., Eli Lilly and Company, GlaxoSmithKline, Intarcia Therapeutics, Inc., Janssen Pharmaceuticals, Lexicon Pharmaceuticals, Inc., MannKind Corporation, Merck, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Pfizer, Inc., Roche Pharmaceuticals, Sanofi, Takeda Pharmaceuticals U.S.A., Inc.
Rotenstein, Lisa S.	Disclosed no conflict of interest.
Roussel, Ronan	*Advisory Panel*: Jannsen, Sanofi; *Board Member*: AstraZeneca/Bristol-Meyers Squibb; *Research Support*: Sanofi; *Speaker's Bureau*: Jannsen, Merck Sharp & Dohme Limited, Novartis, Sanofi.
Ruan, Ting	Disclosed no conflict of interest.
Ruderman, Neil B.	Disclosed no conflict of interest.
Rueedi, Rico	Disclosed no conflict of interest.
Ruetten, Hartmut	*Employee*: Sanofi.
Runzis, Sarah	*Employee*: Medtronic.
Rustan, Arild C.	Disclosed no conflict of interest.
Rydén, Lars E.	*Consultant*: AstraZeneca, BristolMyersSquibb, Merck, Sanofi; *Research Support*: Bayer, Roche, Swedish Diabetes Association, Swedish Heart Lung Foundation.
Ryu, Ja Young	Disclosed no conflict of interest.
Saatman, Kathryn	Disclosed no conflict of interest.
Sacks, Frank M.	Disclosed no conflict of interest.
Saghatelian, Alan	Disclosed no conflict of interest.
Saglam, Kenan	Disclosed no conflict of interest.
Saito, Tsugumichi	Disclosed no conflict of interest.
Sakaguchi, Masaji	Disclosed no conflict of interest.
Sakuma, Stephen	Disclosed no conflict of interest.
Salam, Muhammad T.	Disclosed no conflict of interest.
Salbe, Arline	Disclosed no conflict of interest.
Salsali, Afshin	*Employee*: Boehringer Ingelheim Pharmaceuticals, Inc.
Samoylova, Julia	Disclosed no conflict of interest.
Samuel, Varman T.	Disclosed no conflict of interest.
Sanal Kumar, Prathibha	Disclosed no conflict of interest.
Sanchez, Rosalia	Disclosed no conflict of interest.
Sandbaek, Annelli	Disclosed no conflict of interest.
Sands, Arthur	*Board Member*: Lexicon Pharmaceuticals, Inc.; *Employee*: Lexicon Pharmaceuticals, Inc.; *Stock/Shareholder*: Lexicon Pharmaceuticals, Inc.
Sands, Michelle	Disclosed no conflict of interest.
Santarossa, Maressa	Disclosed no conflict of interest.
Saremi, Aramesh	Disclosed no conflict of interest.
Sargsyan, Ashot	Disclosed no conflict of interest.
Sari, Ramazan	Disclosed no conflict of interest.
Sarkar, Urmimala	Disclosed no conflict of interest.
sarlak, Hakan	Disclosed no conflict of interest.
Sathananthan, Airani	Disclosed no conflict of interest.
Sathyanarayana, Padma	Disclosed no conflict of interest.
Satin, Leslie S.	Disclosed no conflict of interest.
Sato, Kyoko K.	Disclosed no conflict of interest.
Satoh, Tetsurou	Disclosed no conflict of interest.
Saunders, Jeff	*Employee*: Ember Therapeutics; *Stock/Shareholder*: Ember Therapeutics.
Schauer, Philip R.	*Consultant*: Ethicon EndoSurgery, Inc.
Scheer, Marsel	Disclosed no conflict of interest.
Scheja, Ludger	Disclosed no conflict of interest.
Scherer, Philipp E.	Disclosed no conflict of interest.
Scherneck, Stephan	Disclosed no conflict of interest.
Schernthaner, Gerit	Disclosed no conflict of interest.
Schernthaner, Guntram	Disclosed no conflict of interest.
Scheuner, Donalyn	*Employee*: Eli Lilly and Company.
Schiavon, Michele	Disclosed no conflict of interest.
Schillinger, Dean	Disclosed no conflict of interest.
Schliess, Freimut	Disclosed no conflict of interest.
Schmid, Sebastian M.	Disclosed no conflict of interest.
Schmitt, Patricia	Disclosed no conflict of interest.
Scholey, James W.	Disclosed no conflict of interest.
Schulz, Nadja	Disclosed no conflict of interest.
Schulz, Tim J.	Disclosed no conflict of interest.
Schulze, Gunnar	Disclosed no conflict of interest.
Schur, Ellen A.	Disclosed no conflict of interest.
Schürmann, Annette	Disclosed no conflict of interest.
Schurr, Daniel	*Research Support*: Oramed Pharmaceuticals.
Schwartz, Frank L.	*Research Support*: Medtronic.
