Late Breaking Abstracts

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COMPLICATIONS—HYPOGLYCEMIA

1-LB

Hypoglycemia and Glycemic Variability in Chronic Kidney Disease

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Introduction: Chronic kidney disease (CKD) affects glycemia via variable clearance rates of insulin and other glucose-lowering medications, decreased renal gluconeogenesis, malnutrition, and possibly blunted counter-regulatory response.

Study Design: 81 subjects with T2D and CKD (estimated GFR <60 mL/min/1.73m^2 not on dialysis) treated with insulin or a sulfonylurea were enrolled. Each wore a blinded continuous glucose monitor (CGM, IPro2 with Enlite sensor) for two 6-day periods in a 4 week observational, multicenter study.

Results: Mean (SD) age was 68.0 (9.5) years. 90% were on insulin. Mean eGFR was 37.9 (12.9) mL/min/1.73m^2, and A1C was 7.7 (1.6)%. Mean CGM blood glucose was 167.7 (37.3) mg/dL; mean coefficient of variation was 30.9 (5.7)%; and median (IQR) rate of hypoglycemia episodes (<70 mg/dL) was 7.3 (2.3-17.2) per 30 days. There was no clear pattern of association of estimated GFR with hypoglycemia or glucose variability, but lower A1c was associated with a markedly higher incidence of hypoglycemia (Table). Each 1% lower hemoglobin A1c was associated with 2.7 additional hypoglycemia episodes per month (95% CI 0.7, 4.8, p=0.01).

Discussion: Hypoglycemia is common in T2D with moderate-severe CKD receiving hypoglycemic agents, and lower hemoglobin A1C is a strong risk factor for hypoglycemia in this population.

Table.

		Hypoglycemia incidence rate (events per 30 days)		Coefficient of variation (SD/mean BG)	
	N	Median (IQR)	Adjusted* difference of the mean (95% CI)	Mean (SD)	Adjusted difference* (95% CI)
Estimated GFR 45-59 mL/min/1.73m2	29	5.3 (2.7, 10.6)	0 (ref)	29.6 (5.1)	0 (ref)
Estimated GFR 30-44 mL/min/1.73m2	31	10.6 (5.3, 21.3)	3.3 (-4.6, 11.1)	33.0 (5.8)	3.7 (0.6, 6.8)
Estimated GFR <30 mL/min/1.73m2	21	2.7 (0.0, 13.3)	-2.4 (-11.0, 6.3)	29.6 (5.9)	0.4 (-3.0, 3.8)
Hgb A1c <7%	28	16.0 (0.0, 29.3)	16.4 (8.5, 24.3)	30.9 (6.7)	0.62 (-2.84,4.08)
Hgb A1c 7-7.9%	27	8.0 (2.7, 16.0)	2.7 (-5.8, 11.13)	31.2 (5.9)	0.50 (-3.09,4.09)
Hgb A1c ≥8%	26	2.7 (2.7, 8.0)	0 (ref)	30.6 (4.7)	0 (ref.)

* Adjusted for age, sex, race/ethnicity, and (for estimated GFR) A1c.

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2-LB

Differences in Beliefs between Adults with Intact and Impaired Awareness of Hypoglycemia in Type 1 Diabetes: A U.S. Sample

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Background: Severe hypoglycemia (SH) is a barrier to optimizing glycemic control in T1D. There is growing evidence that cognitive factors play a role in patients' ability to prevent SH. The Attitudes to Awareness questionnaire (A2A) comprises 19 items defining beliefs about hypoglycemia and its treatment. A UK study identified 3 groups of unhelpful beliefs using A2A: 1.) Minimizing concern about hypoglycemia, 2.) Prioritizing avoiding hyperglycemia and 3.) Normalizing asymptomatic hypoglycemia.

Aim: To investigate the prevalence of unhelpful beliefs about hypoglycemia and their association with morbidity in a U.S. population of adults with T1D.

Methods: The A2A questionnaire was sent to 6200 adults in the T1D Exchange Clinic Registry. 1978 responses were received (response rate 32%). Mann Whitney U tests compared scores for unhelpful beliefs by level of awareness (intact vs. impaired, latter, IAH, defined as a Gold Score ≥ 4) and by frequency of SH (Recurrent SH, RSH, defined as ≥ 2 episodes in the past year in which people were unable to treat themselves).

Results: Mean age of participants was 40 ± 16 yrs, T1D duration 23 ± 14, HbA1c 7.8 ± 1.4%; 62% female. 37% had IAH and 14% had RSH. Of those with IAH, 22% had RSH. The IAH group minimized concern about hypoglycemia less (p<0.001) and prioritized avoiding hyperglycemia more (p=0.002) than those with intact awareness. Those with RSH minimized concern about hypoglycemia less (p<0.001) and normalized asymptomatic hypoglycemia more (p=0.019) than those without RSH. Within the IAH group, those with RSH minimized concern around hypoglycemia more (p=0.037) than those without RSH.

Conclusion: Those with IAH or RSH have appropriately increased concern about hypoglycemia. However, those with IAH have greater concern about high glucose than those with intact awareness. The highest risk group (IAH + RSH) showed a worrying low level of concern about hypoglycemia. These problematic beliefs may be areas to tackle to reduce the risks of SH.

3-LB

Reduced Burden of Hypoglycemia Related to Dipeptidyl Peptidase-4 Inhibitor Use

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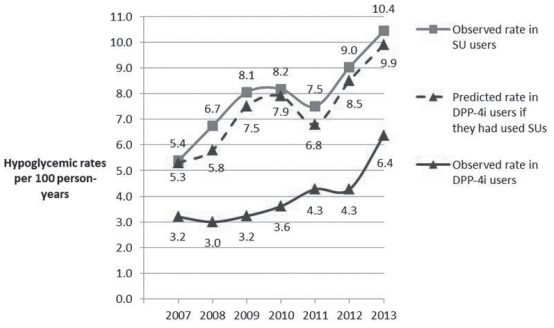
Newer diabetes medications, including dipeptidyl peptidase-4 inhibitors (DPP-4is), are associated with a lower risk of hypoglycemia than sulfonylureas (SU). Given the increasing use of DPP-4is following their availability, it could be hypothesized that this may have resulted in reduced hypoglycemic burden. Using a predictive modeling approach, our study aimed to estimate hypoglycemic rates in the absence of DPP-4i availability.

Using MarketScan Commercial Claims (2007-13), hypoglycemia, defined by a previously validated algorithm (ICD-9 codes), was assessed during 12 months after SU (n=245,201) or DPP-4i (n=176,786) initiation in adult T2D patients. A Poisson model was built/validated based on SU users, and then applied to DPP-4i users to predict hypoglycemic events if they had received SUs while adjusting for baseline patient characteristics.

The model based on SU users (n=122,601) showed good prediction of hypoglycemic rate in a split sample (n=122,600) as well as in a bootstrap sample (n=500,000). The observed average hypoglycemic rate per 100-person years was 7.9 (95% CI: 7.8-8.1) in SU users. Our model showed that the predicted rate in DPP-4i users was 7.4 (95% CI: 7.2-7.5) if they had used SUs instead. However, the observed rate in patients who received DPP-4is was only 4.0 (95% CI: 3.9-4.1).

Our predictive model suggests that use of DPP-4is, instead of SUs, over the last decade avoided nearly 50% hypoglycemic events.

Figure. Hypoglycemic rates in sulfonylurea (N = 245,201) and dipeptidyl peptidase-4 inhibitor (N=176,786) users.



Supported By: Merck & Co., Inc.

4-LB

Repeat Subcutaneous Dosing of Exendin 9-39 Reduces Hyperinsulinemic Hypoglycemia and Neuroglycopenic Symptoms in Patients with Post-Bariatric Hypoglycemia

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Post-Bariatric Hypoglycemia (PBH) is a rare but serious complication of bariatric surgery manifested by frequent episodes of symptomatic postprandial hypoglycemia, for which there are no approved pharmacotherapies. A central role for exaggerated meal-induced secretion of the incretin hormone, glucagon-like peptide-1 (GLP-1) with dysregulated insulin secretion has been established, making GLP-1 receptor antagonism an attractive targeted therapeutic approach. Studies evaluating the use of a single intravenous infusion or subcutaneous injection of the GLP-1 receptor antagonist, exendin

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9-39 (Ex-9) have demonstrated that a single dose of Ex-9 can prevent postprandial hypoglycemia, normalize beta cell function, and reduce neuroglycopenic symptoms in patients with PBH. We present interim data from the first multi-dose, multi-day study aimed at evaluating the efficacy, tolerability, and pharmacokinetic profile of subcutaneous Ex-9 in patients with PBH.

In this Phase 2a, single-blind, multiple ascending dose study conducted at the Stanford University Clinical and Translational Research Unit, 11 participants underwent a baseline oral glucose tolerance test (OGTT) followed by random assignment to up to 3 days of BID subcutaneous doses of Ex-9 ranging from 0.05-0.45 mg/kg with a repeat OGTT on the final day of dosing. Treatment with Ex-9 reduced the magnitude of hypoglycemia at all dose levels. Participants receiving doses of ≥ 0.2 mg/kg did not require rescue, and on average achieved a 50 ± 13% reduction in peak insulin concentrations with a 44 ± 18% reduction in neuroglycopenic symptoms. These interim data provide preliminary evidence that multiple doses of Ex-9 prevent severe and symptomatic postprandial hypoglycemia in patients with PBH during OGTT.

Supported By: Eiger BioPharmaceuticals

5-LB

Differential Associations of Impaired Hypoglycemia Awareness and Severe Hypoglycemia with Cognition, Quality of Life, and Distress in T1D Adults

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Impaired hypoglycemia awareness (IHA) affects 20% to 40% of T1D patients and increases risk of severe hypoglycemia (SH). IHA has been associated with low concern about hypoglycemia, despite high risk of SH, and with reduced ability to change behavior to avoid future hypoglycemia. We assessed hypoglycemia awareness (HA) and sought correlations with cognition, quality of life (QoL), and distress in 85 T1D adults with HA and IHA. HA status was determined using the Gold Score (GS) and the Clarke score (CS), with ≥4=IHA for each. SH was evaluated by 2 questions (3 and 4) included in the CS. All subjects completed the Montreal Cognitive Assessment (global cognition); the INECO Frontal Screening (executive functions); the Diabetes Health Profile (DHP, QoL); and the Hospital Anxiety and Depression Scale. Participants' mean±SD age and diabetes duration were 38.4±12.5 and 19.1±11.7 years, respectively; 54.1% were male; median and interquartile ranges for GS and CS 3 [1-4] and 1 [0-3], respectively. 32% had IHA by GS and 17% by CS, the 2 scores correlating moderately (r_s=0.58, P < 0.001). 86% of IHA patients by CS vs. only 41% with IHA by GS had had SH in the past 6 months, with 50% vs. 19% reporting seizure, or parenteral treatment for SH in the last year and no reports of such SH in participants with IHA by GS only. Correlation analysis of the whole group showed that increased GS and CS associated with lower performance in naming subtest and higher barriers to activity in DHP. Only CS associated with higher psychological distress in DHP, and higher anxiety and depression, while 38% of subjects scoring positive for IHA with GS only had evidence of executive dysfunction.

In conclusion, people with T1D and IHA, at known high risk for SH, show evidence of impaired cognition and psychological distress. The association of a positive CS but not GS with increased psychological distress suggests the association may be driven by SH, while IHA alone may drive executive dysfunction.

6-LB

Racial Differences in Emergency Department Visits for Hypoglycemia in Older Insulin Recipients, 2004-2013

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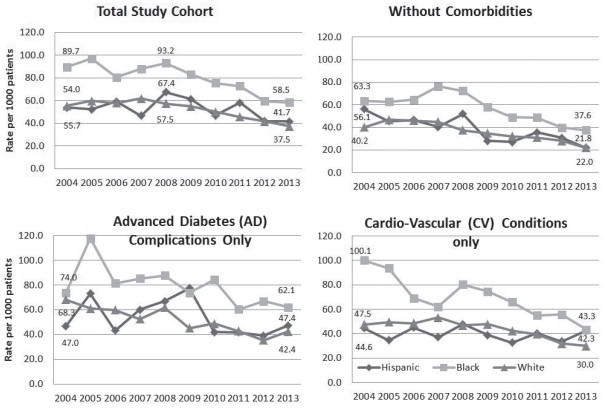
We evaluated annual trends in emergency department (ED) visits for hypoglycemia (HYPO) in veterans receiving Veteran Health Administration (VHA) care using linked VHA and Medicare databases. Patients on insulin and ≥65 years were stratified by race/ethnicity and four comorbidity categories (cardio-vascular (CV), advanced diabetes complications (AD), diminished life expectancy, and mental health/neurologic). Patients on insulin increased from 55,882 (11.2% of older diabetes patients) in 2004 to 100,175 (15.5%) in 2013. 80-82% were white, 10-11% black, 5-6% Hispanic, and <2% women. 79-83% had ≥1 comorbidity categories: AD only: 8-9%, CV only: 24-29%, AD and CV only: 16-21%. Cumulative ED visits were 37,494 (3,266-4,056/year) for 24,760 (2,563-3,266/year) unique patients; 5,094 (14%) events had subsequent hospitalization. Rates declined from 2008 for all races/ethnicity (rate ratio: 0.65; 95% CI=0.62-0.68 from a Poisson regression). Blacks had higher rates than whites (58.5 vs. 37.5 events per 1,000 patients in 2013). Compared to those without comorbidities (24.4 in 2013), rates were 46.4 for AD only, 31.3 for CV only, 49.6 for AD and CV only, and 70.1 for having 3 or 4 comorbidity categories in 2013. Racial differences persisted in all comorbid categories despite marked declines in HYPO_ED rates. We propose case management for high risk patients, especially minority groups.

Figure.



Supported By: U.S. Department of Veterans Affairs

7-LB

Prediction of Hypoglycemia during Aerobic Exercise in Individuals with Type 1 Diabetes Using Decision Trees

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Individuals with type 1 diabetes (T1D) indicate the fear of exercise related hypoglycemia as the major barrier to regular physical activity. There is currently no validated prediction algorithm that can help these individuals ascertain the risk of hypoglycemia prior to the start of aerobic exercise. We developed and evaluated 3 separate prediction algorithms with increasing levels of complexity to identify the risk of hypoglycemia at the start of exercise. A metadata set was used from over 130 observations of in-clinic aerobic exercise in 37 adults with T1D from 3 different studies (17M; weight, 72±12 kg; age, 33±6 years) to train and validate the prediction algorithms. Subjects performed either moderate or mild aerobic exercise at different times of the day (morning, midafternoon, or late afternoon) and exercised for durations ranging from 25 min to 45 min. We developed and tested the following three prediction algorithms using a ten-fold cross-validation approach and included anthropomorphic, exercise, glucose and insulin features. Model 1: Simple decision tree model. Model 2: Complex decision tree model. Model 3: Random forest model for use in automated insulin delivery systems

Table.

Classifier	Number of features	Accuracy (%)	Sensitivity (%)	Specificity (%)
Model 1	2	80.00	72.92	84.15
Model 2	5	83.85	85.42	82.93
Model 3	8	97.69	100	96.34

After further validation, these models could potentially be used by both artificial pancreas and decision support systems to help people with T1D avoid exercise related hypoglycemia.

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8-LB

Suppressed Catecholamine Release following Recurrent Hypoglycemia Involves Altered Adrenal Function

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Insulin-induced hypoglycemia activates the counter-regulatory response (CRR), a hormonal and neuronal mechanism that restores euglycemia. A major component of the CRR is the release of epinephrine from neuroendocrine chromaffin cells in the adrenal medulla. Epinephrine acts on a variety of target tissues including the liver and adipose tissue to increase glucose production. However, with repeated activation of the CRR, epinephrine release becomes progressively impaired. Although the reasons are not clear this could involve central or peripheral mechanisms or a combination of the two. To determine whether the altered CRR involves a change in adrenal function we quantified catecholamine release from chromaffin cells from (i) control mice; (ii) mice exposed to one episode of insulin-induced hypoglycemia (IIH: blood glucose < 60 mg/dl) and (iii) mice exposed to three episodes of insulin-induced hypoglycemia. Catecholamine release was evoked optogenetically from single chromaffin cells in vitro isolated from THcre x ChR (tdTomato) mice. Secretion was triggered by a train of light flashes and

For author disclosure information, see page LB107.

quantified using carbon fiber amperometry. Recurrent hypoglycemia led to a significant reduction in catecholamine release compared to control mice. Prior exposure to one episode of IIH led to an increase in catecholamine release compared to controls. A single episode of IIH was also associated with an increase in the adrenal expression of tyrosine hydroxylase, the rate limiting enzyme for catecholamine synthesis but no change in expression was observed after recurrent hypoglycemia. These results are consistent with a model in which impairment of the counter-regulatory response involves a peripheral defect in catecholamine secretion that is localized to the adrenal itself.

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9-LB

Automated Glucagon Administration for Treatment of Postbariatric Hypoglycemia

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A rare complication of bariatric surgery is development of post-bariatric hypoglycemia (PBH). Treatment of hypoglycemia often leads to spikes in blood sugar which trigger more hypoglycemia. Hypoglycemia unawareness can develop and can lead to complications such as loss of consciousness and seizures. An emergency glucagon injection is currently the standard treatment for severe hypoglycemia, but we hypothesized that automated administration of microdose glucagon via a closed-loop bionic pancreas system could be effective at reducing the incidence and severity of hypoglycemia in patients with PBH. To test this hypothesis, we conducted a two-week, randomized, placebo-controlled study involving 10 participants with PBH who reported continued hypoglycemia despite their current medication regimen (including acarbose and/or octreotide). During the study, participants managed their hypoglycemia in a usual care fashion while receiving either glucagon or placebo each day (7 days of each in random order) through a closed-loop bionic pancreas system consisting of a continuous glucose monitor (CGM), an iPhone running the control algorithm, and a pump with a standard infusion set. There was a statistically significant reduction in percentage of time spent with BG <70mg/dl (3.1±3.9% vs. 5.9±5.8% p=0.009) and a nominal reduction in percentage of time <60mg/dl (1.3±2.0% vs. 2.3±2.5% p=0.06) on glucagon vs. placebo days. There was no difference in mean glucose (112±10 vs. 110±11 mg/dl, p=0.07) Mean total daily glucagon dose on glucagon days was 8.3±3.8 mcg/kg/day. Subjects were able to correctly guess their assignment to glucagon or placebo only 23% of the time. These data suggests that automated glucagon administration significantly reduced hypoglycemia without increased mean glucose or hyperglycemia and is well-tolerated in individuals with PBH.

Supported By: Zealand Pharma

COMPLICATIONS—MACROVASCULAR—ATHEROSCLEROTIC CARDIOVASCULAR DISEASE AND HUMAN DIABETES

10-LB

Glycation-Induced Degradation of HDL Proteins in Diet-Controlled Patients with Diabetes

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Hyperglycemia plays a key role in the pathogenesis of cardiovascular complications of type 2 diabetes mellitus (T2D). T2D is associated with HDL dysfunction and the increased degradation of ApoAI, the major protein of HDL. The effect of hyperglycemia-induced glycation on ApoAI stability and HDL metabolism was investigated in 9 diet-controlled T2D (age 59.3±8.5 y, 5M/4F, BMI 31.2±3.3 kg/m^2, fbg 112.4±15.1 mg/dL, Hba1c 6.3 ±0.3) and 8 age- and BMI-matched healthy adults (age 50.7±11.6, 4m/4f, BMI 28.7±3.1, fbg 92.5±11.1, Hba1c 5.5±0.3). The HDL flux and turnover of multiple HDL proteins were studied using the ^2H_2O-metabolic labeling approach. The effect of hyperglycemia-induced glycation on ApoAI stability was evaluated based on the degradation of glycated and native protein. HDL's antioxidant, antiinflammatory and cholesterol efflux properties of HDL determined using in vitro assays.

The control and T2D subjects had similar levels of triglycerides, total cholesterol, HDL cholesterol, and ApoAI. Patients with T2D had increased fractional catabolic rate and production rate but reduced plasma residence time of both HDLc and ApoAI. Several other HDL proteins, including ApoAII, ApoAIV, vitamin D-binding protein, complement 3 and ceruloplasmin also had increased degradation (all P<0.05). HbAc1 was negatively correlated with the half-lives of multiple HDL proteins, including ApoAI (r=-0.46, P=0.003). Proteomics analysis revealed that several HDL proteins were modified with glucose. The kinetic analysis of glycated and native ApoAI peptides show that post-transnational glycation resulted in 3 fold decrease of ApoAI half-life (P<0.05). These alterations in HDL metabolism were associated with significant changes in the cholesterol efflux and antioxidant properties of HDL.

The ^2H_2O method allows the detection of early in vivo changes in HDL flux related to HDL dysfunction in diet-controlled patients with T2D.

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11-LB

miR-126 Enrichment Enhances the Protective Effect of Endothelial Progenitor Cells Derived Exosomes on Hypoxia/High Glucose-Induced Endothelial Cells Injury

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We have previously demonstrated that endothelial progenitor cells (EPCs) have therapeutic effects on ischemic stroke in diabetes. The beneficial effects of stem cells could come from their released exosomes (EXs) which deliver various microRNAs (miRs). We have shown that the vascular protective miR-126 targeting vascular endothelial growth factor receptor 2 (VEGFR2) is down-regulated in diabetes. In this study, we determined whether miR-126 enriched EPC-EXs (EPC-EXs^{miR126}) have better protective effects than EPC-EXs on endothelial cells (ECs) in an in vitro diabetic ischemia model induced by hypoxia and high glucose. Bone marrow EPCs from C57BL/6 mice were transfected with miR-126 mimics to increase the level of miR-126 in both EPCs and EPC-EXs. Human brain vascular ECs were cultured with high glucose (25 mM) medium in a hypoxic incubator (1% O2) for 6 hrs, and treated with vehicle (culture medium), EPC-EXs and EPC-EXs$^{-miR126}$ (50 μg/ml) during reoxygenation for 24 hrs. ECs were harvested for apoptosis and functional analysis (migration and tube formation). The expressions of miR-126 and VEGFR2 were analyzed by real-time PCR or Western blot.

Results showed: 1.) Hypoxia/high glucose increased EC apoptosis (by 35%) and decreased migration and tube formation abilities of ECs (by 60%), accompanied with miR-126 and VEGFR2 downregulation; 2.) EPC-EXs$^{-miR126}$ were more effective than EPC-EXs on decreasing hypoxia/high glucose-induced EC apoptosis (12±1.1% and 23±2.2%) and dysfunction (migration: 61±4 and 52±4 cell/field; tube formation: 29±2 and 37±4 tubes/field, EPC-EXs$^{-miR126}$ vs. EPC-EXs, p< 0.05); 3.) The hypoxia/high glucose-induced changes of miR-126 and VEGFR2 levels were more inhibited by EPC-EXs$^{-miR126}$ (by 25-48%, vs. EPC-EXs, p< 0.05). Data suggest that EPC-EXs$^{-miR126}$ have better efficacy than EPC-EXs in protecting ECs from hypoxia/high glucose-induced apoptosis and dysfunction.

Supported By: American Diabetes Association (1-17-IBS-187 to J.B.)

12-LB

Clinical Trial for Effectiveness of Dapagliflozin on Vascular Endothelial Function and Glycemic Control in Type 2 Diabetes Mellitus Patients: DEFENCE Study

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Recent studies reported that sodium glucose cotransporter 2 (SGLT2) inhibitors potentially reduce the risk of cardiovascular mortality in patients with type 2 diabetes mellitus. However, there is little or no information on the therapeutic effects of SGLT2 inhibitors on the progression of atherosclerosis and endothelial function. Dapagliflozin (Dapa) is a SGLT2 inhibitor. To investigate the effects of Dapa on endothelial function, we performed the first multi-center, prospective, open-label, and randomized parallel study. Type 2 diabetes patients treated with 750 mg of Metformin (Met) (HbA1c≧6.0% and <8.0%, n=80) were randomized to Met 750 mg supplemented with Dapa 5 mg (Dapa group) or Met 1500 mg (Met group), and treated for 16 weeks. Vascular endothelial function was evaluated by flow mediated dilation (FMD) measurement. Changes from baseline in FMD, glycemic control, lipid, body composition and atherosclerosis related markers such as oxidative stress marker were compared between the groups. Although FMD trended to improve in Dapa group, ΔFMD was comparable between the groups. Subgroup analysis of patients with HbA1c >7.0% showed that FMD significantly improved in Dapa group than Met group (ΔFMD=1.05±2.59 vs. -0.94±2.39%, respectively, P<0.05). HbA1c, fasting plasma glucose, plasma glucagon, and body weight significantly decreased in both groups. Interestingly, urine 8-OHdG, a biomarker of oxidative stress, significantly decreased in Dapa group compared to Met group (-0.63±1.82 vs. 1.13±2.17 ng/mg · CRE, respectively, P<0.001).

In summary, this is the first study to reveal the effect of Dapa on prevention of early progression of atherosclerosis. Dapa for 16 weeks improved endothelial function as assessed by FMD in patients with inadequately controlled type 2 diabetes. The reduction of oxidative stress may contribute to the improvement of FMD.

Supported By: AstraZeneca K.K. Japan; Ono Pharmaceutical Co., Ltd.

For author disclosure information, see page LB107.

13-LB

Embolus Localization Correlates with Admission Blood Glucose in Diabetic and Nondiabetic Patients with Acute Pulmonary Embolism

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Aim: The aim of this study was to evaluate the association between admission blood glucose (ABG) levels and embolus localization in large or small vessels detected by computed tomography angiography, as an indirect parameter of embolus size in patients with and without diabetes mellitus (DM) hospitalized for acute pulmonary embolism (PE).

Patients and Methods: Observational data were derived from electronic records of all hospitalized patients ≥ 18 years, admitted for PE between July 2013 and December 2016. Data about ABG levels, diabetes status and computed tomography angiography were collected in all patients. The main outcome was embolus localization in large branches up to the second division of pulmonary arteries or in smaller branches beyond the second division. Patients with emboli in both large and small branches were classified as having an embolus in a larger branch.

Results: Cohort included 319 patients, 52 with DM (mean age 75, 36,53% male), and 267 without DM (mean age 71, 40,36% male). Thirty two patients with DM (61,54%) had an embolus in a large branch, compared to 131 nondiabetic patients (45,32%). There was a significant correlation detected by logistic regression between ABG and embolus localization in large pulmonary arteries in both diabetic (p=0,0227) and nondiabetic patients (p=0.0198). Vice versa, there was a significant inverse correlation between ABG and embolus localization in smaller branches both in diabetic (p=0,043) and nondiabetic patients (p=0,0002).

Conclusion: In patients with and without DM hospitalized for acute pulmonary embolism, elevated ABG correlates with embolus localization and, therefore, indirectly with embolus size and disease severity. This finding corresponds with the fact that abnormal glucose metabolism is associated with multiple deleterious changes in the coagulation system.