Schwarz, Jean-Marc	Disclosed no conflict of interest.
Schweitzer, Matthias A.	*Employee*: Roche Diagnostics GmbH.
Schwenk, Robert W.	Disclosed no conflict of interest.
Schwenke, Dawn C.	Disclosed no conflict of interest.

AUTHOR	RELATIONSHIP/COMPANY
Scirica, Benjamin M.	*Consultant*: Arena Pharmaceuticals, Inc., Boston Clinical Research Institute, Bristol-Myers Squibb Company, Decision Resources, Eisai, Inc., Forest Pharmaceuticals, Inc., Gilead Sciences, Inc., Lexicon Pharmaceuticals, Inc., St. Jude's Medical; *Research Support*: AstraZeneca/Bristol-Meyers Squibb, Bayer Health Care, LLC, Daiichi-Sankyo, Inc., Eisai, Inc., Gilead Sciences, Inc., GlaxoSmithKline, Johnson & Johnson, Merck Sharp & Dohme Limited.
Sealls, Whitney	*Employee*: Eli Lilly and Company.
Seborg, Dale	Disclosed no conflict of interest.
Seino, Yutaka	*Advisory Panel*: Astellas Pharma, Becton, Dickinson and Company, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, GSK, Johnson & Johnson, Novo Nordisk A/S, Sanofi, Taisho, Takeda Pharmaceutical Company, Ltd.
Senerchia, Cynthia	*Consultant*: Merck.
Senesi, Pamela	Disclosed no conflict of interest.
Senthilselvan, Ambikaipakan	Disclosed no conflict of interest.
Seo, Ji A.	Disclosed no conflict of interest.
Sereika, Susan	Disclosed no conflict of interest.
Serveaux, Jean-Pierre	Disclosed no conflict of interest.
Sethupathy, Praveen	Disclosed no conflict of interest.
Shackel, Nicholas	Disclosed no conflict of interest.
Shah, Baiju R.	Disclosed no conflict of interest.
Shah, Kaanan	Disclosed no conflict of interest.
Shamblott, Michael	Disclosed no conflict of interest.
Shan, Bo	Disclosed no conflict of interest.
Shankar, Nandita K.	Disclosed no conflict of interest.
Shankar, Sudha S.	*Employee*: Eli Lilly and Company, Merck (*Spouse/Partner*).
Shantavasinkul, Prapimporn C.	Disclosed no conflict of interest.
Shao, Mengle	Disclosed no conflict of interest.
Shapiro, Hilton	*Research Support*: Roche Diagnostics Australia Pty Ltd.
Sharma, Savita	Disclosed no conflict of interest.
Shaw, Collin	Disclosed no conflict of interest.
Shen, J.F.	*Employee*: Merck Sharp & Dohme Limited.
Shen, Yuefei	Disclosed no conflict of interest.
Shepard, Jaclyn	Disclosed no conflict of interest.
Sherman, Arthur	Disclosed no conflict of interest.
Shi, Xia-jie	Disclosed no conflict of interest.
Shibuya, Takashi	Disclosed no conflict of interest.
Shields, Beverley	Disclosed no conflict of interest.
Shimizu, Shin	*Employee*: Sanofi.
Shin, Chol	Disclosed no conflict of interest.
Shiota, Chiyo	Disclosed no conflict of interest.
Shipkova, Petia	*Employee*: Bristol-Myers Squibb Company.
Shojima, Nobuhiro	Disclosed no conflict of interest.
Shou, Weinian	Disclosed no conflict of interest.
Shpitzen, Shoshi	*Research Support*: Oramed Pharmaceuticals.
Shubrook, Jay H.	*Advisory Panel*: Eli Lilly; *Research Support*: Sanofi Aventis.
Shue, Wayne H-H.	*Speaker's Bureau*: AstraZeneca Pharmaceuticals LP, Bayer Health Care, LLC, Merck Sharp & Dohme Limited, Takeda Global Research and Development, Inc.
Shulman, Gerald I.	Disclosed no conflict of interest.
Shults, Justine	Disclosed no conflict of interest.
Siaw, Melanie	Disclosed no conflict of interest.
Siegel, Robert	Disclosed no conflict of interest.
Silverman, Melvin	Disclosed no conflict of interest.
Simino, Lais A.	Disclosed no conflict of interest.
Simmons, David	Disclosed no conflict of interest.
Simon, Marie-Christine	Disclosed no conflict of interest.
Simpson, Scot H.	Disclosed no conflict of interest.
Sinclair, Ewan F.	Disclosed no conflict of interest.
singh, Narendra	*Research Support*: Gilead; *Speaker's Bureau*: Gilead.
Sinha, Sandeep	Disclosed no conflict of interest.
Sjöstrand, Mikaela	*Employee*: AstraZeneca Pharmaceuticals LP.