14-LB

Effects of Statin in AMI Patients with High Plasma Natriuretic Peptide Level

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Background: The benefit of statin therapy in patients with higher grades of heart failure has yet to be determined. The present study was performed to investigate whether statin therapy affects major clinical outcomes in patients with acute myocardial infarction (AMI) and heart failure within 1 year after AMI.

Methods: A total of 11,592 patients with AMI from a nationwide registry database in Korea were analyzed. The patients who had a natriuretic peptide (NP) measured at admission were divided into quartiles by plasma level of B-type NP (BNP) or N-terminal pro-B-type NP (NT-proBNP). In a separate analysis, selected patients with left ventricular ejection fraction (LVEF) < 40% on initial and/or follow-up echocardiography were evaluated. Major adverse cardiovascular events (MACEs) within 12 months of AMI, including death, nonfatal MI, and revascularization, were assessed, after adjusting for multiple factors.

Results: Among 11,592 AMI patients, statin therapy was included in their medication at least from the hospital discharge in 9,149 (78.9%) patients, whereas not in the remaining 2,443 patients (21.1%), with statin therapy being associated with 24.2% lower risk of MACEs. After adjusting for risk factors, statin therapy was associated with significantly lower the hazard ratios (HRs) for MACEs only in the third and fourth quartiles of plasma NP level. However, statin did not modify the incidence of MACEs in patients with LVEF less than 40%.

Conclusions: Our results show that statin therapy decreased the risk of MACEs in AMI patients with higher plasma natriuretic peptide, but not in patients with severe heart failure.

15-LB

pNaKtide Attenuates Dyslipidemia and Atherosclerosis by Blocking Na/K-ATPase/Reactive Oxygen Species Amplification in ApoE -/- Mice

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Background: We have previously reported that the a1 subunit of the sodium potassium adenosine triphosphatase (Na/K-ATPase) acts as an amplifier for reactive oxygen species (ROS) in addition to its ion pumping function. We have also shown that blockade of this amplification with a novel peptide, pNaKtide, ameliorates oxidative stress and obesity in mice subjected to a high-fat diet.

Hypothesis: Given the importance of oxidative stress in the pathophysiology of atherosclerosis, we chose to examine whether pNaKtide might be effective in ameliorating dyslipidemia and atherosclerosis in ApoE -/- (ApoE knockout) mice.

Methods: pNaKtide was administered in ApoE knockout mouse fed Western diet. 25 mg/Kg pNaKtide was administered intraperitoneally once every 7 days. Lipid profile, glucose insulin levels, and ROS levels were measured. Aortas were dissected and quantification of aortic lesions was done.

Results: Our results show that pNaKtide improved glucose tolerance and HOMA-IR scores in ApoE-/- mice fed a Western diet ($p<0.05$). Also, pNaKtide administered to these mice significantly decreased plasma ALT, triglycerides, FFA, and LDL levels ($p<0.05$). Further, our results show that ApoE -/- mice fed a Western diet had decreased plasma HDL levels and this decrease was reversed by pNaKtide. Plasma ROS levels were significantly attenuated by pNaKtide treatment. Mice fed a Western diet had increased plaque size. Plaque size was significantly decreased by pNaKtide treatment.

Conclusion: This study suggests that the Na/K-ATPase/ROS signaling cascade is a possible mechanism for the development of dyslipidemia and atherosclerosis associated with the metabolic syndrome phenotype and pNaKtide presents a potential novel treatment for these pathologies.

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16-LB

Autophagy Scavenges Ubiquitinated Proteins Induced by Palmitate in Cardiomyocytes

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This study sought to determine that autophagy regulates the turnover of ubiquitinated proteins in a cell model of lipotoxic cardiomyocyte injury.

Results: H9c2 cells were incubated in palmitate (Pal) at 500 μM for various time periods. Cells were then collected in lysis buffer including 1% Triton X-100 (TX-100), and lysates centrifuged at 16,000g. These supernatants are TX-100 soluble fractions. The pellets were then solubilized in 10% SDS followed by the centrifugation at 16,000g, and these supernatants are the TX-100 insoluble fractions. LC3-II, p62, NBR1, and protein ubiquitination in these two fractions were measured. Following Pal treatment, in the TX-100 soluble fraction, LC3-II levels progressively increased and peaked (~3 fold above vehicle-treated cells) at 6 h, but decreased to basal levels at 8 h until 12 h. Unexpectedly, p62 and NBR1 expression were only marginally changed in the TX-100 soluble fraction over the 12 h Pal incubation. In the TX-100 insoluble fraction, LC3-II accumulated with a similar pattern to that observed in the TX-100 soluble fraction, but with an accumulation of p62 and NBR1. During the first 6 h, Pal incubation resulted in an accumulation of ubiquitinated proteins in the TX-100 insoluble fraction (~2.2 fold vs. vehicle), but not in the TX-100 soluble fraction. However, ubiquitinated proteins progressively accumulated in the TX-100 soluble fraction starting at 8 h after Pal incubation. In the presence of Pal, the addition of the autophagy activator Torin1 at 250 nM to the medium 8 h after Pal incubation restored autophagy as showed by LC3-II levels, which was accompanied by decreased ubiquitinated proteins and reduced accumulation of p62 and NBR1 in the TX-100 soluble fraction.

Conclusion: Pal incubation ubiquitinates protein and transiently induces autophagy which correlates with a decrease in ubiquitinated proteins after which they rise in concert with a decline in autophagy. Thus, autophagy may maintain proteostasis following lipotoxic injury in cardiomyocytes.

COMPLICATIONS—NEPHROPATHY—BASIC AND EXPERIMENTAL SCIENCE

17-LB

Shared and Distinct Lipid Metabolic Networks in Diabetic Complications

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Altered lipid metabolism likely contributes to the onset and progression of diabetic complications including diabetic kidney disease, diabetic neuropathy and diabetic retinopathy. Recently, we identified that glucose and fatty acid oxidation are remarkably different in diabetic kidney, nerve and retina. Additionally, transcriptomic analysis revealed several pathways of lipid biosynthesis that were enriched in both diabetic kidney and nerve. The goal of the present study was to identify shared and distinct alterations in complex lipid metabolism in complications-prone tissues. We also sought to determine if tissue lipid changes are reflected in plasma, as plasma represents the most clinically suitable source for monitoring lipid biomarkers of disease progression. We used plasma, kidney cortex, sciatic nerve and retina from BKS db/db mice and db/+ controls at 24 weeks-of-age. Lipid levels were mea-

sured using liquid chromatography-tandem mass spectrometry. Complex lipids and the effects of diabetes were largely tissue-specific, as lipid levels were primarily increased in the diabetic nerve, decreased in the diabetic retina, and glycerophospholipid remodeling was evident in the diabetic kidney. Only 15 lipids, primarily diacylglycerols and glycerophospholipids of the 36:4 composition, were shared across all 3 tissues. We identified co-regulated lipid sub-classes between plasma and each tissue, defining sub-classes of plasma lipids for use as surrogates of altered tissue lipid metabolism. While short chain diacylglycerols and long chain cardiolipins were similarly regulated between plasma and 2 of the tissues, most co-regulated sub-classes were between plasma and only 1 of the tissues examined. Furthermore, we tested the use of correlation analysis to integrate lipidomic and previously published transcriptomic data. We demonstrate this method can identify potentially pathogenic network-specific alterations in lipid metabolism, such as arachidonic acid metabolism in the diabetic kidney.

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18-LB

NLRC5 Deficiency Attenuates Diabetic Nephropathy by Alleviating Macrophage Infiltration and Inflammation

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Objective: Diabetic nephropathy (DN) is the main cause of end-stage kidney disease globally, and inflammation has a critical role in its pathogenesis. As the largest member of NOD-like receptors, NOD-like receptor family CARD domain containing 5 (NLRC5) has received extensive attention because of its important role in regulating immune and inflammatory responses. The current study tests the hypothesis that NLRC5 may play a critical role in the progression of DN.

Research Design and Methods: ODS Role of NLRC5 in DN was examined in genetic NLRC5 deficiency ($NLRC5^{-/-}$) and wild type (WT) mice those were streptozotocin-induced diabetic mice. Fasting blood glucose and 24-hour urinary albumin were measured. Kidney injury and molecular mechanism were observed and analyzed using transmission electron microscopy and molecular biological techniques including immunohistochemistry, qPCR and Western blot. Inflammation status and potential signaling pathways were tested in peritoneal macrophages treated with high glucose in vitro.

Results: NLRC5 expression was up-regulated in STZ induced diabetic mice, db/db mice and human diabetic kidney compared with controls. We found $NLRC5^{-/-}$ mice developed alleviated diabetic kidney injury relative to WT mice as evidenced by a significant decrease in albuminuria (105.5 ± 24.0 vs. 76.3 ± 20.5 μg/d, $P<0.05$), renal fibrosis (collagen IV and fibronectin), renal inflammation (interleukin-6 and tumor necrosis factor-α) and macrophage infiltration, and less reduced protein levels of nephrin and podocin in diabetic kidney. Our research also revealed alleviated inflammation in peritoneal macrophages from $NLRC5^{-/-}$ mice was associated with suppressive activation of nuclear factor-κB pathway.

Conclusions: NLRC5 plays a proinflammatory role in DN by regulating activation of NF-κB pathway in macrophages. Therefore, NLRC5 may represent a promising target for treatment of DN.

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19-LB

Glycation and Carbamylation Reciprocally Compete for Protein Modification

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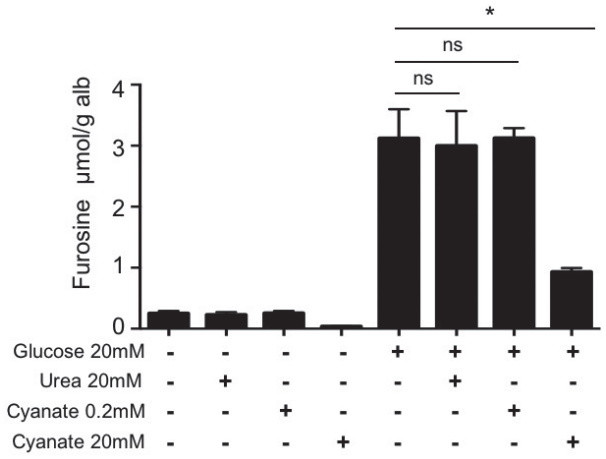
Diabetes and chronic kidney disease (CKD) accelerate protein molecular aging through glycation and carbamylation reactions, which are characterized respectively by the binding of sugars or urea-derived isocyanic acid on proteins. These reactions target the same protein amino groups, especially in diabetic patients with CKD. For example, they can compete for the major site of hemoglobin modification, the N-terminal Val residue of β-chains, modified in HbA_{1c}. This study aims to evaluate their competitive effect in vitro and in vivo. In vitro, albumin is incubated with glucose, urea or cyanate. In vivo, carbamylation is enhanced in normal and diabetic mice by sub-nephrectomy, or by cyanate consumption. Furosine, fructosamine and HbA_{1c} are measured by LC-MS/MS, colorimetric and immunological assays and homocitrulline and carbamylated hemoglobin (carbamylation-derived products) by LC-MS/MS. A reciprocal inhibition between carbamylation and glycation is observed in vitro. In vivo, 5 weeks after induction of CKD, plasma homocitrulline concentrations are similar in diabetic and nondiabetic mice. Fructosamine and HbA_{1c} decreased in CKD-diabetic mice compared to diabetic ones and also in cyanate-drinking compared to water-drinking diabetic mice. Carbamylation competes with glycation in vivo. Thus, classical markers of glycemic control, as the HbA_{1c}, should be interpreted with caution in diabetic patients with CKD.

Figure.



COMPLICATIONS—NEPHROPATHY—CLINICAL AND TRANSLATIONAL RESEARCH

20-LB

Novel Circulating Biomarkers Predict Rapidly Declining Renal Function in Type 2 Diabetes: The Fremantle Diabetes Study

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The ability of baseline patient characteristics including albuminuria and estimated glomerular filtration rate (eGFR) to predict onset/progression of diabetic chronic kidney disease (CKD) is limited. We investigated the role of circulating diagnostic protein biomarkers (APOA4, APOC3, CD5L, C1QB, CFHR2, IBP3) in predicting renal function decline in type 2 diabetes (T2DM). A mass spectrometry platform was used to measure biomarkers at entry in 345 participants from the longitudinal observational Fremantle Diabetes Study (FDS) Phase II. Onset/progression of CKD was defined by i) ≥30% eGFR fall over 4 years, ii) incident CKD (eGFR <60mL/min/1.73m^2), iii) steepest eGFR trajectory, and iv) eGFR decline ≥5mL/min/1.73m^2/year. Multiple logistic regression identified clinical predictors of developing nephropathy. The incremental predictive value of biomarkers was then assessed. The 4 models were validated in an independent FDS cohort (n=447). Of the 345 initial participants, 30 had a ≥30% fall in eGFR over 4 years. After adjustment for the most parsimonious model, APOA4 and IBP3 independently predicted outcome (OR=4.85 [95% CI 2.04-11.50] and OR=0.32 [0.13-0.81], respectively) and improved model fit ($P<0.001$), discrimination (AUC from 0.84 to 0.88, $P=0.14$), and reclassification (NRI=0.81 [0.68-0.94] and IDI=8.1% [1.0%-15.1%]). For the other definitions of rapid decline, APOA4 and IBP3 improved model performance with CD5L and C1QB also independent predictors of steepest eGFR trajectory (OR=0.52 [0.29-0.93] and OR=2.41 [1.14-5.11], respectively). Applied to the validation cohort, the discrimination and accuracy of each model was good (AUC=0.65-0.83; mean square error=0.05-0.10), but calibration was poor ($P<0.05$) due to small numbers in lower deciles. The present study has identified novel plasma biomarkers (APOA4, IBP3, CD5L, C1QB) that improve prediction of indices of CKD in T2DM independently of conventional clinical variables.

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21-LB

miRNAs 1915-3p and 4532 as Novel Noninvasive Biomarkers to Detect Renal-Function Decline in Type 1 Diabetes Patients

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Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease worldwide. Microalbuminuria (MA) is the earliest indicator of DKD in diabetes (DM). However, while MA is a sensitive marker, it is not spe-

For author disclosure information, see page LB107.

cific for the disease process that leads to rapid glomerular filtration rate (GFR) decline. Our group has been searching for urinary markers associated with rapid GFR decline. We previously profiled 2402 human urinary miRNAs and confirmed the top performing miRNAs in two independent cohorts of DM patients (n=58 and 145, respectively) and healthy controls (n=93 and 30, respectively). Three miRNAs (-2861, -1915-3p, -4532) were down-regulated and demonstrated strong c-statistics in their ability to discriminate between patients with DKD vs, either healthy or non-DKD patients in a cross-sectional analysis. To evaluate the ability of these three candidates to predict renal function decline we performed a prospective analysis in urine samples from a new cohort of type 1 DM patients (n=104) with a median follow-up period of 2.5 (±1.2) years. miR-2861, -1915-3p and -4532 were also down-regulated in DM patients with DKD (n=25) compared with non-DKD patients (n=79; P<0.01). miR-1915-3p and -4532 were also associated with rapid estimated GFR (eGFR) decline (P<0.01) in patients that lost more than 3mL/min/1.73m^2 per year of follow-up. Using k-nearest neighbors algorithm prediction model initial eGFR values were used to estimate eGFR loss. The spearman correlation between the predicted and the real eGFR measurements after follow-up-period was 0.9251 (p<.0001). When miR-1915-3p and -4532 expressions were added to the algorithm the correlation increased to 0.972 (p<.0001). The algorithm prediction accuracy was higher than 95% in 80% of the samples.

In conclusion, we have confirmed novel miRNAs that correlate with rapid renal function decline for a more specific and noninvasive detection of DKD progression.

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22-LB

Diabetic Kidney Disease in the Ecuadorian Coast

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Diabetic kidney disease (DKD) is a devastating complication of type 2 diabetes (T2D). Our preliminary study showed that prevalence of T2D, prediabetes (PD) and DKD was startlingly high in the Guayas province, Ecuador. Here, we report the results of our prospective, observational and cross-sectional study done in the provinces of Los Rios, Esmeraldas and Manabi, during 2016, on 813 subjects (95% confidence level, 3.4% margin of error). Their mean age was 48.59±13.78, with 61.38% of them being women. We collected demographic data, blood pressure (BP), body mass index (BMI), blood glucose, HbA1c, creatinine (cr), and microalbuminuria (µAlb). T2D included subjects being diagnosed by physicians, being on insulin or oral hypoglycemic treatment, fasting plasma glucose ≥126 mg/dl, random glucose ≥200 mg/dl and HbA1c ≥6.5%. PD subjects were defined as individuals with fasting plasma glucose between 100 and 125 mg/dl and HbA1c between 5.7 and 6.4%. DKD was defined as T2D subjects with µAlb ≥30 mg/gr-cr and/or estimated glomerular filtration rate <60 ml/min/1.73m2. In the Ecuadorean coast, the prevalence of T2D was 20.54% (CI 95%, 18%-23%), 50.3% of them had DKD, thus the prevalence of DKD in the general population was 10.33% (CI 95%, 8%-13%). The percentage of T2D not diagnosed by clinician was 3.94% of the entire population. The prevalence of PD was 24.11% (CI 95%, 21%-27%). DKD was more prevalent in Esmeraldas province (13.9%) than in Manabi (11.4%) and Los Rios (6.1%) (P <0.05). DKD was more prevalent (P <0.05) in subjects with BMI ≥30kg/m2 (14.50%) than in subjects with BMI <30kg/m2 (8.35%), in subjects with BP≥140/90 (17.14%) than in subjects with BP <140/90 (9.56%), in women having had overweighed newborn children (ONBC) (22.06%) than in women having no ONBC (9.51%). The prevalence of DKD is alarmingly high, Esmeralda is the most affected province. Obesity, hypertension, and women having had ONBC are all associated with DKD. The high prevalence of T2D and PD suggest that DKD could be further prevalent in the more populated region of Ecuador, the coast.

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23-LB

Effects of Serum Uric Acid (UA) Levels on the Decline in Renal Function (RF) in Type 2 Diabetes (T2D)

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The effects of UA on diabetic nephropathy have received much attention; however, most existing studies have considered patients with preserved RF. Here, we examined the effects of serum UA levels at baseline on the decline in RF in diabetic patients, including those with renal insufficiency. This was a single-center, historical cohort study. We studied 6,978 Japanese patients with T2D (mean age: 61 years, men: 65%) who did not receive renal replacement therapy (RRT). The patients were classified into 2 groups based on the baseline estimated glomerular filtration rate (eGFR) as follows: non-CKD: eGFR ≥60 (N= 4,952), CKD: eGFR <60 (N= 2,026). The endpoint was ≥30% decline in eGFR from baseline or the initiation of RRT, whichever came first. To examine the association of UA levels with the endpoint, we used the multivariate Cox proportional hazards models. During the mean follow-up period of 5.4 years, 1,263 patients reached the endpoint. An interaction between the UA levels and baseline eGFR on the endpoint was significant (p< 0.001). The hazard ratio of 1 mg/dL increase in UA was 1.11 (p= 0.007) and 0.94 (p= 0.035) in non-CKD and CKD, respectively. When patients were classified by the quartile of UA levels, the hazard ratio of those with highest quartile (vs. lowest quartile) was 1.50 (p= 0.003) and 0.78 (p= 0.046) in non-CKD and CKD, respectively. The restricted cubic spline analyses of the association between UA levels and the endpoint, in which knots were placed at the 5, 27.5, 50, 72.5 and 95th percentile levels, showed a J-shaped curve (the bottom was approximately in 2.8 mg/dL) and an inverse linear association in non-CKD and CKD, respectively. Sensitivity analyses of 6,208 patients without urate-lowering drugs yielded the similar results.

In conclusion, this study of T2D suggested that the effects of UA on the decline in RF differ depending on the baseline RF. High UA levels are the risk factor only in patients with preserved RF. The potential for low UA levels to have the harmful effects needs further studies.

24-LB

The Value of Renal Resistive Index as an Early Marker of Diabetic Nephropathy in Type 2 Diabetes Mellitus

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Diabetic nephropathy is the leading cause of chronic kidney failure worldwide. The aim of this study was to assess the usefulness of renal resistive index (RI) in the evaluation of early diabetic nephropathy (DN) in patients with type 2 diabetes mellitus. Forty healthy examinees and 120 type 2 diabetes mellitus examinees, divided into 3 groups by DN level evaluated by the urinary albumin excretion (UAE), normoalbuminuria (group 1), moderately increased albuminuria (group 2) and severely increased albuminuria (group 3) were included in the study. Doppler resistive index (RIs) were measured in intrarenal arteries, as indicators of renal vascular resistance. Measured results were compared among groups and correlated with other clinical (age, sex, BMI, disease duration, systolic and diastolic blood pressure) and laboratory parameters (HbA1c, high-sensitivity C-reactive protein/hs-CRP/and renal functional tests). In control group, the mean±SD RI was 0.598±0.025. The mean±SD RI was 0.706±0.039 in DN group 1, 0.731±0.044 in DN group 2, and 0.794±0.041 in DN group 3 (p<0.001). Pathologic values of RI (≥0.70) were observed in 57.5% of patients in DN group 1, in 75% of patients in DN group 2, and in 97.5% of patients in DN group 3. Using Pearson method on a common group of all 120 diabetic patients, we have found a positive and statistically significant correlation between RI and the following parameters: age (r=0.487), duration of DM (r=0.365), systolic blood pressure (r=0.439), diastolic blood pressure (r=0.193), HbA1c (r=0.472), serum creatinine (r=0.309), UAE (r=0.646), hs-CRP (r=0.509) with p<0.005. In multiple regression analysis UAE was independently associated with RI (p<0.001). The increase of RI follows the progression of DN. Resistive Index is associated with DN level in type 2 diabetes.

We conclude that RI elevation in diabetic nephropathy in patients with type 2 diabetes mellitus can be observed in earlier stages of the disease.

25-LB

Uric Acid and Incident Albuminuria in Type 1 Diabetes Patients in DCCT/EDIC: A U-Shaped Association?

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Uric acid (UA) is an important antioxidant in plasma, but elevated levels have adverse reno-vascular effects: therefore, levels that are neither too high nor too low may be optimal. We investigated relationships of serum UA with subsequent albuminuria in type 1 diabetes patients. UA was measured once, in samples collected 1997-9, in 824 EDIC patients (443 males; 381 females) who had normal albumin excretion rates (AER) (<40 mg/24h). After 14 years (median) follow-up, hazard ratios for incident albuminuria (AER ≥ 40 mg/24h on at least 2 occasions) were calculated according to UA quartiles,

For author disclosure information, see page LB107.

adjusting for demographic, behavioral, and clinical covariates (Cox proportional hazard models) (Table). There were 78 incident cases (cumulative incidence: 7.2/1,000 person-years); by UA quartiles 1-4, rates were 5.2, 8.4, 4.2, and 12.1/1,000 person-years respectively (log-rank test, χ^2=13.6, p=0.004). Using the lowest risk (3rd) quartile as reference (multivariate Cox model), hazard ratios (95% CI) for the 1st, 2nd and 4th quartiles were 1.5 (0.6, 3.5), 2.3 (1.1, 4.7), and 2.9 (1.4, 5.7) respectively. Similar results were found in sex-stratified analyses. We thus report a non-linear association of UA with incident albuminuria. Risk was lowest in the 3rd quartile, and significantly lower in 3rd than in the 2nd or 4th quartiles.

Table Associations: baseline uric acid and incident albuminuria

Baseline Uric Acid Quartiles (mg/dl)	N of new cases	Person years (PY) at risk	Cumulative incidence (1/1,000 PY)	Model 1*		Model 2**		Model 3***	
				Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
1.3 –, n=203	14	2677	5.2	1.5	0.7, 3.4	1.6	0.7, 3.7	1.5	0.6, 3.5
3.2 –, n=209	23	2734	8.4	2.1	1.1, 4.3	2.3	1.1, 4.6	2.3	1.1, 4.7
3.9 –, n=229	13	3105	4.2	1 (reference)	1	1 (reference)	1	1 (reference)	1
4.7-8.2, n=183	28	2315	12.1	2.7	1.4, 5.3	2.8	1.5, 5.5	2.9	1.4, 5.7

Adjusted for:
* age, gender, duration of diabetes.
** as above + body mass index, alcohol, smoking.
*** as above + systolic blood pressure, diastolic blood pressure, HbA1c, HDL-C, LDL-C

Supported By: American Diabetes Association (7-12-CT-46 to T.J.L.); National Institute of Diabetes and Digestive and Kidney Diseases; National Eye Institute; National Institute of Neurological Disorders and Stroke; General Clinical Research Centers Program; Clinical Translational Science Center Program

26-LB

A Shift from Glucose to Lipid Oxidation Is Associated with Microvascular Complications-Free Survival in Long-Term Type 1 Diabetes: The PROLONG Study

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There is a lack of specific modalities for the treatment of macro- and microvascular diabetic complications. Understanding the interplay between genetic and physiological mechanisms in patients with long-term diabetes free from diabetic complications may help in identifying novel treatments. The PROLONG (PROtective genetic and non-genetic factors in diabetic complications and LONGevity) Scandinavian initiative aims at identifying genetic and non-genetic factors associated with protection against complications in type 1 diabetes patients. We obtained clinical longitudinal data from 1998 up to 2014 in 1037 patients fulfilling PROLONG criteria from Scania Diabetes Registry and Steno Diabetes Center electronic records. Plasma metabolites were determined by GC-MS and UHPLC/QTOF-MS and were validated by enzymatic methods.

In longitudinal analyses, low plasma triglyceride-rich lipoproteins with extremely narrow range emerged as the strongest factor associated with microvascular complications-free survival, independently of HbA1c (p<0.0001). We next compared the metabolic profile of patients who never developed any complications despite prolonged diabetes duration (>39 years, non-progressors; n=336) with that of patients progressed to microvascular complications within 25 years of disease duration (rapid-progressors; n=78). Despite a lower daily insulin dosage (p<0.01), non-progressors had higher free fatty acids (p<0.05), glyceric acid (p<0.05) and β-hydroxybutyrate (p<0.05) levels. Causally related functional and genetic studies explaining these processes are underway.

These data point at increased lipolysis and lipid beta-oxidation with preferential utilization of ketone bodies over glucose as energy substrates as a potential mechanism maintaining low triglyceride-rich lipoproteins levels protecting from vascular damage.

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27-LB

Diabetic Kidney Disease (DKD) in Nonhuman Primates (NHP's) Is Comparable to Humans for Glomerular Filtration Rate (GFR), Histology, and High-Risk Factors

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Among the approaches to diagnose diabetic kidney disease, histology and glomerular filtration rate have always been described as the gold standards. We evaluated the kidney function of rhesus monkeys by measuring GFR, histology and metabolic characteristics to compare the typical DKD in humans.

Methods: A colony of 56 adult male monkeys (Age: 8-22 yrs, Body weight: 9-15kg) received medical examination and GFR measurement (Iohexol clearance). Renal biopsy was conducted in 3 normal monkeys (GFR >90 ml/min/1.73m^2, FPG<80mg/dL) and 3 diabetic monkeys with low GFR (<60 ml/min/1.73m^2, FPG >100mg/dL). Enalapril was used to evaluate DKD in the rhesus monkey model of diabetes. Eight male diabetic monkeys (GFR: 65±2 ml/min/1.73m^2; SBP: 133±4 mmHg) were randomly assigned to the Enalapril group (N=4, p.o., human equivalent dosage 6.67 μg/kg, b.i.d.) and vehicle group (N=4, p.o., b.i.d.).

Results: GFR of these 56 monkeys ranged from 43.05 to 91.33 ml/min/1.73m^2, which showed strong correlation with fasting plasma glucose (FPG, r=-0.40, p<0.01), serum creatinine (CR-S, r=-0.80, p<0.01) and systolic blood pressure (SBP, r=-0.29, p<0.05). The pathological examination of the 3 monkeys with low GFR revealed glomerular swelling (HE staining, X400) and basement membrane thickening (PASM staining, X400), which were the typical clinical pathological features of DKD in humans. After 3 months of treatment, the renal function and blood pressure of the Enalapril group ware significantly improved (GFR: 66±2 to 76±1 ml/min/1.73m^2 and SBP: 130±5 to 111±8 mmHg; p<0.05). The renal function and blood pressure of vehicle group were unchanged (GFR: 63±3 to 61±3 ml/min/1.73m^2 and SBP: 135±4 to 137±4 mmHg; p's=NS).

Conclusion: Our study showed that rhesus monkeys have similar GFR to humans, and diabetic rhesus monkeys similarly develop DKD. These DKD rhesus monkeys provide an excellent experimental platform to validate the efficacy of DKD treatments.

28-LB

Accuracy of Glycosylated Hemoglobin in Chronic Kidney Disease

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Introduction: In end stage renal disease, glycosylated hemoglobin (A1C) often underestimates glycemia due to increased erythrocyte turn over and erythropoietin therapy.

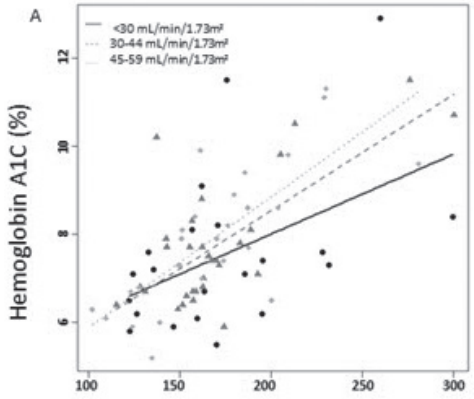
Aims/Objectives: To evaluate the performance of A1C compared to mean blood glucose ascertained by continuous glucose monitoring (CGM) in chronic kidney disease (CKD).

Study Design: 81 subjects with type 2 diabetes mellitus (T2D) and CKD [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 not on dialysis] treated with insulin and/or sulfonylurea therapy were enrolled in a 4-week observational, multicenter study. Each participant wore a blinded CGM (IPro-2 with Enlite sensor) for two 6-day periods separated by 2 weeks. Using mean CGM blood glucose (BG) as gold standard, accuracy of A1C and correlation of A1C with CGM BG were tested across subgroups defined by eGFR and against subjects with T2D who completed the A1C-Derived Average Glucose (ADAG) Study.

Results: Mean (SD) age was 68.0 (9.5) years, eGFR 37.9 (12.9) mL/min/1.73m^2 and A1C 7.7 (1.6)%. There was no bias in A1C by eGFR (Figure 1A), or comparing study participants to ADAG (Figure 1B), each p >0.1. The correlation of A1C with CGM blood glucose was lower with eGFR <30 mL/min/1.73m^2 (r=0.47), compared with eGFR 30-44 or 45-59 mL/min/1.73m^2 (r=0.70, r=0.76) or ADAG Study participants (r=0.84).

Discussion: CKD does not bias the relationship of A1C with blood glucose but may reduce precision of A1C compared with CGM.

Figures.



ADA-Supported Research

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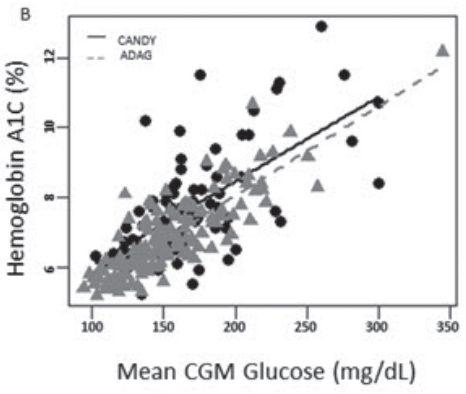

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29-LB

Metabolite Profiling of Mice with Akita Diabetic Mice and Dio Mice Treated with Atrasentan Reveals Model-Selective and Drug-Specific Alterations in Metabolic Pathways

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Atrasentan, an endothelin receptor 1 specific blocker, is being evaluated for benefit in a Phase III trial for diabetic nephropathy, but little is known about the metabolic responses to its treatment. In the present study, LC-MS-based metabolomics was applied to detect changes in the urinary metabolomic profile of mouse models of renal disease with a high fat diet (type 2 diabetic model) and with Akita (type 1 diabetes model) in response to Atrasentan. Starting at 6 weeks of age, mice were fed either high fat diet (HFD) or standard diet (STD) for 14 weeks. Starting at 8 weeks of age mice on HFD or with Akita type 1 diabetes, mice received atrasentan (10 mg/kg of body weight) in the drinking water for 12 weeks. The targeted metabolites in the metabolomics platform included BCAAs and their down-stream catabolic metabolites, tryptophan metabolic pathways, TCA cycle metabolites, carnitine and acyl-carnitines, glutamine/glutamate, and glucose. In HFD, leucine, phenylacethylglutamine and isocitrate were positively correlated and kynurenine, carmitine, c2-carmitine c3-carmitine c4-carmitine, citrate, alpha-keteglutarate, succinate and malate were found negatively correlated with blood glucose. Treatment with Atrasentan did not reverse the changes of the targeted metabolites in the Akita diabetic mice. However, atrasentan significantly reduced the urinary and plasma glucose level in HFD diet-fed group. Atrasentan also increased the Glutamine/Glutamate ratio in HFD mice suggesting that atrasentan may reduce insulin resistance in HFD-induced mouse model.

In conclusion, we found that metabolomics distinguishes between type 1 and 2 diabetes and detected pronounced animal model differences. The beneficial effects of atrasentan are more apparent in HFD mice than in Akita diabetic mice and is able to reduce blood glucose and increase the GLn/Glu ratio in mice on HFD.

COMPLICATIONS—NEUROPATHY

30-LB

Association of Distal Thigh IENFD with Balance Function in DPN

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Introduction: Diabetic peripheral neuropathy (DPN) is characterized by early injury to small unmyelinated axons resulting in pain and sensory loss. Intraepidermal nerve fiber density (IENFD) is a sensitive, quantitative, and reproducible measure of small fiber integrity. IENFD improves in response to exercise based lifestyle interventions for diabetes and DPN, but its relationship to clinically meaningful functional outcomes is unknown. As part of an ongoing clinical trial (Activity for Diabetic Peripheral Neuropathy-The ADAPT Study) we investigated whether IENFD was associated with balance function.

Methods: Distal thigh IENFD was measured in 33 ambulatory participants (60.7±6.9 years old, 19 male) with DPN using standard measures. On a separate day, participants underwent balance assessment with the Mini BESTest, a validated clinical balance assessment that includes 14 items addressing anticipatory postural adjustments, reactive postural control, sensory orientation and dynamic gait. Nerve conduction studies (NCS), the Utah Early Neuropathy Scale (UENS) and validated neuropathy symptom scores were also performed.

Results: Distal thigh IENFD (10.4±5.2 fibers/mm) was significantly associated with Mini BESTest score (22.7±3.3 r=0.34, p=0.05). By contrast, age, NCS, UENS and DPN symptom severity were not significantly correlated with balance.

Discussion/Conclusions: Balance function is considered a large fiber mediated nerve function. However, in this sample, small unmyelinated fiber loss, measured by IENFD better correlated with balance than did traditional large fiber measures such as NCS, supporting its clinical relevance and reinforcing its value as a surrogate marker of DPN severity.

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31-LB

Conserved Gene Expression Changes and Dysregulated Pathways in Complication-Prone Tissues of Streptozotocin-Diabetic Mouse

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Diabetic peripheral neuropathy (DPN) and diabetic nephropathy (DN) are two common complications of diabetes that are associated with a high degree of morbidity. There is therefore a critical need to identify treatment strategies that impact the underlying disease pathogenesis. Using a systems biology approach, we recently reported commonly regulated pathways across different complications-prone tissues in type 1 diabetes (T1DM). However, these post-hoc analyses were performed on data from separate studies, with confounding factors including duration of diabetes and insulin supplementation. In the current study, we employed RNA-Seq on a single cohort of T1DM mice. Diabetes was induced in BKS db/+ mice with a single high-dose 150 mg/kg (i.p.) streptozotocin (STZ) injection at 6 weeks of age. STZ mice developed T1DM phenotypes: significantly lowered body-weight and insulin level, and highly elevated levels of fasting glucose, triglyceride and cholesterol. Sciatic nerves, dorsal root ganglia, kidney renal cortex, and glomeruli tissues were harvested at 16 weeks of age and examined for differential expression between control and STZ-diabetic mice. We identified differentially expressed genes (DEGs) ranging from 53 to 3,586 in four tissues. 173 DEGs were common in three or more tissues, displaying an 80% concordance in the directions of expression change across tissues. We also identified 298 significantly enriched pathways, 205 of which were shared across at least three tissues. These pathways included JAK-STAT, PPAR, LXR/RXR, as well as rheumatoid arthritis-related pathways, which all indicate an active immune response affecting multiple organ systems. Although the gene-level overlap across these tissues was relatively low, there was a significant overlap at the pathway-level. These findings suggest that the systemic inflammation associated with T1DM may be heavily involved in the development of both DPN and DN.

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32-LB

Pathway-Level Effects of Pioglitazone on Neuropathy in the BKS-db/db Mouse Model of Type 2 Diabetes

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Pioglitazone, a thiazolidinedione class drug used for type 2 diabetes mellitus (T2DM), is an insulin-sensitizing peroxisome proliferator-activated receptor gamma (PPARG) agonist, which has various effects such as lipid/glucose lowering and antiinflammation. In our recent studies, pioglitazone reversed diabetic neuropathy (DN) of small but not large myelinated fibers in db/db mice. To better understand these pioglitazone effects on DN, we performed a pathway-centered bioinformatics analysis on RNA-Seq data from sciatic nerves of these mice. Using a graph-theoretic approach focusing on how communication between biological pathways is altered, dysregulated pathways were identified using a cutoff-free enrichment algorithm GAGE between nondiabetic (db/+) and diabetic (db/db) mice, either treated or untreated with pioglitazone. We further determined whether communication between these pathways through common molecules was also altered in

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network models. The untreated db/db mice had 91 significantly dysregulated pathways, which formed a network with 229 connections among them. The largest subnetwork included 61 pathways, involved in neuronal function, signaling, and transport. Three additional smaller subnetworks were also identified, related to other functions such as lipid metabolism. Pioglitazone treatment induced changes in 107 pathways in db/db nerve, with 258 connections among them. Notably, lipid metabolism pathway gained a more central role in this network. Additionally, a subnetwork of Krebs cycle metabolism emerged with pioglitazone treatment. These findings support our recent report of tissue-specific metabolic reprogramming in DN pathogenesis and provide new insights to the system-wide effects of pioglitazone in DN at the pathway-level.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (25034-75 to J.H.); University of North Dakota (to K.G.)

33-LB

Effect of Pioglitazone Treatment on Diabetic Neuropathy in STZ-Diabetic Mice

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Diabetic neuropathy (DN) is the most common complications of diabetes; however, the underlying mechanisms are not fully understood and remain a barrier to effective treatment. In both type 1 and 2 diabetes mellitus (T1DM and T2DM), dyslipidemia has been found to be associated with the development of DN. We recently reported improved dyslipidemia and glycemic control, and in parallel improved DN in T2DM mice with pioglitazone, an insulin sensitizer. To examine the effect of pioglitazone on T1DM, diabetes was induced in BKS db/+ mice with a single high-dose 150 mg/kg (i.p.) streptozotocin (STZ) injection at 6 weeks of age. Mice were fed control chow or pioglitazone-chow (15 mg/kg dose) from 8-16 weeks of age for a total of 8 weeks. STZ mice developed T1DM phenotypes: significantly lowered bodyweight and insulin levels, and elevated fasting glucose, triglyceride and cholesterol. STZ mice also developed neuropathy, with decreased sural and sciatic nerve conduction velocities, decreased intra-epidermal nerve fiber density, and increased hind-paw thermal latency. Pioglitazone treatment did not alter any of these metabolic and neuropathic phenotypes in STZ mice. To examine the treatment effect at the gene expression level, RNA-Seq was performed on sciatic nerve (SCN) and dorsal root ganglia (DRG) tissue from untreated STZ mice (n=6) and pioglitazone-treated STZ mice (n=6), and obtained approximately 30 million 125-bp single-end reads per sample. Bioinformatics analysis identified only 50 and 0 differentially expressed genes (adjusted p-value < 0.05) between untreated and pioglitazone-treated mice in SCN and DRG, respectively. These none to extremely small numbers of DEGs indicate that pioglitazone does not affect the expression profiles in peripheral nerves, thus, supporting the neuropathy phenotypes at a gene expression level.

In conclusion, pioglitazone has no effect on diabetic complications T1DM when the mice have next to no circulating insulin.

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34-LB

RNA-Seq Analysis of Human Diabetic Neuropathy in Subjects with Type 2 Diabetes

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Diabetic neuropathy (DN) is one of the most common complications of diabetes mellitus (DM), affecting over 60% of subjects with diabetes in their lifetime. Previously, we reported that subjects with DN demonstrate variable degrees of peripheral nerve regeneration and degeneration. Based on percent myelinated fiber density change (%delta-MFD) over 1 year, these subjects were divided into three groups (Regenerator, Intermediator, and Degenerator), and we identified HbA1c as the sole significantly associated clinical factor with this grouping. To elucidate the underlying mechanisms leading to nerve degeneration and regeneration in DN, we performed a RNA-Seq profiling on 78 sural nerves from DN patients with type 2 diabetes (T2DM). These groups had high intra-group and low inter-group variations. We performed unbiased clustering analyses on the RNA-Seq gene expression data using hierarchical clustering and principal component analysis, and identified three distinctive groups of samples. Multifactorial logistic regression analyses on the clinical data of these groups identified that these groups were significantly different in terms of baseline HbA1c level and O'Brien neuropathy score. 997 differentially expressed genes were identified between Group1 and Group2, respectively with the highest and lowest average HbA1c levels. Functional enrichment analysis in terms of Gene Ontology terms and KEGG pathways reveals that these DEGs were highly enriched with genes related to extracellular matrix organization, phagosome, antigen processing and presentation pathway as well as adaptive immune system.

In conclusion, a deep-sequencing analysis of the peripheral nerves affected by T2DM revealed that the global gene expression patterns in these samples did not correlate with %delta-MFD. However, they were significantly associated with the baseline HbA1c and O'Brien neuropathy score, suggesting their critical roles in driving gene expression changes in peripheral nerves in T2DM.

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COMPLICATIONS—RETINOPATHY

35-LB

Incretins and Diabetic Retinopathy: Real-World Evidence for Safety

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Recent large trials suggest incretin-based drugs (IBDs) may be associated with an increased risk of diabetic retinopathy (DR). To examine whether IBDs increase DR risk compared with other antihyperglycemics, we implemented an active comparator, new user cohort design identifying initiators of GLP-1RA, DPP-4i, SU, and TZD using a U.S. nationwide 20% random sample of fee-for-service Medicare beneficiaries aged 65+ with parts A, B, and D coverage from 2006-2014. We required patients to have a 2nd prescription of the same drug class and be free of DR treatment and blindness or low vision at that point. The outcome was DR requiring treatment, defined as a procedure code for the following therapies with a DR or diabetes diagnosis code: photocoagulation, intravitreal corticosteroid or anti-VEGF agents, and vitrectomy. Procedures with an age-related macular degeneration diagnosis code within the same claim were not considered as DR. We estimated propensity scores to balance potential confounders across cohorts. We estimated adjusted Hazard Ratio (HR) and 95% CI using standardized mortality ratio weighted Cox proportional hazards models censoring for treatment changes. The initiators of DPP-4i (n=45344), SU (n=120340), GLP-1RA (n=9682), and TZD (n=34486) were followed for a median (IQR) duration of 0.62 (0.29-1.41), 0.75 (0.33-1.70), 0.66 (0.36-1.27), and 0.60 (0.30, 1.32) years, respectively. During follow-up, incident cases of DR was 355, 857, 86, and 264 in DPP-4i, SU, GLP-1RA and TZD initiators, respectively; and incident rate was 7, 6, 9, and 8 per 1000 person-years, respectively. Adjusted HR was 1.12 (95% CI 0.98-1.29) comparing DPP-4i to SU and 0.99 (95% CI 0.71-1.38) comparing GLP-1RA to TZD. Results were consistent across sensitivity analyses with varying exclusion criteria and outcome definitions. Our active comparator, new user cohort study of older patients showed IBDs are not associated with an increased DR risk compared with alternatives. This study is limited by the relatively short duration of treatments.

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36-LB

Sex-Specific Association of a Single Nucleotide Polymorphism in the Gene Encoding Glutathione Peroxidase 4 (GPX4) and Diabetic Retinopathy in Brazilian Type 1 Diabetes Patients

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In hyperglycemic states endothelial retinal cells are exposed to high extracellular glucose concentrations, and are unable to downregulate glucose influx. It results in intracellular activation of deleterious biochemical pathways (DBP) and neuronal and blood vessels damage. Glutathione peroxidases are selenoproteins capable of detoxifying the oxidative stress generated by the DBP. Under conditions of sub-optimal selenium (Sn) availability, selenoproteins are synthesized according to a hierarchy in which GPX4 is in the top of the ranking and GPX1 in the lowest position. GPX4 concentrations and actions are gender specific. A variant in GPX4 located in a critical selenocysteine incorporation area (rs713041) influences the relative position of GPX4

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in the hierarchy of selenoprotein synthesis; the minor T-allele of rs713041 conferred protection against diabetic kidney disease in two cohorts (Brazilian and French/Belgian) of type 1 diabetes patients.

The aim of this study was to test whether rs713041 is also associated with diabetic retinopathy (DR) in the Brazilian cohort. A total of 272 patients (61% female; median age of 34 years-old; median diabetes duration of 22 years; median HbA1c of 8.5%) was submitted to a 7-standard field digital color fundus photography evaluated by the same ophthalmologist trained in retina, genotyping was performed by real-time PCR with fluorescent-labelled probes. Proliferative DR was observed in 29% of the patients. After adjustment for potential confounders, the minor T-allele of rs713041 was inversely associated with the prevalence of proliferative DR only in female patients (odds ratio 0.25, 95% CI 0.09-0.71, p=0.006).

In conclusion, GPX4 rs713041 seems to modulate the risk for DR in a sex-specific manner in type 1 diabetes patients, perhaps because it affects GPX hierarchy in the retinal cells.

37-LB

Age and Duration of Diabetes as Risk Factors for Diabetic Retinopathy: A Case for Prediabetes Screening in Sub-Saharan Africa

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Driven by the need to provide convenient and timely access to diabetes eye care the Zimbabwe Retinopathy Telemedicine Project (ZRTP) was established in Harare, the capital city of Zimbabwe. Routine screening of diabetic retinopathy (DR) using a handheld fundus camera operated by nurses is currently underway at diabetic clinics. As a start towards understanding the distribution of DR among various age groups and risk factors we analysed age and date of diabetes diagnosis data from January through December 2016. Out of a total of 522 patients screened, 136 (26.4 percent, 95% CI) were found to have DR including 35 males (27.7%) and 101 females (74.3%). The mean age was 55 years. The prevalence of DR was 4% in 21-30, 7% in 31-40, 30% in 41-50, 19% in 51-60, 26% in 61-70 and 13% in >70 year age groups. The median number of years between diagnosis of diabetes and detection of DR was 2 years in 21-30, 0.5 years in 31-40, 2 years in 41-50, 9 years in 51-60, 6 years in 61-70 and 3 years in > 70 year age groups. Since duration of diabetes is associated with DR the high prevalence of DR in the younger age groups is cause for concern. Of note, the median number of years between diabetes diagnosis and detection of DR was 2 years for age 41-50 years, the age group with the highest percentage of patients with DR. In this setting, the date of diabetes diagnosis may not be a true reflection of duration of diabetes due to late diagnosis, a common factor in resource limited countries where awareness is low and both undiagnosed and pre-diabetes may contribute to DR. An approach that may minimize the risk of developing DR and contribute towards reducing the burden of DR among diabetic patients in Zimbabwe is to institute prediabetes screening in primary care settings. Awareness of modifiable diabetes risk factors should be emphasised including lifestyle interventions in resource-limited settings where medications to treat diabetes are costly, and the capacity to treat complications is limited.

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38-LB

Large-Scale Study of Eyeart Automated Diabetic Retinopathy Screening Tool on Real-World Varying-Quality Images

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Manual diabetic retinopathy (DR) screening cannot scale to triage the ever-increasing diabetic population at risk of vision loss. EyeArt meets this growing need with an automated, deep learning based screening system with high diagnostic efficacy as demonstrated on large dataset of color fundus images from primary care clinics in EyePACS telescreening.

EyeArt automatically analyzes multiple fundus images of a patient to generate patient-level DR screening output, while flagging and excluding external eye and poor quality images. In this study, EyeArt analyzed 850,908 color retinal fundus images of 107,001 diabetic patient visits or encounters. A patient was deemed negative (non-referral) if there was mild or no signs of DR and no clinically significant macular edema (CSME) surrogate markers in both eyes as per grading by EyePACS experts. 5,291 encounters not having DR/CSME grading due to image quality (also graded by experts) were excluded from this analysis.

In 101,710 cases, EyeArt's screening sensitivity was 91.3% and specificity was 91.1%. Sensitivity for detecting potentially treatable DR was 98.5%. Table 1 provides the performance of EyeArt split across the different quality levels as identified by EyePACS graders.

Automated DR screening using EyeArt achieves high sensitivity and specificity across different image quality levels as demonstrated on a large diabetic population.

Table 1.

		Quality label per EyePACS graders (reference standard)				
	Total	Excellent	Good	Adequate	Insufficient for full interpretation	Missing quality
Num. Encs. (Percentage of Total Encs.)	101,710 (100.0%)	36,218 (35.6%)	36,173 (35.6%)	19,362 (19.0%)	4,543 (4.5%)	5,414 (5.3%)
Sensitivity	91.3%	94.0%	90.5%	88.7%	92.0%	—
Specificity	91.1%	92.9%	91.8%	88.4%	74.0%	—
Positive Predictive Value (PPV)	72.5%	68.1%	72.0%	68.4%	87.8%	—
Negative Predictive Value (NPV)	97.6%	99.0%	97.6%	96.5%	82.1%	—
Treatable DR Sensitivity	98.5%	98.9%	98.9%	97.9%	98.5%	—
Area Under Receiver Operating Characteristics Curve (AUROC)	0.965	0.977	0.965	0.943	0.900	—
Num. Non-screenable Encs. per EyeArt (Percentage of Num. Encs.)	910 (0.9%)	86 (0.2%)	106 (0.3%)	162 (0.8%)	453 (10.0%)	—

Supported By: National Institutes of Health (EB013585, TR000377)

39-LB

Prevalence and Predictors of Retinopathy in Adolescents with Type 1 Diabetes from 2000-2016

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Aims: To assess prevalence and clinical predictors of retinopathy in adolescents with type 1 diabetes (T1D) in modern era of diabetes management.

Methods: Participants aged 12-18 yrs with T1D duration ≥ 5 yrs screened for complications at The Children's Hospital at Westmead (Australia) during 2000-2016 were included (n=1022, visits=4263). Retinopathy grade 21 was defined as ≥1 microaneurysm/hemorrhage on 7-field fundal photography; grade 31 as microaneurysm + hemorrhage/venous bead/loop and grade 41 as moderately severe non-proliferative retinopathy (NPR). Prevalence of retinopathy was determined at the last visit for each patient. Generalised estimating equations (GEE) were used to determine clinical predictors of retinopathy using all visits.

Results: Median HbA1c was 8.7% and BMI SDS 0.80.

One adolescent had moderately severe NPR. Predictors of retinopathy in multivariable GEE were duration (B=1.23, 1.18-1.27; p=0.02), age at diagnosis (1.10, 1.05-1.14; p<0.001), HbA1c (1.15, 1.09-1.22; p<0.001), total daily insulin dose (1.3, 1.0-1.7; p=0.04) and BMI SDS (1.15, 1.03-1.28; p=0.02).

Conclusions: One in five older adolescents have detectable early retinopathy after five years of T1D duration, while NPR is rare. Glycemic control and higher BMI are modifiable risk factors for retinopathy. Higher insulin dose, possibly as an indicator of pubertal insulin resistance, also increases retinopathy risk.

Table. Prevalence of Retinopathy in Adolescents with Type 1 Diabetes Stratified by Age and Duration.

Prevalence	Age 12-<15 yrs	Age 15-<18 yrs	p-value	Duration 5-10 yrs	Duration >10 yrs	p-value
Any retinopathy	15%	21%	0.05	16%	25%	<0.001
Retinopathy grade 21	13%	17%	0.26	13%	21%	<0.001
Retinopathy grade 31	2.7%	3.8%		3%	4.5%	

40-LB

BDNF, GDNF, and VEGF in Müller Cell Viability: Implication in Neuroprotection in Diabetic Retinopathy and in Anti-VEGF Therapies

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To study neuroprotection in diabetic retinopathy (DR), we generated Müller cell (MC)-specific Vascular Endothelial Growth Factor Receptor-2 (VEGFR2) knockout (KO) mice, which demonstrated a significant loss of MC and neuronal density and retinal Glial cell line-Derived Neurotrophic Factor

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(GDNF) and Brain-Derived Neurotrophic Factor (BDNF) in diabetes (diabetes, 64: 3554). To reveal the mechanism further, we examined the role of VEGF on neurotrophin production, the relationship among VEGF, GDNF, and BDNF in promoting MC viability, and the ability of BDNF and GDNF in rescuing accelerated MC loss and neuronal degeneration. VEGF resulted in an increase in BDNF and GDNF secretion in MC cultures. BDNF, GDNF, and VEGF had additive or synergistic effects on MC viability in diabetes/hypoxia, which suggest that VEGF signaling may interact with BDNF- or/and GDNF-specific pathways for MC viability. Finally, intravitreal BDNF and GDNF supplement was capable of rescuing accelerated MC loss and neuronal degeneration in conditional VEGFR2 mice in hypoxia (environment in later stage of DR). Rescuing MC loss and neuronal degeneration by BDNF and GDNF in diabetes is in progress. These results support the notion that VEGF promoted BDNF and GDNF production may be critical to MC viability and neuroprotection in DR and hypoxic retinal diseases. As anti-VEGF drugs are neutralizing antibodies that can potentially interact with VEGF singling in MCs, neurotrophins may be useful in improving the safety of long-term (5-year+) anti-VEGF therapies for DR and diabetic macula edema. Since the loss of MCs and neurons in diabetic/hypoxic conditional VEGFR2 KO mice bears striking resemblance to the abnormally thin retinas in a significant portion (36%) of patients after 5-year anti-VEGF treatment for wet age-related macular degeneration (AMD), our work may also have a significant implication in neuroprotection in designing safer anti-VEGF therapies for wet AMD.