Skovlund, Søren E.	*Employee*: Novo Nordisk A/S.
Skrtic, Marko	Disclosed no conflict of interest.
Skyler, Jay S.	*Advisory Panel*: Boehringer Ingelheim Pharmaceuticals, Inc., Halozyme Therapeutics, Intarcia Therapeutics, Inc., Orgenesis, Sanofi, Valeritas, LLC, Viacyte; *Board Member*: Dance Biopharm, Dexcom, Inc., SynAlpha; *Consultant*: AstraZeneca/Bristol-Meyers Squibb, Elcelyx Therapeutics, Inc., Ideal Life, Novo Nordisk A/S, NPS, PhaseBio; *Research Support*: Mesoblast, Viacyte; *Stock/Shareholder*: Dance Biopharm, Dexcom, Inc., Ideal Life, SynAlpha, Tandem Diabetes Care.
Slama, Michael	Disclosed no conflict of interest.
Sloop, Kyle W.	Disclosed no conflict of interest.
Smiley, Dawn	*Advisory Panel*: Boehringer Ingelheim Pharmaceuticals, Inc., Janssen Pharmaceuticals, Sanofi; *Research Support*: Abbott Nutrition, Merck.
Smith, Anne	*Employee*: Isis Pharmaceuticals; *Stock/Shareholder*: Isis Pharmaceuticals.
Smith, Ulf	Disclosed no conflict of interest.
Smyth, Graham	Disclosed no conflict of interest.
Sochett, Etienne B.	Disclosed no conflict of interest.
Soeters, Maarten R.	Disclosed no conflict of interest.
Softic, Samir	Disclosed no conflict of interest.
Soleymanlou, Nima	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Son, JeeWoong	Disclosed no conflict of interest.
Song, An	Disclosed no conflict of interest.
Song, David	Disclosed no conflict of interest.
Song, Guangyao	Disclosed no conflict of interest.
Song, Hui	Disclosed no conflict of interest.
Song, Min	*Employee*: Eli Lilly and Company.
Sonne, David P.	Disclosed no conflict of interest.
Sorkin, Dara H.	Disclosed no conflict of interest.
Sothiratnam, Radhakrishna	*Advisory Panel*: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Merck Sharp & Dohme Limited; *Research Support*: Merck Sharp & Dohme Limited, Novo Nordisk A/S; *Speaker's Bureau*: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Merck Sharp & Dohme Limited, Novo Nordisk A/S.
Souhami, Elisabeth	*Employee*: Sanofi.
Soula, Gérard	*Stock/Shareholder*: Adocia.
Soula, Olivier	*Employee*: Adocia; *Stock/Shareholder*: Adocia.
Soula, Rémi	*Employee*: Adocia; *Stock/Shareholder*: Adocia.
Soumillon, Magali	Disclosed no conflict of interest.
Sparks, Lauren M.	Disclosed no conflict of interest.
Sparks, Steve M.	Disclosed no conflict of interest.
Speight, Jane	*Research Support*: Roche Diagnostics Australia Pty Ltd.
Spielman, Daniel M.	Disclosed no conflict of interest.
Splawn, Taylor	Disclosed no conflict of interest.
Srodulski, Sarah	Disclosed no conflict of interest.
Stahl, Andreas	Disclosed no conflict of interest.
Staiger, Harald	Disclosed no conflict of interest.
Stangé, Geert	Disclosed no conflict of interest.
Staten, Myrlene	Disclosed no conflict of interest.
Stefanovski, Darko	Disclosed no conflict of interest.
Stein, Corey	Disclosed no conflict of interest.
Steinburg, Helmut O.	Disclosed no conflict of interest.
Steinfeld, Tod	Disclosed no conflict of interest.
Stentz, Frankie B.	Disclosed no conflict of interest.
Stephens, Natalie A.	Disclosed no conflict of interest.
Stettler, Nicolas	Disclosed no conflict of interest.
Stewart, Andrew F.	Disclosed no conflict of interest.
Stiles, Bangyan	Disclosed no conflict of interest.
Stollfuss, Barbara	*Employee*: Bayer Healthcare.
Strachan, David	Disclosed no conflict of interest.
Strassburger, Klaus	Disclosed no conflict of interest.
Stratigopoulos, George	Disclosed no conflict of interest.
Strock, Ellie	*Advisory Panel*: Sanofi; *Consultant*: CeQur, Ltd.; *Research Support*: Abbott Diabetes Care, Halozyme Therapeutics.
Strumph, Paul	*Employee*: Lexicon Pharmaceuticals, Inc.; *Stock/Shareholder*: Lexicon Pharmaceuticals, Inc.
Strychar, Irene	Disclosed no conflict of interest.
Strycker, Lisa	Disclosed no conflict of interest.
Suenens, Krista	Disclosed no conflict of interest.
Suh, David	Disclosed no conflict of interest.