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41-LB

Fenofibrate Ameliorates the Lipoprotein-Mediated Damage in Diabetic Retinopathy

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Combined effects of hyperglycemia and lipoprotein extravasation/modification contribute to diabetic retinopathy (DR). Fenofibrate slows DR progression, but mechanisms of action are unclear. In human studies, benefit is independent of changes in lipid profiles, suggesting possible intra-retinal effects. To investigate these, we employed a diabetic rat model using intraocular injections of modified lipoprotein to accelerate DR.

One week post-induction of STZ-diabetes, diabetic (D) and control (C) Sprague-Dawley rats received chow with or without fenofibrate (0.18%) for 4 weeks (Weeks 0-4). At Week 3, intra-vitreal Highly-Oxidised Glycated Low-Density Lipoprotein (HOG-LDL) was injected to simulate intra-retinal extravasation/modification of lipoproteins (vitreal conc. 25µg protein/ml). At Weeks 0, 3 and 4, electroretinograms (ERG) and ocular coherence tomography (OCT) were recorded. At Week 4, eyes/retinas were harvested for histologic studies.

At Week 0, no ERG or OCT differences were observed between D and C groups (n= 6-9 per group). At Week 3, despite no effects on OCT, amplitudes of ERG A- and B-waves were reduced in D vs. C ($p=< 0.0001$); fenofibrate had no effect. At Week 4, ERG abnormalities were more severe in D vs. C, but diabetic animals receiving fenofibrate exhibited functional ERG recovery ($p=<0.0001$). Qualitative and quantitative OCT analyses also showed protection by fenofibrate in diabetic rats ($p=< 0.0001$).

Histology showed reduction of inflammation and leukocyte infiltration in HOG-LDL-injected diabetic rats that received fenofibrate vs. those receiving normal chow.

In conclusion, while oral fenofibrate did not improve early retinal changes associated with hyperglycemia, it mitigated the more severe retinal injury that followed injection of modified LDL. The data suggest that in mitigating DR, fenofibrate may act mainly within the retina, and on pathways associated with intra-retinal extravasated lipoproteins.

42-LB

Effects of Diabetes on Retinal Inflammation and Barrier Repair following Ischemia-Reperfusion Injury

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Purpose: Diabetic retinopathy may be caused by an imbalance of retinal damage and repair processes. The mouse retinal ischemia-reperfusion (IR) model exhibits neurodegeneration, microgliosis, leukostasis, leukocyte infiltration and vascular permeability, which all normally resolve between 3 and 4 weeks after injury. We tested the hypothesis that negative effects of diabetes on retinal repair processes impede resolution of inflammation and restoration of the inner blood-retinal barrier (iBRB) following retinal IR injury.

Methods: IR injury was unilaterally produced by intraocular pressure elevation for 90 min in control and diabetic mice after 4 weeks of streptozotocin-induced diabetes. Retinal microglia and infiltrating leukocytes were quantified by flow cytometry with CD45, CD11b, Ly6C and Ly6G markers. Vascular permeability was assayed by measuring the retinal accumulation of circulating FITC-BSA.

Results: In normal mice, IR caused a transient proliferation of microglia and a temporal progression of leukocyte infiltration, with granulocytes and $Ly6C^{hi}$ inflammatory monocytes predominating at day 1 and $Ly6C^{neg}$ reparative monocytes peeking at day 7. Surprisingly, at 2 weeks following IR, diabetic mice exhibited a 2.3-fold increase in microglia ($p<0.01$) that was not observed in controls. The numbers of granulocytes and $Ly6C^{hi}$ inflammatory monocytes in retinas at 2 and 4 weeks after IR injury were not significantly altered by diabetes. However, the number of $Ly6C^{neg}$ reparative monocytes was more than 2-fold greater ($p<0.05$) in the IR retinas of diabetic mice at both 2 and 4 weeks following IR. Whereas IR produced 45% less ($p<0.01$) vascular leak in diabetic compared to control mice at 2 days following injury, diabetic mice exhibited a 2.4-fold higher ($p<0.05$) vascular leak at 4 weeks.

Conclusions: Extended microglial and $Ly6C^{neg}$ monocyte responses and lack of iBRB recovery suggests that impaired repair processes can contribute to diabetic retinopathy pathology.

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43-LB

REDD1 Represses Ceramide-Induced Retinal Cell Death

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Improvement in the treatment of diabetic retinopathy requires a better understanding of the molecular mechanisms that cause retinal dysfunction, particularly in type 2 diabetes. Recent studies demonstrate that mice fed a high fat diet exhibit dramatic activation of the c-Jun N-terminal Kinase (JNK) concomitant with retinal degeneration and impaired retinal function. Activation of JNK functions as a key regulator of apoptosis and cell death. Thus, the present study was designed to interrogate mechanisms regulating JNK activation in the retina of mice consuming a high fat/sucrose diet. Retinas of mice fed a high fat/sucrose diet exhibited elevated ceramide concentrations, enhanced JNK activation, and increased expression of the stress response protein REDD1 (regulated in development and DNA damage 1), as compared to those from mice fed a control chow diet. To assess a possible role for ceramides in regulating JNK activation and REDD1 expression, retinal explants and retinal cells in culture were treated with C6-ceramide. Such treatment rapidly (i.e., within 1-2 hr) promoted JNK activation. However, more prolonged treatment was required to induce REDD1 expression, and surprisingly increased REDD1 expression was associated with attenuated, rather than enhanced, JNK activation. In contrast, ceramide-induced JNK activation was exacerbated in REDD1-deficient cells. Moreover, REDD1 expression was sufficient to repress JNK/c-Jun phosphorylation. Thus, REDD1 potentially acts to repress ceramide-induced JNK activation and cell death. Overall, the results support a protective role for REDD1 in the effects of high fat/sucrose on retina, whereby the protein acts to repress ceramide-induced JNK activation and retinal cell death.

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DIABETIC DYSLIPIDEMIA

44-LB

Mechanistic Insights into the KHK-Dependent and -Independent Fructose Metabolism

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In the last several decades, the increase of fructose consumption was closely correlated with the epidemic of type 2 diabetes and nonalcoholic fatty liver disease. Excess fructose intake has been shown to promote the progression of hepatic steatosis and insulin resistance. Within the liver, fructose is metabolized by ketohexokinase (KHK) dependent phosphorylation, and enters glycolysis and the TCA cycle via triose phosphate. Here, our data showed that, in the primary hepatocyte, the function of fructose in enhancing the lipogenic gene expression required the presence of glucose. Compared with the WT control, $KHK^{-/-}$ mice challenged with high carbohydrate diet (HCD) for 1 week showed less liver weight. Chrebp activity was increased and expression of lipogenic genes enhanced after HCD refeeding, and both were reversed by KHK deletion. Our hypothesis is generated fructose-1-phosphate after fructose phosphorylation stimulates glucoki-

For author disclosure information, see page LB107.

nase (Gck) relocalization outside of nucleus to activate Gck and increase the glucose-6-phosphate (G6P) levels. Increased G6P activates Chrebp and then induces the expression of lipogenic genes, consequently increasing the de novo lipogenesis. Interestingly, a KHK independent fructose metabolic pathway was revealed by the observation of an "abnormal" C13 labeling pattern of glucose in fructose-$^{13}C_6$ administrated KHK$^{-/-}$ mice in comparison to WT mice. In contrast to the dominant "normal" +3 and +6 C13 labeled glucose species in WT, dominant +1 and +2 C13 labeling glucose were observed in KHK$^{-/-}$ mice, indicating that fully labeled $^{13}C_3$-triose is not the precursor for glucose synthesized in KHK$^{-/-}$ mice. Effort is in progress to identify the carbon flux from fructose to glucose in this KHK independent pathway. This study adds details to the KHK dependent pathway of fructose metabolism, and reveals the existence of KHK independent fructose metabolism. These results contribute to the complete understanding of the mechanism of fructose in inducing the hepatic lipid disorder.

45-LB

LGCL-1, a Novel and Selective GPR120 Agonist, Treatment Resulted in Antidiabetic and Antimetabolic Disorder Effects in DIO Mice

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GPR120 has been known as an attractive target for type 2 diabetes and metabolic syndrome. GPR120 is the long chain free-fatty acids receptor predominantly expressed in the gut, macrophage, and pancreatic islets. In this study we evaluated the antimetabolic disorder effects of LGCL-1; antidiabetic and anti-steatosis effects on diet-induced obesity (DIO) mice. A rationally designed compound, LGCL-1, was identified as a potent and highly selective agonist of GPR120 receptor (human EC50=31 nM; mouse EC50=71 nM) compared to GPR40 receptor (both species EC50 >10 μM). LGCL-1 was revealed as GPR120-specific agonist by acute treatment of LGCL-1 in C57BL/6 mice: plasma total ghrelin level was significantly reduced (oral administration; 30 mg/kg; 37%; p<0.01) in wild type C57BL/6 mice, but the effect was completely abolished in GPR120-knockout mice. Repeated administration of LGCL-1 on DIO mice showed decreased non-fasting blood glucose levels and improved the HFD-induced insulin resistance to some extent (once-daily oral dosing; 30 mg/kg). The insulin sensitivity effect was quantified by hyperinsulinemic-euglycemic clamp study at a dose of 100 mg/kg of LGCL-1. In addition, LGCL-1 showed decrease in glycosylated hemoglobin (HbA1c) levels (once-daily oral dosing; 100 mg/kg; HbA1c; -0.3). Furthermore, biochemical and histological analysis of the liver disclosed that LGCL-1 ameliorates steatosis with significant reduction in liver weight and triglycerides as well as plasma ALT at the dose of 30 mg/kg after once-daily oral dosing for 7 weeks. These studies provided that GPR120 could be a potent therapeutic target for type 2 diabetes and metabolic syndrome.

46-LB

Comparison of Lipid-Lowering Properties of Anti-PCSK9 Antibodies and Synthesis Inhibitors Using a Quantitative Systems Model of Lipoprotein Metabolism

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Objectives: Proprotein convertase subtilisin/kexin type 9 (PCSK9) cholesterol-regulating properties made PCSK9 a desirable target for anti-hypercholesterolemia therapies. Current anti-PCSK9 treatments can be separated into two major classes of compounds: monoclonal antibodies (mAbs) and synthesis inhibitors. In this work, we evaluated differences in lipid-lowering properties between these classes, using a quantitative systems pharmacology (QSP) model, and compared the effects of mAbs (evolocumab, alirocumab, RG-7652 and LY3015014) to those of siRNA compounds (inclisiran and ALN-PCS), on the following lipid biomarkers: low-density lipoprotein, very-low density lipoprotein, high-density lipoprotein cholesterol (LDLc, VLDLc, HDLc respectively), PCSK9, apolipoprotein B (ApoB), total cholesterol, lipoprotein A and triglycerides (TG).

Methods: Open-source data from 10 clinical studies of alirocumab and evolocumab, 2 studies of RG-7652 and LY3015014, and 3 studies of siRNA compounds were used to build the model. Modeling was performed using the IntiQuan QSP toolbox (http://www.intiquan.com/).

Results: 1. Evolocumab, but not alirocumab, with background statin treatment resulted in a further 10% decrease in LDLc vs. no statin.

2. At equal plasma PCSK9 protein levels, plasma LDLc decreases via either siRNA compound (ALN-PCS, inclisiran) differed only by 2-3% vs. evolocumab treatment, indicating no significant differences in potency between the two modalities (siRNA vs. mAb).

3. No quantitative differences were observed in other lipid biomarkers, including ApoB, TG, HDLc, across the two types of anti-PCSK9 modalities, suggesting that intracellular disruption of PCSK9 synthesis has no additional effects on lipoprotein-related mRNA expression.

47-LB

Apolipoprotein-C3: A Major Determinant of Hypertriglyceridemia in Diet-Induced Metabolic Syndrome

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Apolipoprotein-C3 (Apo-C3) is involved in the upregulation of hepatic de novo lipogenesis and inhibits triglyceride (TG) clearance via lipoprotein lipase leading to increased synthesis and decreased clearance of TG-rich lipoproteins. We have developed and characterized a rhesus monkey model of metabolic syndrome that more closely mirrors lipid metabolism in humans than commonly used rodent models. In these animals, consumption of a high sugar (fructose) diet rapidly induces insulin resistance, accompanied by marked increases of circulating TG and Apo-C3, as we have previously reported in humans. We examined changes of circulating TG and Apo-C3 in 59 adult male rhesus monkeys (15.9 ± 0.3 kg) consuming a high sugar diet for 3 months during which the animals gained 1.6 ± 0.1 kg (%Δ10 ± 1%). Plasma TG increased from 83±5 to 185±22 mg/dl (%Δ=+112 ± 14%, p<0.0001) and Apo-C3 from 4.4 ± 1.6 to 6.4 ± 2.5 mg/dl (%Δ=+46 ± 4%, p< 0.0001). In addition, plasma apolipoprotein-E (Apo-E) increased by 44 ± 7% and fasting insulin by 101 ± 27% (both p< 0.0001). Importantly, the increases of Apo-C3 were highly predictive of increase of plasma TG (r=0.74, p< 0.0001). While increases of Apo-C3 and Apo-E were well correlated with each other (r=0.58, p< 0.0001), neither Apo-E (r=0.22, NS) nor insulin sensitivity, assessed by fasting insulin or HOMA-IR (r=0.18, NS), were predictive of the increases of TG.

In conclusion, increased Apo-C3 is an important independent determinant of hypertriglyceridemia in rhesus monkeys consuming a high sugar diet. Accordingly, Apo-C3 is likely to be a promising target for lowering circulating TG in hypertriglyceridemic patients with metabolic syndrome and type 1 and type 2 diabetes.

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FOOT CARE—LOWER EXTREMITIES

48-LB

Amputation Rates in Diabetic Patients at Montefiore New Rochelle Hospital

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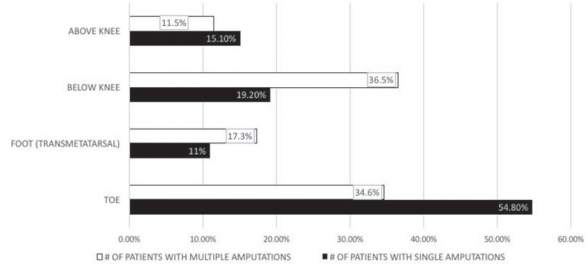
Retrospective chart review of amputations in diabetic patients were reviewed from 2012-2016 at Montefiore New Rochelle (MNR) Hospital (Figure 1). Results revealed diabetic patients with single amputation had the highest percentage (55%) of amputations at the level of the toes. Diabetics with multiple amputations had the highest percentage of amputations at the level below the knee, 37%. Of these patients, 26% below the knee amputations (BKA) converted to above the knee amputations (AKA). Additionally, 47% of diabetic patients with BKA had revisions compared to the 27% of patients with AKA revisions. Given that a majority of these patients were from nursing homes, their overall level of function is decreased. Our community hospital data suggests that the risk of conversion from BKA to AKA and revision procedures must be considered in these diabetic patients, who are already poor wound healers. Thereby our results advise that an AKA may be considered an option in non-functional diabetic patients due to a decreased rate of subsequent procedures.

Figure 1. Single vs. Multiple Amputations in Diabetic Patients by Level.



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49-LB

Concordance between Bone Pathology and Bone Culture for the Diagnosis of Osteomyelitis in the Presence of Charcot Neuroosteoarthropathy

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Background: The aim of this study was to examine the concordance between bone pathology and bone cultures in the presence of Charcot Neuroarthropathy (CN) in the diagnosis of osteomyelitis (OM).

Methods: Two hundred eighty five patients with diabetes mellitus (DM) and CN were identified retrospectively. Of which, 48 patients were identified with OM; confirmed via plain and advanced imaging, ESR and CRP, and by positive probe-to-bone test and intra-operative inspection. Seventy matched pairs of bone pathology and cultures with complete data were compared and analyzed. Statistical analysis included concordance rate, specificity, sensitivity, positive predictive value, and negative predictive value.

Results: Forty eight patients (100%) had a diagnosis of DM, CN, and confirmed OM. Thirty three (68.8%) patients had hypertension, 14 (29.2%) had chronic kidney disease, 9 (18.8%) had end stage renal disease, 9 (18.8%) had peripheral arterial disease and 4 (8.3%) active smokers. The mean glycated hemoglobin was 8.8% ±1.48 (5.3-15), mean body mass index was 32.5 ±8.37 (21.3-47.3), and mean age was 54 years ±14.85 (34-86). Concordance between bone pathology and bone culture was 41.4%; agreement in 29 of 70 paired specimens. The positive predictive value was 72.2%. The negative predictive value was 44.1%. The sensitivity of histopathology for the diagnosis of OM in patients with CN was 57.8%; specificity was 33.3%. When histopathology identified "no osteomyelitis" or "Charcot without evidence of osteomyelitis" an inaccurate diagnosis was tallied; this occurred in 34 of the 70 specimens (48.6%). Microbiology inaccurately identified "no growth" in 35 of 70 specimens (50%).

Discussion: Histopathology and microbiology bone specimens have little concordance, and have a high margin of error when used alone. Thus, a diagnosis of OM in patients with CN should only be interpreted in light of strong clinical, laboratory, and imaging correlate.

50-LB

Characteristics of Patients with Medicare Advantage Coverage and Type 2 Diabetes Stratified by the Presence of a Foot Ulcer or Amputation

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Diabetic foot ulcers (DFU) and amputations significantly impact morbidity and mortality, effects which could be limited by timely diagnosis and following recommended care. Our objective was to describe differences in patients with Medicare Advantage (MA) coverage and type 2 diabetes (T2DM) with and without DFU or amputation.

Patients with MA coverage and T2DM (ICD-9 250.x2, ICD-10 E11 and E13, or evidence of antidiabetic medication including insulin) continuously enrolled from 1/1/14 to 12/31/15 were identified; those with DFU/amputation in 2014 were excluded. Patient characteristics for 2014 were captured from claims and differences between those with and without DFU or amputation in 2015 were described using either Chi-square or ANOVA.

Of the 374,500 patients identified with MA coverage and T2DM (mean age 68.3 years, 50.6% female), 3.3% and 0.3% had a new DFU or amputation, respectively. Patients who developed a DFU/amputation were more likely to be younger, disabled and male. Significantly fewer patients with a DFU/amputation had controlled HbA1c or an annual eye exam, and more specialist visits, compared to those without such complications.

Results suggest that patients with DFU or amputations differ significantly from patients who do not develop these complications. Interventions should be targeted to individual patient characteristics.

Table. Patient Characteristics in 2014, Prior to Developing DFU/Amputation.

	Amputation (n=1,217)	DFU (n=12,268)	Neither (n=361,015)	P value
Mean age in years	65.8	67.6	68.4	<0.001
Percent female	30%	46%	51%	<0.001
Percent under age 65	36%	26%	20%	<0.001
Percent disabled or with ESRD	67%	53%	39%	<0.001
Mean DCSI for 2014	4.6	2.9	2.0	<0.001
Mean DCSI for 2014-2015	6.8	4.7	2.6	<0.001
Percent with annual retinal exam	46%	55%	55%	<0.001
Percent with annual kidney function test	92%	91%	90%	<0.001
Percent with HbA1c in control	29%	39%	47%	<0.001
Percent adherent (PDC>80%) to oral antidiabetic medications (n=181,533)	76%	77%	78%	0.09
Percent with podiatrist visit	40%	25%	13%	<0.001
Percent with endocrinologist visit	13%	12%	8%	<0.001
Percent with vascular surgeon visit	45%	36%	26%	<0.001

51-LB

Dipeptidyl Peptidase-4 Inhibition Improves Diabetic Wound Healing

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Diabetic ulcers (DUs) lead to non-traumatic amputation and seriously affect the life quality of patients. Current studies have found that dipeptidyl peptidase-4 (DPP-4) expression increase in keratinocytes and fibroblasts following skin wound, and our previous studies revealed nuclear factor-E2-related factor 2 (NRF2), might be modulated by DPP-4, contributed to diabetic wound healing. Here the effect of DPP-4 inhibitors on diabetic wound was evaluated in vitro and in STZ-induced diabetic mice, and a randomized, double-blind, placebo-controlled trial (NCT02742233) comprised 63 DUs patients (wagner2-4) was conducted. We found DPP-4 inhibitors accelerate the wound closure rate, significantly promote migration and epithelial mesenchymal transition (EMT) of keratinocytes. Meanwhile, DPP-4 inhibition also promote CXCL12 production of fibroblasts driving EMT of keratinocytes. Consistent with in vitro experiment, DPP-4 inhibitor promotes EMT in epidermis layer, enhance the expression of CXCL12 during wound healing of diabetic mice and patients. Meanwhile the collagen expression and deposition significantly reduced in STZ-induced diabetic mice with DPP-4 inhibitor treatment. Moreover, our clinical trial observed that the time of complete wound closure median reduced from 87 day to 71 day, and the healed ulcer rate of 3 months increased from 56.25% to 87.10% after DPP-4 inhibitor treatment ($P<0.05$). Survival analysis using a Kaplan-Meir curve (Log rank=16.53, $P=0.0004$) further confirmed that DPP-4 inhibitor accelerate diabetic wound healing. Taken together, these results show that DPP-4 inhibitors improve diabetic wound through direct and indirect enhancing EMT and diminishing scar formation. Therefore, this study provides clinical and experimental evidences suggesting that DPP-4 inhibitors are the preferred therapy for DUs.

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52-LB

Influence of Antibiotics on Biofilm-Producing and Planktonic Cultures of Microorganisms Isolated from Patients with Diabetic Osteoarthropathy

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The purpose of our procedure was to investigate influence of antibiotics on planktonic cultures and biofilms of S.aureus isolated from patients with diabetic foot syndrome. The sensitivity of microorganisms to action of antibiotics was studied by CLSI microdilution method. 200 µl bacterial suspensions of S. aureus ($1.8x10^8$ cells/well) were placed in each well of 96-well microplate. The microplate was incubated at 37^0C for 48 hours for formation of biofilms. The antibiotics at dilutions (1, 56-12, 50 mg/ml) in meat-peptone agar with 1% 2, 3, 5-triphenyl tetrazolium chloride (TTC) were added to wells of microplate. We estimated reduction of TTC to purple formazan in viable cells visually after 24 h incubation with TTC. Our results showed that the bio-

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film MIC (minimal inhibitory concentration) for some antibiotics was higher than the planktonic MIC for same antibiotics. Planktonic culture of reference strain S. aureus ATCC 6538p was more sensitive to cefazolin and cefotaxime than biofilm-producing culture. Planktonic culture S.aureus isolated from patients was more sensitive to cefazolin and ceftriaxon than biofilm-producing microbes. And reference strain was more sensitive to antibiotics than isolates. Our results provide a basis for future studies of microbial biofilms associated with its effective elimination from wounds.

Table. MIC Values of Antibiotics in Planktonic Cultures and Biofilm-Producing Cultures (MIC, mg/ml).

Antibiotic	Reference strain (planktonic culture)	Reference strain (biofilm-producing culture)	Isolates (planktonic culture)	Isolates (biofilm-producing culture)
Gentamicin	1.562	1.562	3.125	3.125
Cefazolin	3.125	6.250	6.250	12.50
Ceftriaxon	1.562	1.562	6.250	12.50
Cefotaxime	1.562	3.125	6.250	6.250
Kanamycin	3.125	3.125	6.250	6.250

DIABETES EDUCATION

53-LB

Improvement in Self-Care Behaviors and Glycemic Control following the Integration of Simulation Education and Case Management into Diabetes Self-Management Education for Type 2 Diabetes Patients

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Objectives: This study evaluated disease outcomes at a regional hospital based on the addition of simulation education and case management to a diabetes self-management education (DSME) program for the care of patients with type 2 diabetes.

Design, Setting, and Participants: The study was prospective and followed the patients from enrollment to 6 months. A total of 100 patients who were diagnosed with T2DM were recruited and randomized into the following groups: 1.) an experimental group that received a simulation education (SE) intervention plus nurse case management (NCM) and DSME, The primary patient outcome HbA1c was determined based on laboratory examinations, and secondary outcomes, including adherence to diet recommendations, physical activity, blood glucose self-monitoring, diabetes knowledge (measured by self-care behaviors scale), and other physiological factors (e.g., lipids, blood pressure, and body mass index (BMI)), were recorded. All measures were collected at baseline and after a 6-month follow-up period.

Results: A significant difference in ADA diabetes care standard items was observed between groups at 6 months, which included HbA1c (7.22% ± 1.06% vs. control 8.35 ± 1.46%,p<0.01), FPG (7.19±1.89 mmol/L vs. control 8.09±1.47 mmol/L,p<0.05), and PBG (10.22±2.40 mmol/L vs. 11.96±2.02 mmol/L,p<0.01). Patient-reported outcomes were encouraging. For example, the combined simulation education and case management with DSME intervention program resulted in significant changes in adherence scores in diabetes self-care behaviors, including blood glucose self-monitoring (0.80±0.50 vs. control 0.29±0.34, p=0.000). These changes were significantly associated with HbA1c changes at 6 months.

54-LB

Delivery of Diabetes Telehealth Services to a Rural Clinic

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Introduction: Care delivery systems need to meet the needs of patients with diabetes to improve outcomes (1,2). The utilization of evidence-based guidelines along with systems changes (i.e., electronic health record) has been shown to increase the quality of diabetes care (3,4). Underserved rural communities generally do not receive the same care as those living in urban area (5). Telemedicine health care service delivery appears to be an important tool in improving diabetes care for those living in more remote and underserved areas (6,7,8).

Methods: Altru Health System, a community based health care system in Grand Forks, ND, includes a full service diabetes center. In December of 2013, one of the diabetes center physician providers began a telemedicine clinic service for diabetes patients at the Heart of America Medical Center in Rugby, ND, a community of approximately 3,000 in a remote rural area of north central North Dakota. The onsite Certified Diabetes Educator (CDE) coordinates encounters via a commercial video link application.

Maximum A1C levels of referred patients at a clinic visit prior to being seen by the diabetes telemedicine service will be compared to the best A1C levels in those patients with the requisite visit as extracted from the electronic health record. Likert scale patient satisfaction surveys are included.