Sun, Chenglin	Disclosed no conflict of interest.
Sun, Qi	Disclosed no conflict of interest.
Sun, Xiao-Jian	Disclosed no conflict of interest.
Sun, Yuxiang	Disclosed no conflict of interest.
Sun, Zhonghua	Disclosed no conflict of interest.
Sund, Reijo	Disclosed no conflict of interest.
Sung, Joyce	*Research Support*: Dexcom, Inc.
Svensson, Ann-Marie	Disclosed no conflict of interest.
Sweeney, Gary	Disclosed no conflict of interest.
Sweet, Douglas H.	Disclosed no conflict of interest.
Sweet, Ian R.	Disclosed no conflict of interest.
Syed, Ismail	Disclosed no conflict of interest.
Symons, J. David	Disclosed no conflict of interest.
Szendrödi, Julia	Disclosed no conflict of interest.
Szepessy, Edit	Disclosed no conflict of interest.
Takane, Karen	Disclosed no conflict of interest.
Takeishi, Soichi	Disclosed no conflict of interest.
Tamboli, Robyn A.	Disclosed no conflict of interest.
Tan, Elaine	Disclosed no conflict of interest.
Tan, Sara	Disclosed no conflict of interest.
Tanaka, Yuko	*Employee*: Nippon Boehringer Ingelheim Co., Ltd.
Tang, Jackson	*Research Support*: Merck.

AUTHOR	RELATIONSHIP/COMPANY
Tang, Mei	Disclosed no conflict of interest.
Tang, Qizhi	Disclosed no conflict of interest.
Tankovich, Elizabeth	Disclosed no conflict of interest.
Tantawi, Hyam	Disclosed no conflict of interest.
Taslimi, Mark	*Research Support*: Dexcom, Inc.
Taylor, Susan	Disclosed no conflict of interest.
Tehan, Ben	Disclosed no conflict of interest.
Teitelman, Gladys	Disclosed no conflict of interest.
Tejedor, Natàlia V.	Disclosed no conflict of interest.
Tencerova, Michaela	Disclosed no conflict of interest.
Terauchi, Yasuo	*Other Relationship*: Advisor for EDITION JP Studies, Sanofi; *Research Support*: Astellas Pharma Inc., Astra Zeneca, Bayer Yakuhin Ltd., Boehringer Ingel heim GmbH, Daiichi-Sankyo Company Ltd., DaiNippon-Sumitomo, Eli Lilly and Company, Kissei, Kowa Pharmaceutical Co., Ltd., MSD, Novartis Pharma, Novo Nordisk Pharma Ltd., Ono Pharmaceutical Co., Ltd., Sanofi, Sanwa Kagaku Kenkyusho Co., Ltd., Shionogi & Co, Ltd., Takeda Pharmaceutical Company, Ltd., Tanabe-Mitsubishi Pharma; *Speaker's Bureau*: Astellas Pharma Inc., Astra Zeneca, Bayer Yakuhin Ltd., Boehringer Ingelheim GmbH, Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo Company Ltd., DaiNippon-Sumitomo, Eli Lilly and Company, Johnson & Johnson, Kissei, Kowa Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., MSD, Novartis Pharma, Novo Nordisk Pharma Ltd., Ono Pharmaceutical Co., Ltd., Pfizer, Roche Diagnostics, Sanofi, Sanwa Kagaku Kenkyusho Co, Ltd., Shionogi & Co., Ltd., Takeda Pharmaceutical Company, Ltd., Tanabe-Mitsubishi Pharma, Teijin.
Terruzzi, Ileana	Disclosed no conflict of interest.
Thayer, Sarah	*Employee*: Optum.
Thiering, Elisabeth	Disclosed no conflict of interest.
Thomas, Shane	Disclosed no conflict of interest.
Thompson, Benjamin M.	Disclosed no conflict of interest.
Thompson-Legault, Julie	Disclosed no conflict of interest.
Thoresen, G. Hege	Disclosed no conflict of interest.
Thorn, Peter	Disclosed no conflict of interest.
Threlkeld, Rebecca	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Thrysøe, Samuel	Disclosed no conflict of interest.
Tian, Haoming	Disclosed no conflict of interest.
Tian, Suyan	Disclosed no conflict of interest.
Tidjane, Najla	Disclosed no conflict of interest.
Tilton, Ronald	Disclosed no conflict of interest.
Timm, Derek	Disclosed no conflict of interest.
Tlnahones, Francisco J.	Disclosed no conflict of interest.
Tipton, Kevin D.	Disclosed no conflict of interest.
Tirunagari, Neeraj	Disclosed no conflict of interest.
Tiwari, Sandeep	Disclosed no conflict of interest.
Tobacman, Joanne K.	Disclosed no conflict of interest.
Tofé Povedano, Santiago	*Research Support*: Eli Lilly and Company.