Results: HgA1C values from last contact (mean=7.58, 95% CI, 7.16-8.00) were compared to the maximum values prior to contact (mean=8.68, 95% CI, 8.25-9.11). Analysis revealed a significant difference (t_{38}=6.03, P < .001, 95% CI, .73-1.47; d=.83).

A summary of responses to the Telemedicine project satisfaction Likert scale survey (n=13) showed that for each survey item but one item, responses are "Agree" or "Strongly Agree."

Conclusions: In this group of rural patients served by a diabetes telemedicine service coordinated by an onsite CDE, A1C reduction was significant and patient satisfaction was high. This is a viable model for diabetes care delivery in a rural setting.

55-LB

Advancing Patient Safety and Access to Concentrated Insulin (U-500R) in the Veterans Health Administration (VHA)

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The national epidemic of diabetes and the exposure of Vietnam veterans to Agent Orange has led to insulin resistance requiring concentrated insulin (U-500R) for glycemic control. Initiation of U-500R insulin is limited to endocrinology expertise housed at "hub" Veterans Health Administration's (VHA's) located hours away from smaller "spoke" facilities. To overcome the potential health care disparities and improve patient safety, a program was developed ensuring that all clinicians could co-manage U-500R insulin.

This program evaluation was undertaken to improve patient safety and access to U-500R insulin by improving "spoke" clinicians' knowledge of safe delivery and management of U-500R insulin. We created an order template for U-500R insulin, a patient education template, and pharmacy processes to ensure that all clinicians are able to co-manage U-500R insulin. A convenience sample of clinicians at a "spoke" VHA in northwestern Pennsylvania was evaluated.

Clinicians completed an anonymous survey including: Informed consent, Perceived Competence Scale (PCS), 10-item knowledge scale (KS), and a demographics questionnaire. The post-survey included the PCS and KS.

Results from the between-within ANCOVA testing documented significant pre- to post-intervention differences on perceived competence, F (2,52)=77.42, p <.001, partial eta^2=.598, indicating a very large effect size. Perceived competence scores significantly increased from the pretest (M=4.06, SD=1.49) to the posttest (M=6.21, SD=0.74). A Wilcoxon Signed Ranked Z Test was used to evaluate Knowledge Scores (KS). Pretest KS scores ranged from 20% (F) to 100% (A+). At post test, the mean KS scale score was 94.00 (SD=7.35), equivalent to an "A" grade. Post-test KS scores ranged from 70% (C) to 100% (A+).

In conclusion, our program enhanced health care process and increased provider knowledge and confidence of delivery and management of U-500R insulin for veterans.

56-LB

Dietary Behaviors and Carbohydrate Metabolism in Overweight and Obese Young Adults

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Background: Decreased insulin sensitivity and impaired insulin secretion are key factors progressing from normoglycemia to prediabetes and to diabetes. Sustained hyperinsulinemia increases the risk for beta cell exhaustion and cardiometabolic diseases. Overweight and obese young adults who frequently skip meals and are binge eaters are vulnerable to glucose spikes and hyperinsulinemia leading to develop early onset T2D.

Aim: The purpose of this study was to provide greater understanding of the associations between dietary behaviors and glucose metabolism in overweight and obese young adults in order to increase the precision of nutrition education to prevent early onset T2D. Differences in race/ethnicity and gender were examined to explore population specific diabetes prevention program priorities in overweight and obese young adults.

Method: A descriptive, correlational cross-sectional study design was used. Overweight/obese sedentary young adults ages 18-29 were recruited from the metro Atlanta area using diverse recruitment methods. Self-administered survey questionnaires, anthropometric assessment, blood pressure, and laboratory data collected in a clinical research unit were used.

Result: Overall, dietary quality was fair (mean score 62.49 out of 95) and no racial difference (African Americans [AA] vs. non-African Americans)

For author disclosure information, see page LB107.

was identified in the calorie intakes and dietary quality. Appropriate carbohydrate and protein intakes from good nutritional sources (e.g., fiber rich, unsaturated fat diet) within adequate calorie consumption were contributing factors to increase insulin sensitivity. There was a marginal interaction effect between insulin sensitivity and beta cell function by race; the rate of an inverse relationship between insulin sensitivity and beta cell function was higher in the non-AA group compared to the AA.

Conclusion: Findings are useful to develop an age specific nutrition guideline to prevent early onset T2D in high-risk young adults.

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57-LB

Retainment and Recruitment Challenges to Diabetes Education in the South Bronx

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Lifestyle changes, including diet and exercise, are important components of managing type 2 diabetes. However, achieving these behavior modifications can be especially challenging in low-income neighborhoods, due to limited resources and low health literacy. In an effort to address this disparity, a Department of Family Medicine in the South Bronx participated in a pilot education program that focused on nutrition and physical activity. Targeting the 21% of Department patients diagnosed with diabetes, participants were recruited through telebanking, and waiting room recruitment as well as referred by physicians. Enrolled patients were expected to attend 4 90-minute weekly classes and a booster session 3 months after the final class. The program efficacy was evaluated looking at before and after health indicators, while a qualitative process evaluation was also conducted through patient and CHW interviews. There was an average 1.84% decrease in A1C levels over the course of the intervention. Towards the end of the study A1C levels plateaued, however, this is consistent with similar studies. There was an overall decrease in patients' healthcare charges and ED visits one year after the program. Barriers in retaining attendance and recruitment among patients were significant. Often patients recruited for participation refused, referencing receiving other diabetes education interventions as the reason for their disinterest. Although recruited patients were motivated to improve their health, only 30% of enrollees completed all weekly and booster sessions, even with CHWs calling as a reminder prior to each class. Many patients were often unreachable because phone numbers had changed or were disconnected. Patients also missed classes due to scheduling conflicts but were offered opportunities to make up classes. This study suggests that patient motivations, priorities and levels of commitment need to be better understood and accommodated before implementing classes aimed at lifestyle changes.

58-LB

Readmission Factors of Patients with Type 2 Diabetes

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Background: Hospital readmissions within 30 days of initial discharge occur frequently, but relatively limited research has focused on patients with diabetes. The problem of diabetes among hospitalized patients, is significant, costly, and some are considered preventable. Unfortunately, there is relatively limited research focused on patients with diabetes to identify which aspect of disease management and patient care factors contribute to the costly and preventable readmissions.

Objective: The purpose of this study was to identify the factors associated with 30-day hospital readmissions in patients with type 2 diabetes.

Methods: This retrospective descriptive correlational study involved 400 samples from the 2014-2015 electronic health records (EHRs) in an urban hospital. Samples were patients who were at least 65 years and older and were discharged from the acute inpatient setting with a type 2 diabetes regardless of their admitting diagnosis. Data abstracted included patient characteristics (age, gender, and race), hospital discharge disposition (home, skilled nursing facility, or rehabilitation center), clinical biomarker (Hemoglobin A1C), diabetes medications (oral, insulin, or both), disease management (whether the patient received DSME or seen by an Endocrinologist), length of stay, and comorbidities.

Results: Race, medications, Diabetes Self-Management Education (DSME), and comorbidities are the readmission factors significantly associated with 30-day readmission in patients with type 2 diabetes who are at least 65 years of age.

Implications to Nursing: Findings from this study have important implications for policy development and nursing practice. Identification of the factors associated with 30-day readmission will enable the healthcare team to make better assessments and provide the best possible care to prevent preventable readmissions.

59-LB

Feasibility and Perceived Benefit of a Shared Decision-Making (SDM) Approach to Pediatric Diabetes Retinopathy (DR) Screening

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Intensive education and treatment during childhood and adolescence, in preparation for the transition to adult care, can prevent or delay the onset and progression of diabetes (DM) complications. Yet, availability of developmentally-appropriate strategies to empower youth to make DM self-management decisions is limited. This study evaluated a SDM approach to engage and prepare youth with T1D in understanding benefits of early and routine DR screening, potential risk of eye disease and methods to prevent/delay this complication.

A literature review and focus groups with DM experts and young adults with T1D informed development of a DR screening SDM tool. A DM educator trained pediatric DM clinic nurses on SDM and to administer the tool to eligible patients during routine visits. Youth $\geq$10 y and $\geq$ 2 y T1D duration (n=113, 41% female, 88% white, mean age 15.5±2.8 y, HbA1c 8.5±1.9%) were randomly assigned to either the SDM intervention (n=59) or serve as controls (n=57). Both groups completed a survey with Likert-scale items about attitudes and beliefs related to DR.

Regardless of group assignment, worry about DM-related vision loss positively correlated with age (r=.204; p=.03). The SDM group was in stronger agreement than the control that DM affects eye health (4.27±0.8 vs. 3.77±1.2; p=.01). The SDM group also highly rated the tool, agreeing or strongly agreeing that it helped them learn that DM affects eyes (75%), understand the importance of routine eye exams (86%), learn about the DR screening process (74%), feel more comfortable with getting eyes checked (72%) and improve their interest wanting to take care of their DM to maintain eye health (88%). In addition, 77% of SDM group agreed that tool should be delivered in practice similarly to the study protocol.

These results demonstrate that a SDM approach and use of a tool designed for young patients with T1D is feasible and offers a learning opportunity that may help them make informed decisions about their DM management.

Supported By: The Beckwith Institute

60-LB

Perceptions of Reproductive Health (RH) and Complications among Adolescents and Young Adult (AYA) Males with T1D

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Approximately half of males with T1D report RH complications (e.g., erectile dysfunction, decreased libido, orgasmic dysfunction) as early as 25 yrs. Some RH complications are associated with other serious complications (e.g., neuropathy) and may be delayed/prevented by tight glycemic control. It's imperative to raise this awareness in AYA males, who are vulnerable to suboptimal health care and poor glycemic control. Yet these sensitive topics are rarely discussed by health professionals (HP) during clinic visits.

A Diabetes Transition Care Program (PREP U for Transition) was initiated for AYA with T1D at a major academic Children's Hospital to provide care and small group discussion-education sessions on relevant topics, including RH and sexuality with diabetes, RH complications, risks, prevention strategies, and initiating discussion with HP. Prior to the sessions, a survey was given to all male participants (n=16; 17-22 yrs) to explore their perceptions of RH and rate a list of complications on a scale of 1 (most concerning) to 5 (least concerning).

Highest rated concern was retinopathy; the lowest rated concern was RH. Following the RH session, male participants stated that this information was "new" and "helpful", "never heard this before." Verbal comments were documented to inform program development. The following responses were given when asked, "What should be included in these sessions?" 1.) "give us what you got…all of it…everything specific", 2.) "don't repeat sex ed, maybe just a review…STD's", 3.) "material specific to diabetes", 4.) "contraceptive methods for both guys and girls", and 5.) "start basics for younger teens and keep adding stuff."

AYA males with T1D in a Diabetes Transition Program were receptive to receiving information and discussing RH and complications. Knowing risks, preventative measures, and strategies to initiate discussions with HP could empower AYA males to maintain healthy lifestyles to delay/prevent these complications.

Supported By: Children's Hospital of Pittsburgh

For author disclosure information, see page LB107.

61-LB

Quantifying the Knowledge-Behavior Gap in Youth with Type 1 Diabetes

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Objective: Previous studies demonstrate lower socioeconomic status is associated with poor glycemic control. Frequently, we combat inequalities through education regarding nutrition and carbohydrate counting. A pediatric carbohydrate counting quiz (PCQ) was previously developed and validated at Case Western which demonstrated a strong correlation between carbohydrate counting knowledge and Hemoglobin A1c (HbA1c). We sought to determine whether a similar correlation exists in the pediatric type 1 diabetes population at Los Angeles County Hospital.

Research Design and Methods: As part of a randomized controlled trial for an educational carbohydrate counting game we collected pre-intervention data. The PCQ was administered to 42 pediatric patients in our type 1 diabetic clinic. Scores were correlated with HbA1C.

Results: In the original PCQ validation 41 child participants were recruited with mean PCQ score of 85 ± 11%, mean HbA1c 8.9 ± 1.6% and higher PCQ score correlated significantly with lower HbA1C (r=-0.32, P=0.04). The Los Angeles County pediatric endocrine population is older with longer duration of diabetes, identified more frequently as Hispanic, reported lower parental education, had greater use of multiple daily injections over insulin pump and had higher mean HbA1c than the Case Western group. There was no difference in gender or age at diagnosis. In our study mean PCQ score is 77% ± 15% and mean HbA1c is 10% ± 2%. Higher PCQ scores did not correlate significantly with lower HbA1C (r=-0.20, P=0.20).

Conclusions: In the Los Angeles County group it is more difficult to establish a significant association between carbohydrate counting knowledge and HbA1c. Explanations include poor compliance with insulin, poor knowledge of foods the patient eats and difficulty translating knowledge into action. We propose utilizing the correlation between PCQ score and HbA1c in clinics to quantify the "knowledge-behavior gap." For the under-served mere knowledge is not sufficient to ensure an A1C in the target range.

62-LB

Managing Type 2 Diabetes Mellitus with Shared Medical Visits in a Medically Underserved Setting

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Our study aims to examine an innovative model to increase access to care for patients with type 2 diabetes (DM2), a growing subgroup of the medically underserved. We postulated that patients with DM2 who participated in shared medical visits (SMVs) would demonstrate improved health outcomes at rates that are equal to or faster than the current standard of care (individual medical visits). Specifically, our study highlights the utility of SMVs to meet the needs of patients in an urban Federally Qualified Health Center (FQHC). This retrospective cohort study had primary outcome of time to goal HbA1c of less than 7. Secondary outcomes included time to completion of overdue quality metrics specific to patients with diabetes. Overall, 44% of patients in SMVs (N=36) compared to 28% of patients in the control group (N=103) achieved controlled A1c (approaches sig p=0.07). Controls were 51% less likely to lower A1c below 7.0 compared with SMV patients (p=0.03) adjusting for gender and age (each had no impact on reduced A1c). Of the secondary outcomes examined, two showed statistically significant improvement in SMV patients: pedal pulse palpation was completed in 97% of SMV patients vs. 46% of controls (p<0.01), and diabetic eye exam screenings were performed in 72% of SMV patients vs. 51% of control group patients (p=0.02). Patients at our FQHC with DM2 and poor glycemic control were more likely to reach glycemic control if they participated in SMVs vs. standard medical visits. SMV patients also achieved glycemic control more quickly than patients in the control group. Our secondary outcomes also demonstrated improvements in two of the standard quality metrics for patients with a diagnosis of DM2 that are typically more difficult to achieve; namely pedal pulse checks and diabetic eye exam screenings. Our study not only demonstrates the SMV as an acceptable alternative to the current standard of care, but also suggests an intervention that may reach an increased number of patients in a limited resource setting.

63-LB

Impact of a Diabetes Mobile App with In-App Coaching on Glycemic Control

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In-person diabetes self-care programs have traditionally helped people manage the condition, leading to improved glycemic control (i.e., reducing A1c levels) and prevention of complications. Newer mobile self-care programs are more feasible, but program impact on clinical outcomes must be assessed. We therefore conducted a 12-week-long intent-to-treat single-arm study to evaluate the impact of a mobile diabetes self-care program (One Drop | Mobile app and Experts' coaching program) on glycemic control for 146 individuals with uncontrolled type 2 diabetes (T2D) (A1c ≥ 7.5%).

Study participants used the app to track self-care activities, set goals, receive data-driven insights, community support, tips, advice, recipes, and inspiration. A Certified Diabetes Educator delivered diabetes education and 24/7 on call support via the in-app messaging feature, and participants were provided a glucose meter and test strips. We collected self-reported demographics, and baseline and 12-week A1c. On average, study participants were 52 ± 9 years old, 73% were female, 26% were black or Hispanic, 49% had less than a college degree, 48% were on insulin, and 81% were obese. Duration since T2D diagnosis was 10 ± 7 years, and average baseline A1c was 9.9% ± 2.0%.

A total of 127 participants completed baseline and 12-week A1c data. To correct for missingness, multiple imputation with predictive mean matching generated 13 imputed datasets. According to a pooled unadjusted and adjusted repeated measures model (adjusted for age, sex, race, education, years since diabetes diagnosis, insulin use, and BMI with robust standard errors), A1c improved by -0.8% (p<0.001 for unadjusted and adjusted) from baseline to 12 weeks.

The landmark UKPDS trial showed that a -1.0% A1c improvement is associated with a reduction of diabetes-related complications and deaths. Results from our study suggest that this mobile app and coaching program may reduce the A1c of people with uncontrolled T2D, potentially reducing their risk of complications.

64-LB

Diabetes Education Using Electronic Modules in Rural Communities

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Diabetes self-management education (DSME) is the cornerstone of type 2 diabetes (T2DM) management. With appropriate DSME, people living with diabetes can learn to manage their diabetes which could prevent diabetes complications. Diabetes prevalence is higher in rural areas compared to urban areas. People living with diabetes in rural areas face significant challenges to diabetes care including limited access to diabetes education.

Purpose and Objectives: The purpose of this pilot study was to develop, implement, and evaluate the effectiveness of diabetes self-management educational modules delivered via iPad devices to increase self-management knowledge levels in adults living with T2DM in rural communities. Specific objectives included: develop evidence-based DSME modules for people living with T2DM; conduct a pilot study to provide DSME in the areas of self-monitoring of blood glucose, medication-taking, healthy eating, exercising, and monitoring for complications; and evaluate the effectiveness of the intervention to increase diabetes self-management knowledge among people living with T2DM in rural communities.

Design/Methods: This pilot study involved collaboration between nursing and engineering faculty and students. DSME modules were developed by nursing faculty members. Engineering students prepared the modules for electronic delivery on iPad devices. The modules were presented to people living with T2DM who attended health promotion clinics offered by school of nursing faculty and students in rural communities. Participants completed a diabetes knowledge questionnaire before and after educational modules were presented.

Outcome: Thirty people living with T2DM participated in the pilot study. Participants were predominantly African American females. Preliminary data analysis using the paired t-test found statistically significant (p <.01) differences in diabetes knowledge levels from pre to post-educational intervention.

For author disclosure information, see page LB107.

65-LB

The Use of "Car Culture" as a Way To Engage Mexican-American Men In Diabetes Programs

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U.S. Hispanics are burdened by the diabetes epidemic, and although public health and community diabetes programs have been implemented, Hispanic men are underrepresented in these programs. Engaging men to participate in diabetes programs is important because, relative to women, they are: a) less knowledgeable about the disease, b) less likely to visit diabetes specialists, and c) delay medical care. In El Paso, TX, a city of predominately Mexican-American residents, 1 in 4 residents have diabetes. To improve equitable access and inclusiveness of men in diabetes programs, a community-academic partnership was established to develop a male-specific program. The objective of this research is to: 1.) investigate the enrollment and completion rate of men in diabetes programs compared to women, and 2.) describe the evolution of a community-academic partnership and Community Based Participatory Research to assess the feasibility of an "AutoShop" initiative to engage Mexican-American men.

Methods: Aim 1.) data come from six El Paso Diabetes Association's programs between 2015-2017 and one YMCA Diabetes Prevention Program in 2016-17. A total of 604 individuals were enrolled in the programs (75% female, 25% male). A two-tailed t-test was conducted to compare the mean program enrollment of men and women. Logistic regression was used to assess the relationship between gender and program completion.

Results: Aim 1.) There was a difference in enrollment mean score for women (mean score=65.00) vs. men (mean score=21.28; p=.01) and men were less likely to complete a series of classes (OR=.30, 95% CI: .159-.588). Aim 2.) Local support of the "AutoShop" initiative has led to the development of a) a steering committee, which includes several universities, nonprofit, and hospital stakeholders and b) a working group of Certified Diabetes Educators and auto/vehicle technicians to translate diabetes information into analogous car part and maintenance activities for the production and pilot testing of educational materials.

Supported By: University of Texas at El Paso

EXERCISE

66-LB

Increased Long-Chain Saturated Fatty Acid Content of Intramuscular Diacylglycerol Contributes to Skeletal Muscle Insulin Resistance

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A high intramyocellular lipid content is strongly associated with insulin resistance and diacylglycerol (DG) plays an important role in the development of muscle insulin resistance. Long-chain saturated fatty acids (LCFA) are also important for induction of lipotoxicity in the peripheral tissues and suppression of insulin signaling. In this study, we investigated the relationship between the fatty acid composition of DG and skeletal muscle insulin sensitivity in rats fed a high-fat diet, and we evaluated the acute effect of exercise on the fatty acid composition of intramuscular DG. After Sprague-Dawley rats were fed a high-fat diet for 8 weeks, elevation of the fasting plasma insulin level and the phospho-IRS-1 (Ser307) (pIRS-1) level in gastrocnemius muscle occurred, and insulin sensitivity was low in the insulin tolerance test. The palmitic acid (PA) and stearic acid (SA) content of DG in gastrocnemius was about 1.5-fold higher than in control rats. Then the rats were subjected to resistance training (RT), in which dorsiflexion of the distal hind limb was induced by electrical stimulation of the tibialis anterior (TA) muscle (5 mA pulse at 100 Hz for 1100 msec), and lengthening contraction (LC) of TA was induced at an angular velocity of 100 deg/sec from 45° to 135° (10 contractions every 10 sec with five sets of LC). After six days of RT, the PA and SA content of DG in gastrocnemius was decreased in a training intensity-dependent manner, and pIRS-1 in gastrocnemius was normalized by RT. The level of LCFA, especially PA in DG, was significantly associated with the pIRS-1 level in gastrocnemius. These effects of RT on gastrocnemius were also observed in the contralateral muscle that was not subjected to RT. These findings indicate that the LCFA composition of DG in skeletal muscle plays an important role in the development of muscle insulin resistance. Local application of RT can improve systemic muscle insulin sensitivity by reducing the LCFA content of DG.

67-LB

Mini-dose Glucagon as a Novel Approach to Prevent Exercise-Induced Hypoglycemia in Type 1 Diabetes

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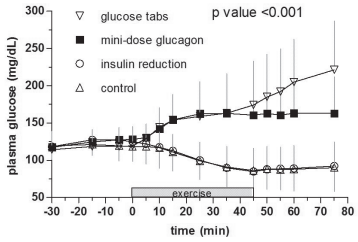
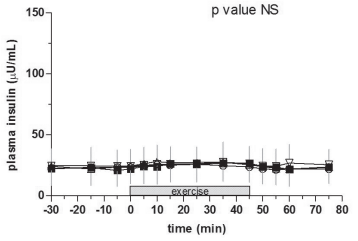
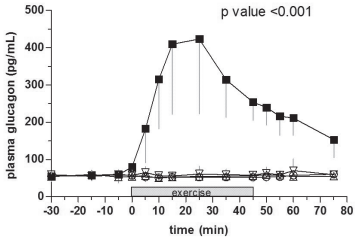
Patients with type 1 diabetes (T1D) who do aerobic exercise have a drop in blood glucose concentration that can result in hypoglycemia. Current approaches to prevent exercise-induced hypoglycemia include reduction in insulin delivery or ingestion of carbohydrates, but these strategies may still result in hypo- or hyperglycemia. We sought to determine whether mini-dose glucagon (MDG) given s.c. before exercise could prevent subsequent glucose lowering, and to compare the glycemic response to current approaches. We conducted a randomized, 4-period crossover trial involving 15 adults with T1D who exercised at ~55% VO_{2max} for 45 min with no intervention (control), 50% basal insulin reduction, 40 g oral glucose tabs, or 150 µg glucagon, all administered 5 min before exercise. During exercise, mean plasma glucose increased slightly with MDG compared to a decrease with control and insulin reduction, and with a greater increase with glucose tabs. Insulin levels were not different, while glucagon increased with MDG. Six subjects experienced hypoglycemia (< 70 mg/dl) during control and 5 during insulin reduction and none with glucose tabs or MDG; 5 subjects experienced hyperglycemia (≥250 mg/dl) with glucose tabs and 1 with MDG. MDG may be more effective than insulin reduction for preventing exercise-induced hypoglycemia, and may result in less post-intervention hyperglycemia than ingestion of carbohydrate.

Figures.







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68-LB

The Effects of Liraglutide Combined with Aerobic Interval Training Is Prior to Single Pharmacological Treatment or Exercise in Alleviating Diabetic Cardiomyopathy

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Aim: LEADER study revealed that Liraglutide, plays a role in heart protection. Aerobic interval training may reduce metabolic complications and enhance cardiac fitness in T2DM patients. The aim of this study is to explore

For author disclosure information, see page LB107.

whether combinations of these two therapies have prior effect than single treatment in alleviating diabetic cardiomyopathy.

Method: Rats were divided into control group (C), diabetes group (D), Liraglutide group (L), aerobic interval training group (A), Liraglutide combined with aerobic interval training group (LA). Rats in L group and LA group were treated with subcutaneous injections of Liraglutide (0.3mg/kg/day) for 8 wks. Rats in A group and LA group were subjected to AIT program for 8 wks. Enzymatic methods and ELISA kits measured serum biomarkers. Histology and morphometric analysis were used HE staining and electron microscope. Hemodynamic characterization and cardiac function were determined by echocardiography.

Results: After intervention, cardiovascular risk biomarkers and BNP concentrations were dramatically decreased in L, A and LA group compared with D groups ($p<0.05$). Compared with single treatment, LA group showed obviously reduced insulin resistance ($p<0.05$). The results of histology analysis revealed myofilament permutation disorder, myocardial fiber gap widening, lipid accumulation and nuclear lysis were alleviating in L, A, LA group, but myocardial fiber was much orderly arranged and less lipid droplets in LA group. The results of echocardiography revealed that all of the three interventions increased LVEF ($p<0.05$); but improved FS, E/A ratio, IVRT, CO all presented in LA group ($p<0.05$).

Conclusion: The findings of the study is that Liraglutide, AIT and the combination therapy can significantly improve cardiovascular risk biomarkers as well preserve heart function, but combination therapy is more effective than single intervention.

69-LB

Exercise Regulates the Concentration of Novel Circulating Factors in Mice

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Exercise can improve metabolic health for all people and patients with diabetes; however, the molecular mechanisms that mediate the exercise response are not well understood. We and others have hypothesized that exercise causes factors to be released from skeletal muscles, adipose tissue, and possibly other tissues into the circulation, and that these factors may contribute to the beneficial effects of exercise on health. To identify novel exercise-stimulated factors, 10-week old female C57BL/6 mice (n=6/group) performed treadmill exercise at 21.5 m/min and 15% grade. Blood was collected at baseline, and at 20, 40, or 60 min of exercise, and 1,134 circulating factors were simultaneously measured using a novel aptamer-based proteomic method. This single bout of exercise significantly altered 6% of the measured circulating factors. In total, 53 unique proteins were increased and 17 proteins were decreased at any time point. Insulin-like growth factor-binding protein 1 (IGFBP1), a protein that binds insulin-like growth factors I and II, increased 5.6-fold at 40 min and 10.6-fold at 60 min into the exercise. Dynein light chain roadblock-type 1 (DLRB1), a protein part of the cytoplasmic dynein 1 complex decreased significantly by ~40% at 40 min and 60 min into exercise. These proteins showed the strongest up- and downregulation, respectively. KEGG pathway analysis showed significant changes of the pancreatic cancer and adipocytokine pathway at all-time points. We estimate ~50% of upregulated proteins have not previously been identified as exercise-regulated proteins.

In summary, proteomic methodology can be used to identify novel exercise-regulated circulating factors in mice. It will now be critical to determine the exercise-induced proteomic response in humans, and to determine if (dys)regulation of these proteins in metabolic disease can mediate the beneficial effects of exercise on health.

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70-LB

Exercise-Enhanced Macrophage Phagocytosis and Resolvin Biosynthesis Is Aborgated by a Diet High in Fat

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Regular exercise prevents the development and progression of chronic inflammatory diseases including obesity, insulin resistance and diabetes. Although dietary modifications and exercise are effective treatment strategies for diabetes, the molecular mechanisms by which they prevent or mitigate disease are unclear. We provide data that exercise (Exe) enhances resolution of acute inflammation in a diet-dependent manner by promoting macrophage (MΦ) phagocytosis and by augmenting resolvin D1 (RvD1) levels. Mice adapted to a 4-week treadmill exercise regimen displayed 1.48-fold higher MΦ phagocytotic activity compared with sedentary controls (Sed) (n=3), and demonstrated earlier neutrophilic clearance (ΔR_i~7 h) during peritonitis. Peritonitis cell extracts from exercise-adapted mice showed higher Alox5 expression (48 h: Sed 0.77±0.15 vs. Exe 1.7±0.27 relative expression, n=4-5) and RvD1 (48 h: 29.0±2.1 vs. 52.6±8.9 pg/mL, n=5). Replacement of fetal bovine serum (FBS) with plasma from exercise-adapted mice stimulated naïve bone marrow macrophage (BMM) phagocytosis; conversely, plasma from sedentary mice diminished phagocytosis (FBS 100.0±11.1% vs. Sed 68.6±7.1% vs. Exe 135.9±6.0%, n=5-8). Interestingly, BMM treated with plasma from mice fed a high-fat diet (HFD; 60% kcal fat) during exercise showed no improvement in phagocytosis. Because RvD1 mitigates inflammatory tone in obesity, we questioned how exercise and HFD affect RvD1 biosynthesis in adipose tissue. In mice fed normal chow, exercise resulted in higher adipose tissue RvD1 (Sed 156.7±12.0 vs. Exe 223.0±24.7 pg/mL, n=5-7) and increased antiinflammatory MΦ ($F4/80^+CD301^+$; Sed 17.5±3.2 vs. Exe 40.9±4.5% $F4/80^+$, n=4-6); whereas HFD prevented these exercise-mediated effects. These results suggest that an exercise stimulated plasmatic factor enhances resolution of inflammation. Our findings put forth the concept that poor dietary choices can block the beneficial pro-resolving effects of exercise.

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71-LB

Exercise Training Results in Beiging of White Adipose Tissue (WAT) in Male, but Not Female Mice

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Exercise training can cause WAT to become more metabolically active and increase marker genes for beiging. Most animal studies investigating beiging have been in male mice, and little is known whether WAT from females adapt to training. To determine if exercise training induced adaptations to WAT are sex-specific, 10 wk old male (n=16) and female (n=16) C57BL6/J mice were housed for 11 days in individual cages with (trained) or without (sedentary) attached running wheels. Females performed more voluntary exercise compared to males (8.1±1.6 vs. 6.0±3.4; km/day; $p<0.001$). In females, there was no difference in body weights between sedentary and trained, likely due to increased food intake in trained mice (36%; $p<0.001$). In contrast, trained males tended to have lower body weights ($p=0.08$), and did not significantly increase food consumption. Exercise training in both sexes similarly decreased fat pad weights of subcutaneous/inguinal (iWAT) (59%; $p<0.001$) and visceral/perigonadal (pWAT) (50%; $p<0.001$). Metabolic and beiging markers in iWAT from male mice revealed that exercise training increased Ucp-1 protein (86%; $p<0.001$), and Glut4 (90%; $p=0.05$), Dio2 (280%; $p<0.01$), and Ucp-1 (360%; $p<0.05$) mRNA, and only tended to increase Prdm16 and Cidea. In contrast, there was no effect of training on expression of any of these proteins or genes in iWAT from females. In pWAT, training in males increased gene expression of Cidea (100%; $p<0.05$) and Tfam (50%; $p<0.05$), but not Ucp-1, Glut4, or Dio2. In females, there was no effect of training on any of the genes; but interestingly, baseline expression of Ucp-1, Cidea and Dio2 were ~10 fold higher in females vs. males. These results demonstrate: 1.) exercise training-induced beiging of iWAT only occurs in male mice; 2.) pWAT is less responsive to training compared to iWAT; and 3.) baseline expression of numerous genes is different between male and female mice. These pronounced sex-specific differences must be considered in future research investigating WAT beiging.

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72-LB

Differing Relationships between Daily Physical Activity Time and Glycemic Control by BMI

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Background: Physical activity is recommended for treatment of glycemic control in people with T1DM. However, declines in glucose levels associated with physical activity may result in hypoglycemia. Treatment of this hypoglycemia may result in increased glucose levels, blunting the positive effect of exercise. Studies have shown that body mass index (BMI) is increasing among people with T1DM. The relationships among exercise, glycemic control, and BMI are little understood. Therefore, determination of the potential impact of BMI on the relationship between physical activity and glycemic control is necessary to identify appropriate exercise interventions.

For author disclosure information, see page LB107.

Aim: Our study examined the associations among daily time spent in moderate to vigorous physical activity (MVPA), glycemic control, and BMI in young adults with T1DM.

Methods: Correlational analysis was conducted to examine the relationships among MVPA, glycemic control (daily glucose means), and BMI.

Results: The mean age of participants (n=35) was 26 years (SD=4.4; range=19 to 35 years), the mean disease duration was 13.6 years (SD=6.8), and the mean BMI was 27.1 (SD=3.7). Spearman rho correlational analysis was conducted. There was no statistically significant relationship between glycemic control and MVPA. In addition, partial correlational analysis between glycemic control and MVPA while controlling for BMI showed no statistically significant relationship. This insignificant relationship was shown because of non-linearity between BMI and MVPA. However, BMI was negatively related to MVPA (r=-.32, p=.026) and to average Mets (r=.-42, p=.03).

Discussion: MVPA exercise was negatively related to high BMI in young adults with T1DM. Further investigation is needed to examine the role of BMI in the relationship between MVPA and glycemic control in young adults with T1DM.

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NUTRITION—CLINICAL

73-LB

Pretreatment Fasting Plasma Glucose and Insulin Determine Long-Term Dietary Weight Loss Success on Low-Carbohydrate vs. Low-Fat Diet

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Background: The optimal diet for weight loss and maintenance remains controversial. We studied levels of fasting plasma glucose (FPG), insulin (FI) and insulin sensitivity (SI) measured by intravenous glucose tolerance test as prognostic markers for successful weight loss and maintenance among obese participants consuming a low-carbohydrate (CHO) or low-fat diet for 2 years.

Methods: Participants were randomized to a low-CHO diet (20 g/d as low glycemic index vegetables with unrestricted fat and protein and a CHO increase of 5g/d per week after 3 months until a stable desired weight was achieved) or a low-fat diet of limited energy intake (1200-1800 kcal/d; ≤30% calories from fat). Both diets included comprehensive behavioral treatment. Participants were categorized as normoglycemic (FPG <100 mg/dl) or prediabetic (FPG≥100-125 mg/dl) and also by median FI or SI. Modifications of dietary effects by pretreatment FPG, FI and SI were examined in linear mixed models.

Results: Prediabetic individuals with high FI lost a mean 7.19 kg more on the low-fat diet (n=17) than low-CHO diet (n=8) (-6.93 vs. 0.26 kg, respectively; P=.004), whereas prediabetic individuals with low FI tended to lose more (6.09 kg) on the low-CHO diet (n=7) than low-fat diet (n=6) (-16.03 vs. -9.94 kg, respectively; P=.084). There was a significant 13.28 kg difference in response between the groups (P=.002 for diet by group interaction). No difference between diets was found for normoglycemic individuals with high FI (n=66) or low FI (n=67) (0.58 kg; P=.78). Using SI instead of FI produced similar results.

Conclusion: Pretreatment fasting insulin in prediabetic obese individuals determines long term weight loss success by ad libitum low-CHO or caloric restricted low-fat diets. These results may be helpful developing personalized strategies for weight loss.

Supported By: Gelesis

74-LB

Count with the Lion, an App to Count Carbohydrates and Beyond

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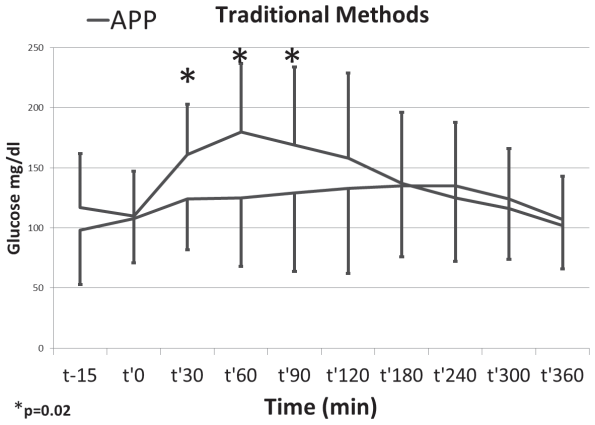
Background and Aim: As carbs counting poses sometime difficulty for children with type 1 diabetes (T1D), they often guesstimate food amount without performing a real calculation. The aim of the study was to evaluate the accuracy of carbs estimation using the mobile APP Conta con il Leone.

Methods: Twenty-five children with T1D on pumps (0.7-5.9 years), ages 8-19 years, with T1D duration since 8.1±4.2 years, in fairy good metabolic control (HbA1c 7.55±0.67%), estimated the number of carbs and fat/protein units appropriate for main meals, randomly using traditional methods (50 meals) or the APP (50 meals).

Results: No difference has been observed about pre-prandial bolus insulin dose when using traditional carbs counting methods or the APP (6.9±4.7 U vs. 6.8±4.4 U, p=0.754). However, following APP suggestion, patients used double wave bolus (DWB) (n=32) more than simple bolus (SB) (n=18) when using the APP, than when using traditional methods (DWB=9, SB=41) (chi-square test, p=0.004). Glycemic profiles are shown in the Figure.

Conclusions: Carbohydrate counting and insulin dose estimation using a specific-designed APP have been effective in managing post-prandial glucose excursions after principal meals in children with T1D, with a more flat profile especially in the first 90 min after meals. Insulin bolus dose was similar in the two study arms, however using the APP resulted in significantly more meals managed with DWB than SB.

Figure.



75-LB

Pretreatment Fasting Glucose Concentration Predicts Weight Loss on a High-Fiber, Low Glycemic Load Diet: The Healthy Weight for Living Study

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Background: Identifying predictors of weight loss success may be important for individualizing obesity treatments. Several behavioral predictors have been suggested; however, a need exists for simple, easily measurable biomarkers that can be used to match individuals to effective treatments. An analysis of weight loss in participants on a high fiber, low glycemic load diet was conducted to determine whether pretreatment fasting glucose (FG) concentration is a biomarker of success.

Methods: Participants who were overweight or had obesity received a 6-month comprehensive behavioral intervention with recommendations to consume a reduced energy (approximately -500 to -800 kcal/day), low glycemic load, high fiber diet (~45% energy from carbohydrates). Participants were dichotomized using criteria defined by a previous study into low (<90 mg/dl) and high (90-125 mg/dl) FG groups, and differences in weight loss were examined using linear mixed models adjusted for baseline BMI, age, gender and site or Fisher's exact tests.

Results: Participants with high FG (n=58) lost 9.48% (-10.94% to -7.88%) of their body weight at 6 months which was significantly more than participants with low FG (n=12) who lost 4.13% (-6.91%, to 1.35%; P=0.038). Approximately 80% of those with high FG achieved a 5% weight loss compared to 50% in those with low FG (P=0.064). Fasting glucose, as a continuous variable, tended to predict inverse weight change at 6 months (β -0.12%; -0.26% to .011%; P=0.072).

Conclusion: Pretreatment FG is a simple, objective biomarker that predicted weight loss success in participants on a high fiber, low glycemic load diet. This is consistent with previous associations of weight loss with measures of insulin sensitivity published by our team. These results are also consistent with other studies presented at this conference and may facilitate matching individuals to optimized treatments.

Supported By: Gelesis

76-LB

Remote Care Promotes Low Carbohydrate Diet Adherence and Glycemic Control Allowing Medication Reduction in Type 2 Diabetes

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Multiple studies demonstrate that reduced dietary carbohydrate can significantly improve glycemic control and reduce medication use; however, safety and sustainability of this approach has not been tested in a large population. We evaluated if patients with type 2 diabetes (T2D) could be supported by a remote care team to sufficiently limit dietary carbohydrate and protein to improve glycemic control, reduce weight, and reduce medications over one year. 262 adults with T2D enrolled in this ongoing, 2-yr intervention where they received personalized nutrition and behavioral recommendations via continuous remote care by a health coach, medication management by a physician, biometric feedback, and peer support. At the time of this interim analysis, 130 of 158 subjects remain actively enrolled past the 1-yr time point (82% retention). Of these, we have data from 111 patients (mean±SEM; 54±1 y, 40±1 kg·m-2, 75% female) who have completed 1-yr testing. HbA1c at enrollment (7.4±0.1%) improved to 6.1±0.1% (p<.0001) at 1-yr, and 58% of patients achieved HbA1c <6.5% at 1-yr while taking no diabetes medications or Metformin only. Insulin was reduced or halted in 97% of users; oral glucose control prescriptions (excluding Metformin) were reduced from 51 at baseline to 8 at 1-yr. Weight was reduced 13.6±0.8% at follow-up (116±2 kg to 100±2 kg, p<.0001). At 1-yr, significant improvements in TG (176±13 to 132±11 mg·dL-1, p=.002), HDL-C (46±1 to 53±1 mg·dL-1, p<.001), hsCRP (7.5±0.6 to 5.0±0.6 mg·dL-1, p<.0001), and ALT (29.7±2.7 to 20.8±1.2 U·L-1, p=.0011) were achieved. LDL-P (1269±42 to 1218±39 mmol·L-1, p=.16) was unchanged.

There were no significant adverse events attributed to the intervention. These initial data demonstrate that adults with T2D can be supported by a remote care team to maintain adequate carbohydrate restriction and achieve significant reductions in HbA1c, weight, and medications. Ongoing work will assess 2-yr safety, efficacy and sustainability.

77-LB

Diet Quality and Glycemic Control in Patients with Type 2 Diabetes

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Evaluation of relationship between diet quality and glycemic control in type 2 diabetes patients (T2DM). Cross-sectionally, T2DM patients underwent clinical, laboratory, and nutritional evaluations. Dietary information was assessed by a quantitative food frequency questionnaire and converted into daily intakes. Diet quality was evaluated by the Healthy Eating Index (HEI) version 2010. HbA1c was measured by HPLC method. A ROC curve evaluated cut-off points of diet quality, considering good glycemic control (values of HbA1c <7%). Characteristics of patients with HEI values >65% considered higher diet quality (AUC ROC=0.60; Sensitivity=71.2%; Specificity=52.1%; P=0.018) were compared to low quality diet by Chi-square, Student's t or Mann-Whitney tests. Logistic regression models were performed with HbA1c≥7% as dependent variable, adjusted to age, current smoking, diabetes duration and treatment, diabetes kidney disease, and sedentary lifestyle. PASW Statistics 18.0 (P<0.05). A total of 229 T2DM outpatients [63.0 (58.0-68.5) years; 10.0 (5-19) years of diabetes; IMC=30.8±4.3kg/m^2; HbA1c=8.1(6.9-9.7%)] were evaluated. Patients with low quality diet had a lower median of age and a higher frequency of current smoking compared to patients with good diet quality (P<0.05). More patients with low diet quality had poor glycemic control compared to patients with good diet quality (83.5% vs. 66.4%; P=0.004). Regarding HEI components, there was a negative correlation between adherence to recommendation of whole grains, empty calories and overall diet quality with HbA1c values (Spearman coefficients; P<0.05 for all analyses). Patients with low diet quality had 3.93 times the chance of poor glycemic control (OR=3.93; 95% CI=1.71-9.05; P=0.001) compared to good diet quality group, after adjusted to confounder variables.

In conclusion, diet quality evaluated by HEI <65% was associated with poor glycemic control in this sample of T2DM patients.

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78-LB

Pretreatment Fasting Plasma Glucose Determines Weight Loss on High-Fat Diets: The Predimed Study

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Background: Identification of optimal diets for patients with diabetes and prediabetes, where weight loss appear more difficult than in subjects with normal glucose control, has been elusive. We studied fasting plasma glucose (FPG) concentration as a determinant of weight change on two diets high in fat in the PREDIMED trial.

Methods: We analyzed the 1,846 participants with high cardiovascular risk, but without overt disease, who were randomized to receive one of two high fat diets for 5 years and who had complete data for yearly determinations of body-weight. Participants were stratified into glycemic categories by pretreatment FPG (<100 mg/dL; 100-114.9 mg/dL; 115-125.9 mg/dL; ≥126 mg/dL). Weight change by pretreatment glycemic categories were examined by linear mixed models for repeated measures adjusting for sex, age, baseline weight, T2D, hypertension, hypercholesteremia, and diet intervention.

Results: Mean BMI was 29.8 kg/m^2 (SD 3.7) and the two diets contained 41 E% from fat, 16 E% from protein, and 40 E% from carbohydrate. Weight change after 5 years was -0.20 kg (CI: -0.84 to 0.43) in participants with FPG<100 (n=746), -0.06 kg (CI: -0.84 to 0.72) in participants with FPG between 100-114.9 (n=329), -1.92 kg (CI: -3.04 to -0.79) in participants with FPG 115-125.9 (n=174), and -1.63 kg (CI: -2.51 to -0.75) in participants with FPG ≥126 (n=597) (Overall P=0.004). Consequently, participants with FPG≥115 (n=771) lost more weight [-1.64 kg (CI: -2.29 to -0.99)] than participants with FPG <115 (n=1075) [-0.19 kg (CI-0.66 to 0.30)] (P <0.001). Further adjustment for T2D treatment did not change the results.

Conclusions: Participants with elevated pretreatment FPG lost more weight than participants with lower FPG. These results are important to develop personalized dietary strategies for weight management in patients with diabetes and prediabetes where weight loss has been reported to be more difficult than in individuals with normal glucose control.

79-LB

Diabetes Risk Prediction and Lifestyle Modification

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Background: Diabetes is a major cause of death and disability. Lifestyle modification decreases diabetes risk. Our goal was to develop a risk prediction model, apply it, and to document benefits of lifestyle modification.

Methods: Framingham Offspring Study participants were followed after laboratory testing to develop models for predicting diabetes risk using logistic regression analysis. The best model was applied to a large population. Those with prediabetes or diabetes were assessed before and after being given a lifestyle plan restricted in dietary sugar, animal fat, and calories with increased activity; in some cases with telephone coaching.

Results: 2,416 fasting subjects (mean age 58 years) free of diabetes had specialized testing, and were followed for 9.3 years for new diabetes (166 or 6.9%). The following variables entered the model (p < 0.05, C statistic 0.924): serum glucose, body mass index, adiponectin, glycated albumin, parental diabetes, triglycerides, and cholesterol medications (C statistic 0.898 with only chemistries). In 126,996 subjects the estimated 10 year diabetes risk was 0.3% in normals and 5.6% in prediabetics. In 8,984 prediabetics with follow-up, those receiving the Life Plan (12%) had significant (p<0.001) decreases in diabetes risk (from 5.9% to 3.2%) in contrast to those who did not receive a Life Plan. Life Plan subjects also had significantly (p<0.01) greater reductions in HbA1c, insulin, LDL-C, and triglycerides, than those not receiving this intervention. Similar results were seen in 2,015 diabetic subjects, with 5.2% being no longer diabetic when receiving a Life Plan.

Conclusions: A specific and sensitive model for predicting diabetes risk was developed and applied to a large prediabetic and diabetic population. Their diabetes risk, glucose homeostasis markers, LDL-C, and triglycerides were significantly lowered with lifestyle modification as compared to those not receiving this intervention.

Supported By: Boston Heart Diagnostics

80-LB

Association of Diabetes Status with Household Food Availability and Expenditure in the U.S. Adult Population

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Diabetes (DM) diagnosis leads to higher individual healthcare costs and may leave less money for other household necessities, including food. This is especially important since a healthy diet plays a central role in DM management and control. Using data from 12,355 participants aged ≥18 years in the 2007-2010 National Health and Nutrition Examination Survey, we examined whether DM diagnosis was associated with household food availability and expenditures, and whether food security status modified the association. DM status was determined by self-report of a physician's diagnosis. Self-reported household availability of fruits, dark green vegetables, salty snacks, soft drinks, and fat-free/low fat milk was categorized as always/most of the time, sometimes, or rarely/never for each item. Household food expenditure during the past 30 days at supermarkets, restaurants, takeout, and other stores was self-reported in U.S. $ and adjusted for the number of people living in the household. Household food security was determined by the Food Security module and categorized as food secure or food insecure. An ordinal logistic regression model controlling for sociodemographic, behavioral and clinical characteristics was used to estimate the associations between diabetes and food availability/expenditures. On average, households spent $640.5 (CI%, $630.5-$650.6) on food in the past month. We found no bivariate association between diabetes status and food expenditure ($630.12 in people with DM vs. $641.35 in those without DM, p=0.44). Availability of food did not vary by DM status with one exception; household availability of fat-free/low-fat milk was positively associated with diabetes (p=0.04). The results showed no statistically significant associations between diabetes and food availability by food security status. Understanding consumer behavior may inform diabetes prevention and treatment efforts and ultimately make them more successful.

PSYCHOSOCIAL, BEHAVIORAL MEDICINE

81-LB

Impact of Collaborative Home Visits and Care Management on Adults with Diabetes and Mental Illness

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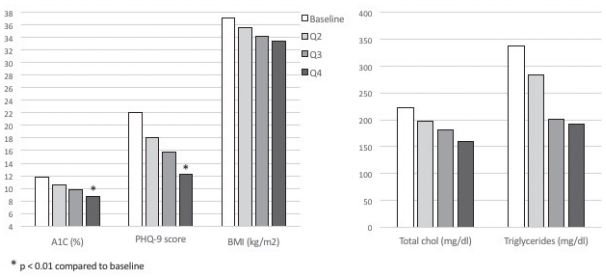
Diabetes and mental illness generally results in worse outcomes and greater burden of illness. Our program sought to engage patients with mental illness, poor adherence and elevated A1c despite established outpatient care. A nurse practitioner (NP) and licensed clinical social worker (SW) team, liaising with psychiatry and primary care, conducted risk assessments, interventions and education via both clinic and home visits, provided diabetes and mental health treatment, counseling, support and case management services, and addressed barriers to care and adherence. We present data on the first 30 enrollees (22 female, age 52±12 yrs, 50% Hispanic/32% black) of this quality improvement initiative. Over the course of 12 months, improvement was documented in mean A1c (11.75±2.2 to 8.74±1.8%, p<0.01), mean BMI (37.1±9.0 to 33.5±8.5 kg/m2, p=NS) and mean PHQ-9 scores (22±3 to 12±5, p<0.01). Emergency room visits fell from an average of 3.0±2.8 to 1.1±1.4 visits/year (p<0.05). We found significant correlations between change in PHQ-9 scores and both change in A1c (r=0.65, p < 0.01), and reduction in emergency care visits (r=0.37, p=0.046). Integrating mental and medical health services through a team based approach led by an NP and a SW was an effective approach towards improving metabolic outcomes and acute health care utilization in this challenging patient population.

Figure. Depression Scores and Metabolic Outcomes from Baseline to 12 Months.



Supported By: The Meadows Foundation, Inc.

82-LB

Diabetes-Related Stress, Perceived Stress, Coping Strategies, and Eating Behavior in Type 2 Diabetes

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Although nutrition therapy is considered a cornerstone of type 2 diabetes (T2DM) treatment, there are a limited number of studies examining whether eating behavior is important in the treatment of T2DM. The goal of this study is to determine the relationships among stress (perceived stress and diabetes-related distress), coping strategies (task-, emotion-, and avoidance-oriented coping), and eating behavior (restrained-, external-, and emotional- eating behavior) in T2DM. A cross-sectional study design provided valuable information about the relationships among stress, coping strategies, and eating behavior. Our analyses included 183 adults with T2DM (age 54.7 ± 8.8 years; 51.9% female; 68.3% African American) living in the Chicago area. Average duration of T2DM: 10.0 ± 8.0 years; HbA1c: 7.8 ± 2.0%; and BMI 33.6 ± 8.2 kg/m^2. Participants completed the following self-report questionnaires: the Diabetes Distress Scale (DDS), Perceived Stress Scale (PSS), Coping Inventory for Stressful Situations (CISS), and Dutch Eating Behavior Questionnaire (DEBQ). Path analysis was used to test specific direct and indirect relationships among diabetes-related stress, perceived stress, coping strategies, and eating behavior in people with T2DM.

Results of the study indicated that perceived stress and diabetes-related stresses were positively associated with restrained-, external-, and emotional-eating behaviors (R^2=.440).

In addition, the results of this study suggest that only emotion-oriented coping was a mediator in the relationship between stress and eating behaviors. The proposed study will be beneficial to providers treating people with T2DM by alerting them to recognize whether patients have restrained-, external-, and/or emotional-eating behavior. Additionally, this will provide the foundation for the development of interventions designed to modify dysfunctional eating behaviors to healthy eating behaviors.

83-LB

Disparities in Diabetes Self-Care among Adults in Volusia County, Florida

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Data was abstracted from FloridaCHARTS, Florida Department of Health, Division of Public Health Statistics and Performance Management. Descriptive analyses were conducted to identify differences in diabetes self-care behaviors by race/ethnicity, age and sex. More men (13.0%) than women (11.9%) reported ever having been told that they had diabetes. Women reported practicing more self-care behaviors than men: having had two A1c tests in the past year (65.9% vs. 51.4%); having had an annual foot exam (57.3% vs. 52.5%); self-monitoring of blood glucose at least once a day on average, (77.9% vs. 41.5%), and having had an eye exam (73.1% vs. 72.9%). Men (60.4%) more than women (52.6%) reported ever having had diabetes self-management education. Prevalence of diabetes was similar amongst adults 65+ and 45-64 compared to younger (18-44) adults (17.1%, 15.1% and 5.0% respectively). Older adults (68.6%) reported self-monitoring of blood glucose at least once a day on average, 77.0% of older adults reported having had two A1c tests in the past year, and having had an annual foot exam compared to adults ages 45-64 (74.6% vs. 45.6%). More adults between the ages of 45-64 reported having had an annual eye exam compared to adults 65+, (77.6% vs. 74.7% respectively), and received self-management education than those 65+ (63.5% vs. 49.3%). More Hispanic (27.3%) than non-Hispanic black (12.5%) and non-Hispanic white (10.2%) adults have been told they had diabetes. Non-Hispanic whites (69.4%) with diabetes reported self-monitoring blood glucose at least once a day on average. Non-Hispanic whites (79.6%) reported having had two A1c tests in the past year. Non-Hispanic whites (69.4%) reported having had an annual foot exam, having an eye exam (72.2%), and reported ever having had diabetes self-management education (58.3%). Minority groups remain under-represented in reporting of diabetes care and management. This exclusion from scientific literature speaks to the urgency to fill the knowledge gaps in minority health and health disparities.