Toledo-Corral, Claudia M.	Disclosed no conflict of interest.
Tominaga, Tatsuya	Disclosed no conflict of interest.
Tomita, Kimio	Disclosed no conflict of interest.
Tong, Jenny	Disclosed no conflict of interest.
Tong, Xin	Disclosed no conflict of interest.
Torquati, Alfonso	Disclosed no conflict of interest.
Torres, Jason M.	Disclosed no conflict of interest.
Torres, Pablo	Disclosed no conflict of interest.
Torsoni, Adriana S.	Disclosed no conflict of interest.
Torsoni, Marcio A.	Disclosed no conflict of interest.
Toyoda, Masashi	Disclosed no conflict of interest.
Trahair, Laurence G.	Disclosed no conflict of interest.
Traust, Jeniece	Disclosed no conflict of interest.
Trautmann, Michael	Disclosed no conflict of interest.
Trigo, Enrique	Disclosed no conflict of interest.
Tripathi, Anand	Disclosed no conflict of interest.
Triplitt, Curtis	Disclosed no conflict of interest.
Troshina, Ekaterina A.	Disclosed no conflict of interest.
Trost, Denisa	Disclosed no conflict of interest.
Truran, Seth	Disclosed no conflict of interest.
Tsai, Jia-Ling	Disclosed no conflict of interest.
Tsai, Shihyin	Disclosed no conflict of interest.
Tsao, David	*Employee*: Pfizer, Inc.
Tunceli, Kaan	*Employee*: Merck; *Stock/Shareholder*: Merck.
Turner, Carol	Disclosed no conflict of interest.
Turner, Kati	Disclosed no conflict of interest.
Twigg, Stephen M.	*Advisory Panel*: Sanofi.
Tyagi, Vidhi	Disclosed no conflict of interest.
Uchimura, Kohei	Disclosed no conflict of interest.
Umezawa, Akihiro	Disclosed no conflict of interest.

AUTHOR	RELATIONSHIP/COMPANY
Umpierrez, Guillermo E.	*Advisory Panel*: Boehringer Ingelheim Pharmaceuticals, Inc., Merck, Sanofi; *Research Support*: Boehringer Ingelheim Pharmaceuticals, Inc., Merck, Novo Nordisk Inc., Sanofi.
Unger, T.J.	*Employee*: Ember Therapeutics; *Stock/Shareholder*: Ember Therapeutics.
Urano, Fumihiko	*Research Support*: Ono Pharmaceutical Co., Ltd.
Urlaub, Diana	Disclosed no conflict of interest.
Urlaub, Diana M.	Disclosed no conflict of interest.
Urquiza, Susana	Disclosed no conflict of interest.
Usui, Ryota	Disclosed no conflict of interest.
Vadrevu, Suryakiran	Disclosed no conflict of interest.
Valensi, Paul	Disclosed no conflict of interest.
Valladares Salgado, Adan	Disclosed no conflict of interest.
Van Brunt, Kate	*Employee*: Eli Lilly and Company; *Stock/Shareholder*: Eli Lilly and Company.
Van de Bunt, Martijn	Disclosed no conflict of interest.
Van Eldik, Linda	Disclosed no conflict of interest.
van Leeuwen, Elisabeth M.	Disclosed no conflict of interest.
Vangala, Pranitha	Disclosed no conflict of interest.
Vargas-Ojeda, Adriana C.	Disclosed no conflict of interest.
Vasavada, Rupangi	Disclosed no conflict of interest.
Vassileva, Maria T.	Disclosed no conflict of interest.
Vatner, Daniel F.	Disclosed no conflict of interest.
Vaughn, Daniel E.	*Employee*: Halozyme Therapeutics; *Stock/Shareholder*: Halozyme Therapeutics.
Veettil, Sona	Disclosed no conflict of interest.
Veillard, Anne-Sophie	Disclosed no conflict of interest.
Vella, Adrian	*Consultant*: Sanofi.
Velloso, Licio A.	Disclosed no conflict of interest.
Venkat, Manu V.	Disclosed no conflict of interest.
Vera, Nicholas B.	Disclosed no conflict of interest.
Verberne, Hein J.	Disclosed no conflict of interest.
Verma, Narsingh	Disclosed no conflict of interest.
Vernochet, Cecile	Disclosed no conflict of interest.
Vijayakumar, Archana	Disclosed no conflict of interest.
Vilà, Laia	Disclosed no conflict of interest.
Vilsbøll, Tina	*Advisory Panel*: Bristol-Myers Squibb/AstraZeneca, Merck Sharp & Dohme Limited, Novo Nordisk A/S, Takeda Pharmaceutical Company, Ltd.; *Speaker's Bureau*: AstraZeneca/Bristol-Meyers Squibb, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Merck Sharp & Dohme Limited, Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Sanofi, Zealand Pharma A/S.