For author disclosure information, see page LB107.

84-LB

Clinically Significant Cognitive Impairment in Older Adults with Type 1 Diabetes

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Little is known about cognition in older adults with type 1 diabetes (T1D). The goal of this study was to determine the degree to which older adults with T1D perform below normative data on neuropsychological testing and to determine correlates of clinically significant cognitive impairment.

Neuropsychological, diabetes-related (hypoglycemia unawareness, severe hypoglycemic events, presence of diabetes complications) and glycemic (A1c, Continuous Glucose Monitoring; CGM) data were collected from 201 community dwelling older adults (≥60 years) with longstanding T1D (≥20 years).

Clinically significant cognitive impairment (2 or more tests ≥1.5 SD below published norms) was present in 55% of the sample. Those with any diabetes complication, hypoglycemia unawareness, or ≥2 severe hypoglycemic events in the past year were approximately twice as likely (odds ratios 2.72, 2.20 and 2.11 respectively) to have clinically significant cognitive impairment than those without these factors. In univariate analyses, cognitive impairment was associated with higher A1c (7.9% vs. 7.5%) and night time average CGM glucose (171 mg/dL vs. 157 mg/dL). Those with cognitive impairment spent less time below 60 mg/dL at night than those with normal cognition. These glycemic variables did not, however, uniquely predict cognitive impairment when added to the model that included complications, hypoglycemia unawareness, and recent severe hypoglycemic events. Diabetes duration, age of onset, daytime CGM, and lifetime severe hypoglycemic events were not related to cognitive impairment status.

The majority of older adults with T1D in our sample had clinically significant cognitive impairment. Novel correlates of cognitive impairment were identified, including hypoglycemia unawareness, recent severe hypoglycemic events, and CGM variables. Longitudinal research is needed to determine if these risk factors are prospectively associated with cognitive change over time and if their modification alters outcomes.

85-LB

Digital Behavioral Counseling for Diabetes Risk Reduction in a Workforce

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The objective of the study was to evaluate program participation and risk factor reduction from a digitally delivered, intensive behavioral counseling program for a workforce at risk for obesity-related chronic disease. Eligible employees of a global corporation were offered a digital health program modeled after the Diabetes Prevention Program. Annual biometric and self-reported health assessments conducted on the workforce were used to examine changes in chronic disease risk factors (i.e., weight, fasting blood glucose) in program participants relative to a propensity-matched comparison group of non-participating employees. A total of 829 employees participated in the program; among them, 634 had annual biometric data available for analysis. A comparison group was matched on baseline demographics and chronic disease risk factors, resulting in a 2:1 match. In longitudinal analyses, the workforce on average was gaining an average of 3.5 pounds annually before program inception. Engagement in the program was positive; 83% of all enrollees completed the majority of the curriculum and 31% lost at least 5% of their starting weight. Compared with propensity-matched, non-participating peers, the program participants demonstrated greater reductions in body weight, improved fasting blood glucose and improved nutritional intake after a year. The digital health program was effective for engaging employees in health behavior change and reducing risk for type 2 diabetes. Digital options can facilitate widespread implementation and should be considered as part of a comprehensive strategy to reduce risk for obesity-related chronic conditions.

86-LB

Development and Feasibility of mHAT: A Smartphone App to Improve Awareness of Hypoglycemia

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Background: As part of an online psychobehavioral intervention to prevent severe hypoglycemia, we developed and piloted a smartphone "app", based on the diary feature of Blood Glucose Awareness Training (BGAT) designed to improve awareness of hypoglycemia. "mHAT" (mobile Hypo Awareness Training) guides users through 4 steps each time they check their blood glucose routinely: 1.) reflecting on external cues (insulin, food/drink, activity); 2.) identifying hypoglycemic symptoms; 3.) recording their estimated glucose level, and 4.) checking/recording their actual level.

Methods: In user acceptance testing, 6 adults with type 1 diabetes (T1D) worked through the app in the presence of a researcher, giving feedback on content, format, and ease-of-use. Following revisions, adults with T1D were recruited into a pilot study, to use the app for 3 weeks and complete a pre/post survey. A sub-sample was interviewed.

Results: 24 participants used mHAT: 15 women, mean (SD) age 42(15) years, T1D duration 17(13) years, 13 using an insulin pump, 7 had IAH. Of 576 datapoints, 26 (5%) showed ≥6 mmol/L discrepancy between estimated and actual glucose (13 under-, 13 overestimations). 84 (15%) of actual glucose levels were ≤4 mmol/L: 50 (60%) were estimated accurately, 16 as 4.1-5.9 mmol/L, 9 as 6.0-7.9 mmol/L, and 9 as ≥8mmol/L. 16 users completed the 3-week follow-up survey and 10 were interviewed. 14/16 reported the app as easy to use and 8/16 as helpful. Suggestions for improvement included: more detailed feedback and visualization of glucose data, more options on the cues list (e.g., additional hypo/hyperglycemia symptoms; sleep, exercise).

Conclusions: As an alternative to a paper diary, an app has significant benefits for the end user, but transferring content to a mobile platform was challenging. mHAT was feasible and acceptable to users, who gave positive feedback and constructive critique. This will inform the next version, which will be evaluated by people with established impaired awareness of hypoglycemia.

Supported By: Ian Potter Foundation

87-LB

Team-Based Care Improves A1c and Psychosocial Function in Patients with Diabetes

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Diabetes is a common and increasingly prevalent chronic disease that currently affects at least 29.1 million people in the U.S.A. Most patients are managed by primary care physicians and estimated annual cost attributable to diabetes management averages 245 billion dollars. Patients with diabetes are known to have a lower quality of life than individuals without diabetes. They also have a higher risk for depressive symptoms which may have an additional negative effect on their quality of life. Team-based care for chronic illnesses has been shown to improve health outcomes. In our institution, the Diabetes Specialty Center care model (DSC) was recently implemented to create increased access to endocrinologists, pharmacists, dieticians, behavioral health specialists and nutritionists to provide comprehensive care to patients with diabetes. After an initial in office visit with an endocrinologist, pharmacist, diabetes educator and behavioral health specialist, patients have short-term intensive contact for a period of 12 weeks with a minimum of weekly tele visits with a team member to address medication adjustments and provide educational and emotional support. Patients entering the program were assessed using the Diabetes Distress Scale (DDS), a measure of diabetes related emotional distress, before starting the program and at the end of 12 weeks. Mean A1c improved significantly from 9.2% to 7.05% at the end of the 12 weeks. Patients have also demonstrated significant improvement in distress: over half show improvement in their DDS score. This effective short-term approach may be a better use of limited resources leading to significant changes while cost-effective. To see if benefits are sustained over time, long-term follow-up is planned.

Supported By: Richard King Mellon Foundation

88-LB

Patient Commitment and Its Relationship to A1c and BMI

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Patients who actively participate in healthcare decisions report greater satisfaction, faster recovery from illness, and better quality of life. We examined the relationship between patient commitment and A1c and BMI in a military diabetes specialty clinic. The Diabetes Center of Excellence (DCOE) and Altarum Institute examined patient engagement with their healthcare and relationship to diabetes management. Adult Department of Defense beneficiary patients reported demographic information and completed the Altarum Consumer Engagement (ACE) measure. Next, clinical information was extracted from electronic medical records, which included retrospective A1c and BMI. Data were merged using a unique identifier. The sample included 273 participants; 58.2% male; mean age of 58.5. Participants were

For author disclosure information, see page LB107.

primarily white (74.8%) and African American (19.5%); nearly one-third were Hispanic. The Commitment subscale was significantly inversely related to A1c trends. Furthermore, when A1c was categorized as 1.) low < 7.0%; 2.) moderate=7.0% to 8.9%; and 3.) high ≥ 9.0%, there was a similar trend. Low Commitment patients were 18% more likely to have a high A1c than high Commitment patients. Over time, this increased from 18% to a sizeable 131%. Patients with high commitment were 16% more likely to keep their HbA1c under 7.0%; over time, this increased to 65%. About 3/4 of low Commitment patients and moderate Commitment patients were obese (76.1% and 76.8%, respectively). In contrast, 61.7% of high Commitment patients were obese, which was a significant difference, z=2.05, p=.04. Low Commitment patients were 2 ½ times as likely to say they were in poor or fair health (43.1%) compared to high Commitment (16.7%), z=3.2, p=.001. Increasing patient commitment to management of diabetes has potential to improve A1c over time. Thus, developing strategies to empower patients to take a more active role in their healthcare may improve clinical measures.

89-LB

KALMOD: Novel Holistic Clinical Tool to Improve Consultations and Outcomes

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Background: KALMOD, based on the Kaleidoscope Model of Care, is a clinical tool based on a decision-tree questionnaire to enhance patient-HCP consultations by identifying patient priorities. Supporting holistic, person-centred healthcare for adults with T1D KALMOD fosters a collaborative approach between the person with T1D and their HCP. It identifies and articulates barriers to optimal diabetes control thus helping HCPs to better understand the individual needs of their patients in order to match the right patient to the right therapy at the right time. The purpose is to enhance the healthcare experience and improve clinical and psychosocial outcomes.

Methods: Mixed-methods pilot study utilising data from focus groups and interviews and quantitative survey data, to determine the usability, acceptability and relevance of the novel KALMOD tool for adults with type 1 diabetes. Qualitative data were analysed thematically with descriptive analyses of quantitative data.

Results: Three focus groups (n=12) and 6 interviews were conducted with adults with T1D completing the tool and providing feedback, with a further 24 participants completing the tool and online survey. Key positive themes were: relevance, personalised feedback and simplicity of the tool. The tool was revised in line with recommendations regarding wording of some questions to aid clarity and remove ambiguity. Survey data showed all participants thought that the tool was intuitive, easy to use 100% (n=24) and relevant 95.8% (n=23). It met expectations 91.6% (n=22), was well-balanced 87.5% (n=21), would improve their consultation with their healthcare team 66% (n=16) and would help the healthcare team better understand individuals' needs 58.3% (n=14).

Conclusion/Discussion: The KALMOD tool is acceptable, relevant and tailored to individual needs of adults with T1D in this small pilot study. Further minor modifications are underway to refine the tool further prior to validation in a multi-center RCT.

Supported By: Roche Diabetes Care

90-LB

U.S. Media Portrayals of Type 1 and Type 2 Diabetes: A Celebrity Effect of Mary Tyler Moore?

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The role of mass media in diabetes has attracted little research attention despite the powerful influence of media message framing on health policy, funding, public perceptions and practice of care. Health issues can receive substantial publicity when a celebrity is diagnosed with a medical condition, undergoes a procedure or dies. This study aimed to characterize how U.S. media portrays diabetes, specifically the definition and framing of messages about T1D and T2D. A secondary objective was to determine whether the death during the study period of Mary Tyler Moore, who had T1D and was a strong advocate, influenced media coverage. Articles in major U.S. newspapers were systematically identified on the Factiva database via date-limited keyword searches using terms diabetes, type 1 diabetes and type 2 diabetes within headlines and lead paragraphs. Overall data analysis was conducted on articles sourced from a 12-month time frame. A subset of search results were compared for a 6-week period before and after January 25, 2017. Both quantitative (frequency and type of article references, specific use of terminology, context) and qualitative variables (themes of causal attributions, seriousness, personal responsibility and psychosocial issues) were included in the analysis. Inter-rater reliability was assessed using Cohen's Kappa. Over 75% of the articles did not differentiate between T1D and T2D. T1D received little specific coverage (average 4% of the total), framing was focused on technology and no increase in frequency or change in framing was observed after Mary Tyler Moore's death. Quantity of media coverage overall was unaffected during National Diabetes Month. The frames of personal responsibility and lifestyle change dominated articles about T2D. Media coverage presents confusing messages about diabetes and differences between T1D and T2D. Media advocacy could usefully reframe diabetes messages to improve public understanding and potentially reduce adverse effects such as social stigma.

91-LB

WITHDRAWN

92-LB

Factors Influencing Health Behaviours and Preferences for a Lifestyle Intervention after Gestational Diabetes

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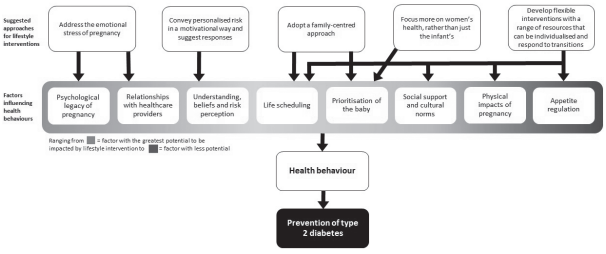
Women diagnosed with GDM are at high risk of developing T2DM. This could be prevented or delayed through lifestyle intervention. We explored factors influencing women's health behaviour and preferences for lifestyle intervention. We analysed data using Framework Analysis from 6 focus groups (n=35 women) and semi-structured interviews with 15 women with prior GDM from a diverse UK population. We identified 8 themes relating to factors influencing health behaviour: psychological legacy of pregnancy; relationships with healthcare professionals; physical impacts of pregnancy; social support and cultural norms; life scheduling; understanding, beliefs and risk perception; appetite regulation; and prioritisation of the baby. Overall, participants wanted increased postpartum follow-up with specific individualised lifestyle advice and support. Views on the intervention delivery and content differed, emphasising the need to tailor interventions and provide choice and control. Suggested approaches for interventions are: address the emotional stress of pregnancy; focus more on women's health rather than just the infant's; develop flexible interventions with a range of resources that can be individualised and respond to the transitions of pregnancy and motherhood; adopt a family centred approach; and convey personalised risk in a motivational way, with suggested responses (Figure).

Figure. Suggested Approaches for Lifestyle Interventions to Help Prevent Type 2 Diabetes.



Supported By: National Institute for Health Research, UK

93-LB

Does Time-in-Range Matter? Perspectives from People with Diabetes on the Success of Current Therapies and Drivers of Improved Outcomes

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Objective: To evaluate patients' perspectives on the success of current diabetes therapies, factors having the greatest impact on their daily lives, and potential drivers of patient-reported improvement in mindset and diabetes management.

For author disclosure information, see page LB107.

Research Design and Methods: In August 2016, 4,746 members of the dQandA Patient Panel were invited to participate in a 25-question online survey, which received responses from 3,461 (72.9%) people with type 1 and type 2 diabetes (n=1,026 and 2,435, respectively).

Results: In terms of outcomes for assessing diabetes therapies, "time spent in the ideal blood glucose range" was rated as having the biggest impact on daily life, higher than the impact of HbA1c for type 1s (T1), type 2s on insulin (T2I), and type 2s not on insulin (T2NI). Only 23% of T1, 25% of T2I, and 38% of T2NI said that their current therapies are "very successful" at delivering in-range numbers (70-180 mg/dl), with the lowest scores for post-meal glucose values <180 mg/dl. Emotional well-being was strikingly low across all three groups, with a minority rating therapies as "very successful" on this outcome (22-34%). Success on weight maintenance scored the lowest in T2 respondents of any question in the survey. A substantial proportion of respondents in each group (26% T1, 35% T2I, 50% T2NI) reported that a change in "diet and exercise" would have the biggest positive impact on diabetes management. For 54% of T1 and 36% of T2I respondents, "Your blood glucose numbers are on-target all day" ranked as the highest driver of a positive mindset.

Conclusions: Our results suggest that time-in-range is a crucial outcome to people with diabetes, and current therapies have significant room to improve on this metric. Combined with low overall success on emotional well-being, diet and exercise, and weight maintenance, these data support the need for therapies that improve outcomes beyond HbA1c alone.

Supported By: Eli Lilly and Company; Dexcom, Inc.

94-LB

Pathways between Food Insecurity and Glycemic Control in Individuals with Type 2 Diabetes

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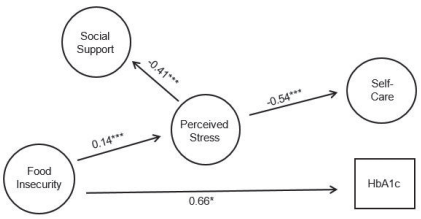
Background: Food insecurity has been shown to influence self-care and glycemic control in patients with type 2 diabetes, however, little has been done to understand pathways through which this relationship exists to develop targeted interventions.

Methods: 615 adults with type 2 diabetes completed validated questionnaires after recruitment from two primary care clinics. Structured equation modeling was used to investigate mechanisms through which food insecurity influences diabetes self-care behaviors and glycemic control.

Results: The final model (see Figure) showed that higher food insecurity was directly significantly related to increased stress (r= 0.14, p<0.001) and increased HbA1c (r= 0.66, p=0.03). Higher stress was significantly related to poorer self-care (r= -0.54, p<0.001), and lower social support (r= -0.41, p<0.001). There was no significant direct association between food insecurity and self-care, or perceived stress and glycemic control.

Conclusion: Stress serves as a pathway through which food insecurity influences self-care, suggesting efforts to address stress may influence the ability to perform self-care behaviors. The direct effect between food insecurity and glycemic control, suggests interventions that provide healthy food choices for individuals with diabetes who are food insecure is also needed to support healthy diet necessary for good glycemic control.

Figure. Final Model of Influence of Food Insecurity, Perceived Stress, and Social Support on Self-Care and Glycemic Control.



Note: Coefficients are standardized path coefficients.
Overall Model Fit: Chi^2 (158)=301.97, p<0.001; R^2=0.98, RMSEA=0.038, CFI=0.977, TFI=0.972) *p<0.05, **p<0.01, ***p<0.001

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95-LB

Behaviors to Avoid Hypoglycemia in Adults with Type 2 Diabetes

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Few studies have examined the specific behaviors related to avoiding hypoglycemia in T2D. We assessed the frequency and type of hypoglycemia-avoiding behaviors of patients with T2D treated with oral medications and/or insulin, and examined the relations between these behaviors and illness factors. T2D adults (N=120, M (SD) age=56 (9.7); 64% female; 62% black) were recruited from primary care clinics in the Bronx, NYC. Baseline assessments included A1c, self-monitoring of blood glucose (SMBG), and self-reports for hypoglycemia-avoiding behaviors and diabetes distress. Descriptive analyses were used to characterize the frequency of reported hypoglycemia-avoiding behaviors. Bivariate correlation with an applied 10,000 bootstrap and Chi-square evaluated the relations between commonly reported behaviors and illness factors. Average (M(SD)) A1c was 7.9(1.9), 6.7% of participants reported significant hypoglycemia in the past three months, 41% were on insulin, and average SMBG frequency over the past week was 6.1(7.2). Eighty-five percent endorsed hypoglycemia-avoiding behaviors, which were associated with worse A1c (p=.005) and greater diabetes distress (p<.001). The most frequently endorsed behaviors were eating large snacks (56%), keeping blood sugar above 150 mg/dL (52%), limiting physical activity (45%), and staying home (42%). In contrast to prior studies, relatively few endorsed limiting their driving (22%). Insulin users were more likely to report keeping blood sugar above 150 mg/dL (p=.007). Limiting physical activity and staying home were associated with greater emotional distress (r=0.30, p=.002; r=.42, p<.001, respectively) but only restriction of physical activity was associated with higher A1c (r=.26, p=.007). SMBG frequency was not associated with any reported behaviors. Consistent with previous reports in other patient populations, behaviors to avoid hypoglycemia were common in T2D. Specific hypoglycemia-avoiding behaviors should be more routinely assessed in these patients.

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96-LB

Evaluation of the Pathway between Adverse Childhood Experiences and Type 2 Diabetes in Adulthood

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Introduction: Adverse Childhood Experiences (ACE) are stressful events that occur throughout the developmental stages of a child's life that can have traumatic effects and impact on health and behavior in adulthood. ACEs include three domains of abuse (psychological, physical, and sexual), and household dysfunction. Greater understanding of the relationship between ACEs and type 2 diabetes will help guide the development of interventions to minimize the detrimental impact of ACEs on the development of type 2 diabetes in adulthood.

Methods: Behavioral Risk Factor Surveillance System (BRFSS) data for 2011 was used to examine the relationship between ACEs and diabetes in adulthood. 48,526 participants completed the ACE module in 2011. Multiple logistic models using complex sampling procedures taking into account stratification, clustering, and sampling weight were used to examine the relationship between increasing ACE scores (categories for scores of 0-8) and the odds of diabetes in adulthood. Additional logistic models examined the relationship between the eight individual categories of ACEs (sexual abuse, physical abuse, verbal abuse, mental illness, substance abuse, incarceration, separation/divorce, and violence) and the odds of diabetes in adulthood.

Results: Odds of diabetes increased significantly with increasing ACE scores up to a score of 4. Of the eight individual ACE categories and diabetes, experiencing sexual abuse during childhood showed the strongest effect on odds of diabetes (OR 1.81, CI 1.402; 2.330), followed by the physical abuse component (OR 1.26, although only trend for statistical significance).

Conclusion: For each increase in ACE score, the odds of diabetes increased, up to a score of four. The sexual abuse component of ACEs had the strongest positive association with diabetes suggesting that sexual abuse is an important category linking the pathway between ACEs and diabetes and an important focus for future interventions.

Supported By: National Institutes of Health

97-LB

Continuous Glucose Monitoring-Related Behaviors in the DIaMonD Randomized Controlled Trial

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In the 6-month DIaMonD study, 176 people using multiple daily insulin injections (99 with T1D, 77 with T2D, mean baseline A1C 8.6±0.6%, mean age 52±14 Y) were introduced to continuous glucose monitoring (CGM). CGM adoption was associated with favorable glycemic changes and an overall ~30% decrease in blood glucose monitoring frequency. We studied the frequency of CGM screen views (SV) in a subset of 117 subjects with adequate SV data, and the relationship of SV frequency to changes in hemoglobin A1c

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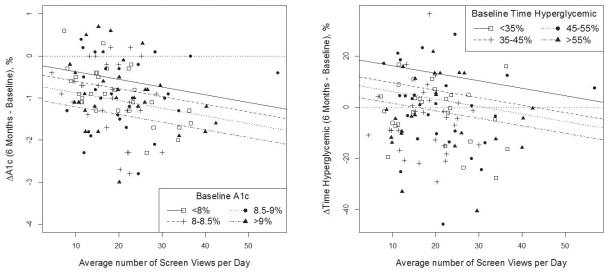
(ΔA1c), changes in time in range (ΔTIR) (70-180 mg/dL), changes in time low (ΔT_{low}) (<70 mg/dL), and changes in time high (ΔT_{hi}) (>180 mg/dL). Subjects with T1D (n=36) performed 38 SV/d at wk 1, 32/d at wks 2-4, and 22/d at mo 6. Subjects with T2D (n=23) performed 37/d at wk 1, 30/d at wks 2-4, and 18/d at mo 6 (between-times p<0.001; between-groups p >0.05). The Figure shows correlations of SV frequency with ΔA1c (left), where each increase of 10 SV/d correlated with a -0.2% ΔA1c (p=0.02, 95% CI, -0.04 to -0.4%) and with ΔT_{hi} (right), where each increase of 10 SV/d correlated with a -2.9% ΔT_{hi} (p=0.05, 95% CI, -0.03 to -5.8%). Increasing SV also correlated with a non-significant decrease in T_{low} (p=0.61) and a non-significant increase in TIR (p=0.06). CGM data were checked frequently throughout the study and enable real-time adjustments which contribute to lower A1c and less time in hyperglycemia in both T1D and T2D.

Figure.



98-LB

Mental Health and Behavioral Screening in Children and Adolescents with Type 1 Diabetes

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Objectives: To describe the findings of mental health and behavioral screening performed as part of routine pediatric type 1 diabetes care.

Methods: A retrospective chart review focused on children aged 11 to 17 with type 1 diabetes cared for in a multidisciplinary pediatric endocrinology practice. The Strengths and Difficulties Questionnaire (SDQ) self-reported version was completed by patients as a behavioral and mental health screening tool. Scores from the 5 domains of the SDQ and the impact supplement were collected and compared to age-matched normative data from parent-reported SDQ.

Results: SDQ results were collected from 128 patients with type 1 diabetes. A significantly higher proportion of the group aged 11 to 14 with type 1 diabetes had an abnormal score in the impact category when compared with normative data (28.4% vs. 15.1% respectively, p=0.002). For patients aged 15 to 17 years, there was a significantly higher proportion of type 1 diabetes patients with abnormal scores across multiple domains, including total difficulties (20.4% vs. 10.9%, p=0.02), emotional problems (23.7% vs. 14.2%, p=0.04), peer problems (38.9% vs. 19.8%, p=0.0002), and impact score (25.4% vs. 13.7%, p=0.009).

Conclusions: This study suggests that patients with type 1 diabetes, particularly older teenagers, have a higher burden of behavioral issues and emotional symptoms when compared to their peers without diabetes. Older teens scored higher in domains suggesting risk for psychologic disorders including anxiety and depression, in addition to difficulty interacting appropriately with peers. Furthermore, the significant elevation of the impact score indicates that these patients perceive that there has been some impairment of their daily function. These findings highlight the importance of routine behavioral and mental health screening in pediatric patients with diabetes, in addition to underscoring the need for a multidisciplinary management team including social work and psychology.

99-LB

Feasibility, Acceptability, and Initial Efficacy of a Web-Based Physical Activity Intervention for Latina Adolescents

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Background: Ethnic minority girls report the lowest levels of physical activity (PA) of all demographic subgroups. Relatedly, rates of overweight/obesity are nearly 50% higher for adolescent Latinas than for non-Latino white girls, and over half of Latina girls are projected develop type 2 diabetes in their lifetime. As lifetime health habits are developed in adolescence, interventions to increase PA in Latina girls are urgently needed to reduce disparities.

Objectives: To assess feasibility, acceptability, and preliminary efficacy of a web-based PA intervention for Latina adolescents through a single-arm 12-week demonstration trial.

Methods: Latina girls (age 12-19) engaged in a one-on-one goal setting session, then accessed a personalized PA website with tools for goal setting and logging activity, a message board, lists of free places to be active, and individually tailored PA information based on responses monthly questionnaires. PA was measured via 7-Day Physical Activity Recall Interview (7-Day PAR) and accelerometers at baseline and 12 weeks, when they completed a consumer satisfaction questionnaire.