Vinet, Laetitia	*Consultant*: Sanofi.
Vinik, Aaron I.	*Advisory Panel*: Merck, Pfizer, Inc.; *Consultant*: Isis Pharmaceuticals, Merck, Pamlab, LLC, Pfizer, Inc.; *Research Support*: ADA, Impeto Medical, Intarcia Therapeutics, Inc., IPSEN-Formulation Innovation, NIH, Novo Nordisk Inc., Pfizer, Inc., Sanofi, VM Biopharma; *Speaker's Bureau*: Merck.
Vistisen, Dorte	Disclosed no conflict of interest.
Vivot, Kevin	Disclosed no conflict of interest.
Von Eynatten, Maximilian	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Vora, Jiten	Disclosed no conflict of interest.
Voronenko, Pavel Alexandrovich	Disclosed no conflict of interest.
Wagner, Robin S.	*Employee*: Roche Diagnostics.
Wakeman, Christian	Disclosed no conflict of interest.
Wallace, Jane	*Employee*: Bayer HealthCare.
Waltl, Maren	Disclosed no conflict of interest.
Wan, Min	Disclosed no conflict of interest.
Wang, Carol	Disclosed no conflict of interest.
Wang, Chao	Disclosed no conflict of interest.
Wang, Chen-Pin	Disclosed no conflict of interest.
Wang, Gang	Disclosed no conflict of interest.
Wang, Guixia	Disclosed no conflict of interest.
Wang, Haiqing	Disclosed no conflict of interest.
Wang, Jing	Disclosed no conflict of interest.
Wang, Josh J.	Disclosed no conflict of interest.
Wang, Jue	*Employee*: Merck Sharp & Dohme Limited.
Wang, Jun	Disclosed no conflict of interest.
Wang, Liangsu	*Employee*: Merck; *Stock/Shareholder*: Merck.
Wang, Liheng	Disclosed no conflict of interest.
Wang, Mingming	Disclosed no conflict of interest.
Wang, Na	Disclosed no conflict of interest.
Wang, Rong	Disclosed no conflict of interest.
Wang, Shan	Disclosed no conflict of interest.
Wang, Weiya	Disclosed no conflict of interest.
Wang, Youqing	*Research Support*: Eli Lilly and Company.
Ward, William K.	*Advisory Panel*: Xeris Pharmaceuticals; *Board Member*: Pacific Diabetes Technologies, Inc; *Employee*: Pacific Diabetes Technologies, Inc; *Stock/Shareholder*: iSense Corp, Pacific Diabetes Technologies.

AUTHOR	RELATIONSHIP/COMPANY
Wardecki, Marek	*Employee*: Sanofi; *Stock/Shareholder*: Sanofi.
Wardle, Sophie L.	Disclosed no conflict of interest.
Warodomwichit, Daruneewan	Disclosed no conflict of interest.
Wasson, Jonathon	Disclosed no conflict of interest.
Watada, Hirotaka	Disclosed no conflict of interest.
Watanabe, Abby	*Employee*: Ember Therapeutics; *Stock/Shareholder*: Ember Therapeutics.
Watanabe, Richard M.	Disclosed no conflict of interest.
Watkins, Renecia A.	Disclosed no conflict of interest.
Watson, Kathleen T.	Disclosed no conflict of interest.
Watts, Lynnetta	*Employee*: Isis Pharmaceuticals; *Stock/Shareholder*: Isis Pharmaceuticals.
Watts, Margaret	Disclosed no conflict of interest.
Weaver, Jeff	Disclosed no conflict of interest.
Webb, Mary F.	Disclosed no conflict of interest.
Weber, Katharina S.	Disclosed no conflict of interest.
Wei, Cheryl	*Employee*: AstraZeneca Pharmaceuticals LP.
Wei, Li	Disclosed no conflict of interest.
Wei, Rong	Disclosed no conflict of interest.
Wei, Shaolong	Disclosed no conflict of interest.
Wei, Wenhui	*Employee*: Sanofi.
Weigelt, Clara	Disclosed no conflict of interest.
Weinrib, Stephen	Disclosed no conflict of interest.
Weir, Daniala L.	Disclosed no conflict of interest.
Weir, Gordon	*Advisory Panel*: Beta O2 Technologies; *Consultant*: Merck (*Spouse/Partner*), Novo Nordisk Inc. (*Spouse/Partner*); *Research Support*: Johnson & Johnson.
Weitsman, Stacy	Disclosed no conflict of interest.
Wen, Michael	Disclosed no conflict of interest.
West, Amy	Disclosed no conflict of interest.
Wheeler, Michael B.	Disclosed no conflict of interest.
White, David	*Employee*: Ember Therapeutics; *Stock/Shareholder*: Ember Therapeutics.
White, Neil H.	Disclosed no conflict of interest.
Whittard, Toni	Disclosed no conflict of interest.
Wiersch, John	Disclosed no conflict of interest.
Wild, Sarah	Disclosed no conflict of interest.
Williams, Ann S.	*Board Member*: American Association of Diabetes Educators.
Williams, Desmond	Disclosed no conflict of interest.
Williams, Kathryn H.	Disclosed no conflict of interest.
Williams, Kevin W.	Disclosed no conflict of interest.
Willis, Erik	Disclosed no conflict of interest.
Wilson, Bryan R.	*Employee*: Biodel, Inc.
Wisherd, Chris	Disclosed no conflict of interest.
Witard, Oliver C.	Disclosed no conflict of interest.
Witkowski, Piotr	Disclosed no conflict of interest.
Witte, Daniel R.	Disclosed no conflict of interest.
Wlodarczyk, Catherine S.	Disclosed no conflict of interest.
Woerle, Hans J.	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Woerle, Hans-Juergen	*Employee*: Boehringer Ingelheim GmbH & Co. KG.
Wohlgemuth, Stephen D.	Disclosed no conflict of interest.
Wolpert, Howard A.	Disclosed no conflict of interest.
Woo, Jessica	Disclosed no conflict of interest.
Wood, Richard	Disclosed no conflict of interest.
Woodlief, Tracey	Disclosed no conflict of interest.
Wu, Gongxiong	Disclosed no conflict of interest.
Wu, Hongyu	Disclosed no conflict of interest.
Wu, Jing	Disclosed no conflict of interest.
Wu, Jun	Disclosed no conflict of interest.
Wu, Margaret	*Employee*: Merck; *Stock/Shareholder*: Merck.
Wu, Tongzhi	Disclosed no conflict of interest.
Wu, Vincent	Disclosed no conflict of interest.
Wu, Xionghua W.	*Employee*: Halozyme Therapeutics.
Wu, Ying	Disclosed no conflict of interest.
Xanthakos, Stavra	Disclosed no conflict of interest.
Xia, Shuting	*Employee*: Isis Pharmaceuticals; *Stock/Shareholder*: Isis Pharmaceuticals.
Xian, Yang	Disclosed no conflict of interest.
Xiang, Anny H.	Disclosed no conflict of interest.
Xiao, Xianchao	Disclosed no conflict of interest.
Xiao, Xiangwei	Disclosed no conflict of interest.
Xiao, Xiaoqiu	Disclosed no conflict of interest.
Xie, Jun	Disclosed no conflict of interest.
Xie, Xinmin	Disclosed no conflict of interest.
Xin, Jiang	Disclosed no conflict of interest.
Xin, Ying	Disclosed no conflict of interest.
Xu, Eric E.	Disclosed no conflict of interest.
Xu, X. Julia	Disclosed no conflict of interest.
Xu, Xianmin	Disclosed no conflict of interest.
Xu, Yuping	Disclosed no conflict of interest.
Xu, Z.R.	Disclosed no conflict of interest.
Yabe, Daisuke	*Advisory Panel*: Novartis Pharma AG, Sanofi.
Yamada, Eijiro	Disclosed no conflict of interest.
Yamada, Masanobu	Disclosed no conflict of interest.
Yamada, Tomohide	Disclosed no conflict of interest.
Yamamoto, Mitsuko Lynn	*Employee*: Pfizer, Inc.
Yamazaki-Inoue, Mayu	Disclosed no conflict of interest.
Yan, Chaofeng	Disclosed no conflict of interest.
Yan, Cheng	Disclosed no conflict of interest.
Yan, Linda	Disclosed no conflict of interest.
Yan, X.D.	Disclosed no conflict of interest.
Yang, Alex	*Consultant*: ZS Pharma, Inc.
Yang, Fang	Disclosed no conflict of interest.
Yang, Gary	Disclosed no conflict of interest.
Yang, Liu	Disclosed no conflict of interest.
Yang, Wenying	*Research Support*: Eli Lilly and Company.
Yang, Zunyuan	Disclosed no conflict of interest.
Yao, Jun	*Employee*: Merck; *Stock/Shareholder*: Merck.
Yarchoan, Mark	Disclosed no conflict of interest.
Yavatkar, Manali	Disclosed no conflict of interest.
Yawe, Joseph	Disclosed no conflict of interest.
Yawe, Joseph C.	Disclosed no conflict of interest.
Yengo, Loic	Disclosed no conflict of interest.
Yilmaz, M. Temel	Disclosed no conflict of interest.
Yin, Lei	Disclosed no conflict of interest.
Yin, Xueyao	Disclosed no conflict of interest.
Ying, Wei	Disclosed no conflict of interest.
Yki-Järvinen, Hannele	*Speaker's Bureau*: Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Merck Sharp & Dohme Limited, Sanofi.
Yoo, Hye Jin	Disclosed no conflict of interest.
Yore, Mark M.	Disclosed no conflict of interest.
Yorek, Mark A.	Disclosed no conflict of interest.
Young, Andrew	Disclosed no conflict of interest.
Young, Richard L.	Disclosed no conflict of interest.
Yu, dan	Disclosed no conflict of interest.
Yu, Hongling	Disclosed no conflict of interest.
Yu, Ji Hee	Disclosed no conflict of interest.
Yu, Run	Disclosed no conflict of interest.
Yu, Shengsheng	*Employee*: Merck; *Stock/Shareholder*: Merck.
Yu, Yang	Disclosed no conflict of interest.
Yuan, G.Y.	Disclosed no conflict of interest.
Yuen, Kevin C.	*Research Support*: Lilly, Lone Star Heart, Pamlab, LLC, Pfizer, Inc., Prolor, Teva Pharmaceuticals, Versartis, Inc.
Yumura, Takayuki	Disclosed no conflict of interest.
Yung, Chi-Wah (Rudy)	Disclosed no conflict of interest.
Zamarron, Brian	Disclosed no conflict of interest.
Zambrowicz, Brian	*Employee*: Lexicon Pharmaceuticals, Inc.; *Stock/Shareholder*: Lexicon Pharmaceuticals, Inc.
Zee, Pamela	*Employee*: Bristol-Myers Squibb Company.
Zekry, Amany	Disclosed no conflict of interest.
Zeng, Ni	Disclosed no conflict of interest.
Zeng, Wen	Disclosed no conflict of interest.
Zhan, Ming	Disclosed no conflict of interest.
Zhang, Aimee Y.	Disclosed no conflict of interest.
Zhang, Bo	Disclosed no conflict of interest.
Zhang, BS	*Employee*: Merck Sharp & Dohme Limited.
Zhang, Deqiang	Disclosed no conflict of interest.
Zhang, Dongwei	Disclosed no conflict of interest.
Zhang, Dongyan	Disclosed no conflict of interest.
Zhang, Jinping	Disclosed no conflict of interest.
Zhang, Li	Disclosed no conflict of interest.
Zhang, Lu	Disclosed no conflict of interest.
Zhang, Ming	Disclosed no conflict of interest.
Zhang, Quan-Jiang	Disclosed no conflict of interest.
Zhang, Saifei	Disclosed no conflict of interest.
Zhang, Sarah X.	Disclosed no conflict of interest.
Zhang, Shangfu	Disclosed no conflict of interest.
Zhang, Tejia	Disclosed no conflict of interest.
Zhang, Xiangxun	Disclosed no conflict of interest.
Zhang, Xian-Man	Disclosed no conflict of interest.
Zhang, Xiao Juan	Disclosed no conflict of interest.
Zhang, Yi	Disclosed no conflict of interest.
Zhang, Yumin	Disclosed no conflict of interest.
Zhang, Yurong	Disclosed no conflict of interest.
Zhao, Dong	Disclosed no conflict of interest.
Zhao, Shangang	Disclosed no conflict of interest.
Zheng, Fenping	Disclosed no conflict of interest.
Zheng, Quan	*Employee*: Pfizer, Inc.
Zheng, Yan	Disclosed no conflict of interest.
Zhou, Beiyan	Disclosed no conflict of interest.
Zhou, Fangli	Disclosed no conflict of interest.
Zhou, Shan-lei	Disclosed no conflict of interest.
Zhu, Liwen	Disclosed no conflict of interest.

AUTHOR	RELATIONSHIP/COMPANY
Ziegler, Ralph	*Consultant*: Roche Diagnostics.
Ziemen, Monika	*Employee*: Sanofi.
Zijlstra, Eric	*Other Relationship*: Novo Nordisk A/S.
Zimering, Mark B.	Disclosed no conflict of interest.
Zimmermann, Alan G.	*Employee*: Eli Lilly and Company, Eli Lilly and Company (*Spouse/Partner*); *Stock/Shareholder*: Eli Lilly and Company, Eli Lilly and Company (*Spouse/Partner*).
Zinman, Bernard	*Advisory Panel*: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Eli Lilly and Company, Merck, Novo Nordisk Inc., Sanofi, Takeda Pharmaceutical Company, Ltd.; *Research Support*: Boehringer Ingelheim Pharmaceuticals, Inc., Merck, Novo Nordisk Inc.
Zisser, Howard C.	*Consultant*: Animas Corporation, CeInovo, Insulet Corporation, MannKind Corporation, Roche Pharmaceuticals; *Employee*: Insulet Corporation; *Research Support*: Abbott Diabetes Care, Animas Corporation, Dexcom, Inc., Eli Lilly and Company, Insulet Corporation, Lifescan Animas, Inc., Medtronic, Novo Nordisk Inc., Roche Pharmaceuticals, Sanofi.
Zoughbie, Daniel E.	*Disclosed no conflict of interest*