Results: 20 girls (mean age=15.1) attended the initial session, of which 18 returned at 12 weeks. As measured by the 7-Day PAR, PA at baseline was 24.4 (SD=26.9) minutes/week. At 12 weeks, mean PA was 78.9 (44.3) minutes/week, with a mean increase of 60.7 (42.6) minutes/week. Accelerometer data will be presented. The goal setting tool was ranked as the most useful feature of the website. The majority (72%) said they were satisfied with the program, and 72% would recommend it to others. The most common complaint was having to log in to use the website. The most common suggestion was to incorporate texting and/or an app.

Conclusions: The intervention showed good initial efficacy and retention was high. While acceptability was generally high, shifting the intervention to a smartphone app may be more appealing and would bypass the inconvenience of logging in.

Supported By: National Institutes of Health (R03NR014329)

100-LB

The Relationship between Program Engagement and Weight Loss in the First Year of a Digital Diabetes Prevention Program Translation

S. CAMERON SEPAH, LUOHUA JIANG, ROBERT J. ELLIS, KELLY MCDERMOTT, ANNE L. PETERS, *San Francisco, CA, Irvine, CA, San Raphael, CA, Los Angeles, CA*

Objective: Translations of the Diabetes Prevention Program (DPP) have proliferated in recent years, with increasing expansion to digital formats. Although these digital DPPs have consistently shown favorable clinical outcomes, investigations of how participant engagement predicts those outcomes have largely focused on the simple correlation of in-person attendance or online lesson completion. The present study took a more statistically detailed approach to this question.

Research Design and Methods: In a single-arm, non-randomized trial, 220 patients with prediabetes were enrolled. During the first year, participant engagement with a suite of online resources (curriculum, tracking tools, and interaction with a human health coach and peer support groups) was quantified. Relationships among these engagement metrics were examined using factor analysis, and relationships with weight loss at 16 weeks and 52 weeks (obtained via a wirelessly connected scale) were explored using regression analysis.

Results: Metrics of participant engagement were significantly correlated with 16-week and 52-week weight loss. Factor analysis of engagement metrics revealed two underlying dimensions, one comprising lessons and tracking consistency, and the other comprising website logins and group participation. When these two factors were used to predict weight changes at 16-week and 52-week weight loss, only the logins and group participation factor remained a statistically significant predictor of weight loss.

Conclusions: This study adds to the growing DPP translation literature by highlighting the need to clarify which aspects of program engagement predict weight loss—and which do not. This question is particularly timely given the exponential growth of digital DPPs, accelerated by their anticipated reimbursability via the Medicare Diabetes Prevention Act.

101-LB

Gender Invariance in the Relationship between Social Support and Glycemic Control

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Background: The aims of this study were to investigate which components of social support (SS) influenced glycemic control and if the relationship differed between men and women with type 2 diabetes (T2DM).

Methods: 615 adults were recruited from two clinics in the southeastern United States. Components of SS included emotional/informational, tangible, affectionate, and positive social interaction. Structural equation modeling (SEM) was used to understand pathways between SS and glycemic control based on a theoretical model.

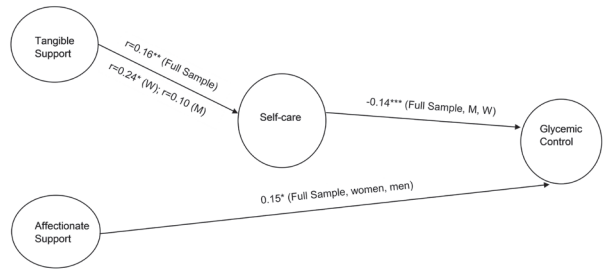
Results: In the model for men and women, tangible support was significantly associated with self-care (r=0.16; p=0.046) and affectionate support was marginally associated with glycemic control (r=0.15; p=0.08). Using SEM to test gender invariance, there was no statistically significant difference in the meaning of SS between men and women. Unique invariance

For author disclosure information, see page LB107.

in responses occurred, including a stronger relationship between tangible support and self-care for women (r=0.24; p=0.061).

Conclusions: Of the four components of SS, tangible and affectionate support had the strongest influence on glycemic control. While affectionate support will improve glycemic control in both men and women, tangible support will improve self-care management, particularly among women.

Figure. SEM for SS and Glycemic Control and Self-Care.



Statistically significant differences at *p<0.08, **p<0.05, ***p≤0.01. Abbreviations: W=women; M=men; FS=full sample

Supported By: National Institutes of Health

102-LB

Behavioral Strategies Designed to Lower A1c in Those with Type 2 Diabetes May Also Lower Risk of Coronary Heart Disease (CHD)

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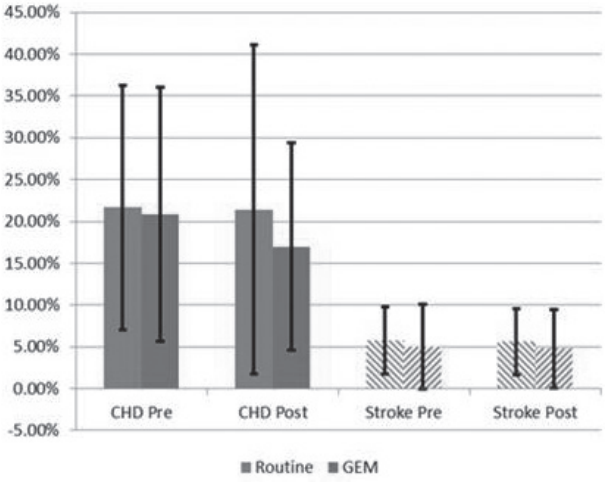
Diabetes and CHD have commonalities: lack of diabetes control and longer duration of diabetes increase the risk of future CHD, and behavioral interventions to lower A1c and risk of CHD are similar. The UKPDS-OM21 predicts the probability that those with type 2 diabetes will have a CHD or stroke event in the next 10 years. It uses 5 fixed (age, sex, diabetes duration, ethnicity, presence of atrial fibrillation) and 5 modifiable risk factors (smoking, A1c, SBP, total cholesterol and HDL), the latter being potentially impacted by a lifestyle program. We applied the UKPDS-OM2 risk engine to data from a previously published lifestyle RCT (GEM)2 targeting post prandial glucose (PPG) that significantly lowered A1c.37 adults (mean age 56 y., 54% female, mean A1c 8.4) were randomized to Routine Care or Routine Care+GEM. Pre-post risk of CHD went from 21.6% to 21.4% for Routine Care and 20.9% to 17.0% for GEM. This was a significantly greater reduction in risk for GEM (p<.05, one-tailed). In contrast, risk for stroke or fatal stroke was lower and not impacted by GEM, going from 5.8% to 5.6% for Routine Care and 5.0% to 4.8% for GEM. These data suggest a lifestyle intervention to lower PPG may specifically reduce risk of CHD but not stroke.

Figure.



Supported By: LifeScan, Inc.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—GLUCOSE MONITORING AND SENSING

103-LB

Serum Fructosamine: A Simple and Inexpensive Test for Assessing Preoperative Glycemic Control

NOAM SHOHAT, MAJD TARABICHI, SERGE JABBOUR, JAVAD PARVIZI, *Philadelphia, PA*

The proper metric for assessment of preoperative glycemic control remains unclear. Serum fructosamine reflects the average glycemic control in a shorter time period compared to glycated hemoglobin (HbA1c).

Our aim was to examine its role in predicting complications following total joint arthroplasty (TJA). During 2012 we prospectively screened all patients undergoing TJA preoperatively using serum HbA1c, fructosamine and blood glucose levels. Based on the recommendations of the American Diabetes Association, 7% was chosen as the cut off for HbA1c being indicative of poor glycemic control. This threshold correlated to a fructosamine level of 292umol/L. All patients were followed and TJA complications evaluated. Patients with fructosamine levels≥292umol/L were compared with those with fructosamine levels <292umol/L. Complications that were significant in the univariate analysis were evaluated in a multiple logistic regression model. A total of 829 patients undergoing primary TJA were included in the present study. There were 119 patients (14.3%) with a history of diabetes and 308 patients (37.1%) with HbA1c levels in the prediabetic range. Overall, 51 patients had fructosamine levels≥292umol/L. Twenty patients (39.2%) had a fructosamine level≥292umol/L but did not have HbA1c level ≥7%. Patients with fructosamine levels≥292umol/L had a significantly higher risk for deep infection (p=0.02), readmission (p= 0.04) and reoperation (p=0.03). PJI and reoperation rates remained significant after adjusting for age, sex, BMI and comorbidities (p=0.02, 0.04). Compared to fructosamine, HbA1c levels ≥7% failed to show any significant correlation with adverse outcomes. Serum fructosamine is a simple test that appears to be a good predictor of complications in patients with known diabetes and those with unrecognized diabetes or hyperglycemia. Our findings suggest that fructosamine can serve as an alternative to HbA1c in the setting of preoperative glycemic assessment.

104-LB

Development of FAD-Dependent Glucose Dehydrogenase for CGM Sensor

YOSUKE MASAKARI, YASUKO ARAKI, RYOICHI SAKAUE, *Noda, Japan*

Continuous glucose monitoring (CGM) is an important system for diagnosing and managing diabetes. Currently, the strips of all commercial CGM devices are based on glucose oxidase (GOD), but most systems require calibration generally every 12 h during the sensor's lifetime. The one of the reason is that loss of GOD activity occurs rapidly upon incubation at ambient temperature (30-40 °C). In this study, we tried to introduce some mutations to Mucor-derived FAD-dependent glucose dehydrogenase (Mp-FADGDH) having accurate substrate specificity and obtain new excellent enzyme in long-term stability. The thermostability of Mp-FADGDH was improved by random mutagenesis approaches. We combined some beneficial mutations found from random mutagenesis screening and constructed highly thermostable Mp-FADGDH (Mp-FADGDH-MT1). Solutions of 1 mg/ml Mp-FADGDH-MT1 and commercial Aspergillus-derived GODs (purchased from Sigma-Aldrich, Toyobo and Wako) in PBS buffer were incubated at 40 °C. Mp-FADGDH-MT1 retained 80% of its initial activity after incubation at 40 °C for a week, however, the activity of GODs (Sigma-Aldrich, Toyobo and Wako) rapidly decreased to 35%, 30% and 23% of its initial activity, respectively. Also, Mp-FADGDH-MT1 has high substrate specificity, and the relative activity for maltose and xylose compared with glucose was under 1%. Therefore, we expect that Mp-FADGDH-MT1 is suitable for CGM sensor application which does not require finger stick calibrations.

105-LB

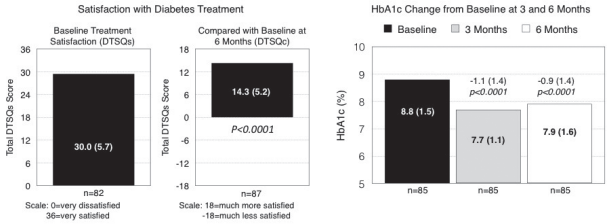
Use of the Accu-Chek Connect System Is Associated with Increased Treatment Satisfaction and Improved Glycemic Control in Individuals with Insulin-Treated Diabetes

PABLO MORA, ANN BUSKIRK, MAUREEN LYDEN, CHRISTOPHER PARKIN, LENA BORSA, BETTINA PETERSEN, KERSTIN REBRIN, *Plano, TX, Indianapolis, IN, Tampa, FL, Boulder City, NV, Mannheim, Germany*

The ability to automatically transfer data to clinicians and receive timely guidance in therapy adjustments via remote consults can positively impact patients' perceptions about quality of care, which is positively associated with glycemic control. The Accu-Chek Connect system consists of a blood glucose meter, Smartphone app and online web portal. The meter connects

wirelessly to the user's Smartphone app, which provides multiple functions to facilitate diabetes management. Glucose test results and other relevant data are automatically transmitted to secure clinician and personal web portals. This 6-month, prospective, multi-center study assessed the impact of using the system on treatment satisfaction and glycemic control among 87 adults with insulin-treated diabetes (multiple daily insulin injections [MDI] and basal only). The Diabetes Treatment Satisfaction Questionnaire (DTSQs) was administered at baseline and 3 months, and DTSQc at 6 months. Improvements in DTSQ scores and HbA1c were observed at 6 months regardless of treatment modality. (Figure 1) The availability to automatically share glucose data and other diabetes information with clinicians via use of the Accu-Chek Connect system is associated with increased treatment satisfaction and improved glycemic control among individuals with insulin-treated diabetes.

Figure 1. Changes in Diabetes Treatment Satisfaction and HbA1c.



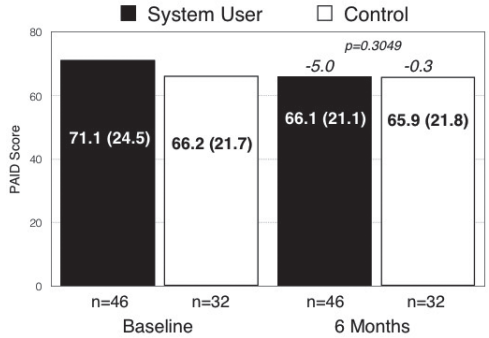
106-LB

Use of the Accu-Chek Connect System May Reduce Diabetes-Related Distress in Parents of Type 1 Diabetes Children/Adolescents

GNANAGURUDASAN PRAKASAM, CHRISTEN REES, MAUREEN LYDEN, CHRISTOPHER PARKIN, LENA BORSA, PHIL FLEMING, *Sacramento, CA, Indianapolis, IN, Tampa, FL, Boulder City, NV*

The daily burden of managing children's/adolescents' type 1 diabetes (T1D) can lead to distress and diminished quality of life among parents. Parental stress is often driven by fear of hypoglycemia, which can lead to poor glycemic control. The Accu-Chek Connect system may address this issue. The system consists of a blood glucose meter, Smartphone app and online data management web portal. The meter connects wirelessly to the user's app, which provides multiple diabetes management functions. Glucose test results and other data are automatically transmitted to secure clinician web portals and to parents via text messages and personal web portals. This prospective, interventional, multi-center, post-market, pilot study randomized 78 parents of T1D children/adolescents to system use (N=46) or control (N=32). The study used the Problems Areas in Diabetes (PAID) scale to assess the impact of system use on diabetes-related distress at 3 and 6 months. A strong trend toward improvement from baseline PAID scores was seen at 6 months among system users but not control group parents. (Figure 1) The majority (88.6%) of system users self-reported that they were less worried about hypoglycemia. The availability of near real-time glucose data and related information may reduce diabetes-related distress among parents of T1D children/adolescents.

Figure 1. Change in Diabetes-Related Distress.



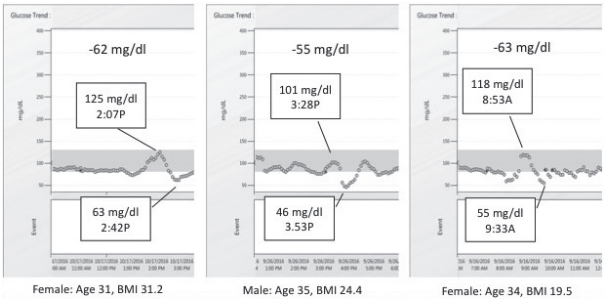
107-LB

Use of CGM in Real-World Clinical Practice: Beyond Diabetes

KAI CHIN, SHALIN PANDYA, QUANG NGUYEN, JEFFREY TRUESDELL, DANIEL PONTORIERO, CHRISTOPHER PARKIN, *Las Vegas, NV, San Diego, CA, Boulder City, NV*

Reactive hypoglycemia (RH) describes a condition characterized by recurrent episodes of symptomatic hypoglycemia occurring within 4 hour after a high carbohydrate meal. Although diagnosis is often based on mixed meal evaluation, a high percentage of symptomatic patients test negative when using this approach. We assessed the diagnostic value of short-term use (7 days) of continuous glucose monitoring (CGM) in 3 patients (1 male, 2 female) with suspected reactive hypoglycemia who had no diagnosis of diabetes. Median age was 33 (31,35) years; median BMI 25.2 kg/m2 (19.5, 31.7). In all 3 patients, a significant decrease in glucose was observed in response to carbohydrate intake. These decreases occurred within approximately 30-40 minutes following peak post prandial glucose. (Figure 1) Magnitude and timing of RH were not associated with gender or BMI. RH can result in debilitating symptoms similar to those experienced by patients with diabetes. Diagnosis of RM may be missed using mixed meal testing. Utilization of CGM may provide a practical means for confirming reactive hypoglycemia in nondiabetic individuals, facilitating early intervention with diet modification.

Figure 1. Magnitude and Timing of Reactive Hypoglycemia.



108-LB

Sharing the Outcomes and User Experience from India in the First 750 Type 2 Diabetes Patients with the New Libre Pro 14-Day Glucose Sensor

JOTHYDEV KESAVADEV, SR., LAKSHMY RAMACHANDRAN, ARUN SHANKAR, SR., ASHWIN DAVID, GOPIKA KRISHNAN, SHEEJA SRINIVAS, ANNIE AJAI, GEETHU SANAL, SUNITHA JOTHYDEV, *Trivandrum, India, Kochi, India*

Aim: FreeStyle Libre Pro (FSLP), is the first ever retrospective CGM with factory calibrated sensor. Clinical outcomes of T2DM patients deployed with FSLP were analysed and experiences evaluated.

Methods: Clinical outcomes (n=425) were compared. Experiences recounted (n=750) in terms of user friendliness, acceptability and sensor failure were evaluated.

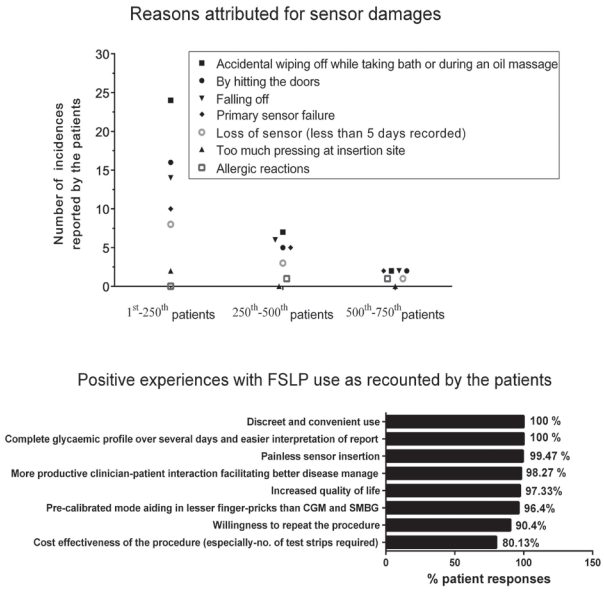
Results: Significant clinical improvements were noted in FSLP group (Table 1). Reasons for sensor failures were identified. Majority recounted a positive experience with FSLP (Figure 1).

Conclusions: FSLP led to clinical improvements and was widely appreciated. These benefits come at the cost of extra time and efforts spent in analyzing, interpreting and translating the findings into therapeutic and behavioural modifications.

Table 1. Improvements in the Clinical Profile of T2DM Patients (n=425) at 6 Months.

Clinical Parameter	**FSLP group** (age 55.06 ± 13.48y; 70.59% male; T2DM duration 13.89 ± 8.31y; 38.11% on OHAs; 61.89% on insulin+OHAs) **Baseline change at 6 months, p value** (Baseline vs. 6 months)	**Control group** (age 56.42 ± 10.08y; 75.41% male; T2DM duration 12.96 ± 7.84y; 39.71% on OHAs; 60.29% on insulin+OHAs) **Baseline change at 6 months, p value** (Baseline vs. 6 months)
HbA1c%	*-0.37, <0.0001*	-0.11, 0.074
FBS (mg/dL)	*-13.76, <0.0001*	-2.99, 0.1682
PPBS (mg/dL)	-3.2, 0.1209	*+14.87, 0.0361*
BMI (kg/m²)	*-0.2, 0.0325*	-0.14, 0.3729
WC (cm)	-0.02, 0.9267	-0.17, 0.6514
TDD (U)	-0.22, 0.5353	*+1.51, 0.0202*

Figure 1.



109-LB

The Economic Impact of Adopting Professional Continuous Glucose Monitoring with the FreeStyle Libre Pro™ System

SHENGSHENG YU, *Alameda, CA*

Professional continuous glucose monitoring (PCGM) reveals glucose patterns and trends that may not be apparent from HbA_{1c} or self-monitoring of blood glucose. Previous studies suggested PCGM reduces HbA_{1c} and hypoglycemia in insulin users through more informed clinical decision-making. However, high equipment costs and workflow challenges of existing technology (ET), such as Medtronic iPro®2 and Dexcom G4 Platinum, have prevented wide adoption. The FreeStyle Libre Pro™ system (the SYSTEM) has been designed to overcome these barriers. Compared with ET, it is simpler to use, requires little patient involvement with fully disposable factory calibrated sensors, monitors multiple patients with a single reader, and captures up to a 14-day glucose profile.

This study aims to assess the costs associated with adopting PCGM using the SYSTEM from an integrated delivery network (IDN) perspective.

The equipment costs were based on the prices listed on the most recent physician order forms. Eight interviews were conducted at eight U.S. endocrinology offices to assess the clinical workflow using either the SYSTEM or ET. Based on the published literature, we estimated the medical cost savings associated with reduced HbA_{1c} and hypoglycemia associated with PCGM use. All costs are in 2016 USD.

The estimated yearly equipment cost of ET (excluding sensor cost) is $1,170. This can instead cover 1 reader and 18 PCGM procedures using the SYSTEM. The improved workflow may reduce estimated staff cost per procedure from $30 for ET to $6.67 for the SYSTEM. After PCGM, patients may experience a 0.4% point HbA_{1c} reduction and 43% hypoglycemia event reduction, resulting in estimated cost savings of $56.42 and $24.73 per patient-year, respectively. With a $60 sensor cost, the SYSTEM offers a potential cost saving solution for IDNs.

In conclusion, with lower equipment and staff costs, the SYSTEM may facilitate wider adoption of PCGM, improved diabetes management, and notable cost savings.

110-LB

FreeStyle Libre Use for Self-Management of Diabetes in Children and Adolescents

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The impact of using the FreeStyle Libre™ Flash Glucose Monitoring System has been reported in adults with diabetes. This study aimed to evaluate the use of FreeStyle Libre as a replacement for self-monitoring of blood glucose (SMBG) in young people (4-17 years) with type 1 diabetes (T1D).

Patients (n=76, 58% CSII users, 46% males) enrolled in a 10 week single arm European study (UK, Ireland and Germany) underwent 2 weeks baseline masked (blinded) wear, followed by 8 weeks open use according to labeling. The primary endpoint was non-inferiority of glycemic control assessed using time in range.

Patients were aged 10.3±4.0 years (mean±SD) with baseline HbA1c 7.9±1.0% (62.9±11.1 mmol/mol), T1D duration 5.4±3.7 years and self-reported SMBG tests 7.3±2.7/day.

Time in range (70-180 mg/dL) significantly improved vs. baseline by 1.0±2.8 hours/day (mean±SD), p=0.0056. HbA1c significantly improved vs. baseline, -0.4±0.6%, p<0.0001.

Time in hyperglycemia (>180 mg/dL) significantly reduced vs. baseline by -1.2±3.3 hours/day, p=0.0038, while no statistically significant changes were observed for time in hypoglycemia (time <70 mg/dL, baseline, 1.1±1.2 hours/day).

Total daily insulin dose increased by 1.4±3.5 units (p=0.0010).

Scan frequency of FreeStyle Libre was on average 12.9 times daily, whereas SMBG tests dropped from a median of 8.0 (baseline) to 1.0/day during open use.

Diabetes Treatment Satisfaction Questionnaire showed increased overall treatment satisfaction for parents (n=70), 21.7±6.6 (mean change score±SD), p<0.0001 and teens (13+years) (n=23), 18.7±5.6, p<0.0001.

Occurrences of mild or moderate sensor insertion site symptoms were as expected with device use (96 from 42 patients). Three device-related adverse events (AEs), all mild (dry collection, dry flaky skin and redness) were reported by 3 patients. There were no device-related serious AEs.

Use of FreeStyle Libre by children and adolescents with T1D improved glycemic control, reduced HbA1c and improved treatment satisfaction.

Supported By: Abbott Diabetes Care

111-LB

A New Method to Evaluate Analytic Performance of CGM Devices

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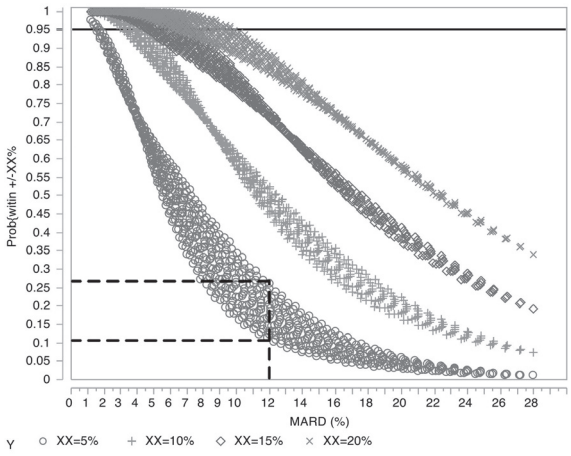
The mean absolute relative difference (MARD) between CGM and reference method glucose measurements (RMGM) is commonly used to describe analytic performance of CGMs, but quantitative analysis demonstrates that it may be insufficient to characterize CGMs performance. A more complete characterization can be obtained by computing the absolute relative difference (ARD) of each CGM and RMGM pair, for each subject/sensor combination. While MARD is easily computed by taking the average, one may empirically construct the distribution of ARD and fit it to known parametric probability distributions. Data from 30 T1D subjects over a month (NCT01835964) were used to construct such histograms. Only the Gamma distributions family passed goodness-of-fit tests for all subject/sensor combinations, out of 7 parametric distributions. This model and its parameters, shape and scale, easily provide the expected MARD, and the probability that CGM and RMGM would be within pre-specified bounds. Figure 1 shows various probabilities plotted against MARD, for shape 0.8 to 3.5, and scale 1.5 to 8.0 (756 combinations), highlighting that similar MARDs (from 1.2% to 28%) may mask different error characteristics: e.g., MARD=12% may correspond to CGM within 5% of RMGM anywhere between 10% to 25% of the time.

In conclusion, the error probability calculation facilitated by the gamma distribution model may be a valuable tool for assessing CGM analytic performance.

Figure 1. Probability of Errors within ±XX% by MARD.



Supported By: Ascensia Diabetes Care

For author disclosure information, see page LB107.

112-LB

A Randomized Trial Comparing Telemedicine Therapeutic Intervention with Routine Care in Young Adults with Type 1 Diabetes Mellitus Treated by Insulin Pumps

MARIANNA YARON, BRURIA SHER, MINA SHOMER, NOA LEVEK, DANIEL SOREK, TALLI SCHILLER, MONICA GASPER, RACHEL FRUMKIN BEN-DAVID, KINERET MAZOR-ARONOVITCH, YONI SHAPIRA, EFRAT TISH, ORIT PINHAS-HAMIEL, *Tel Aviv, Israel, Ra'anana, Israel, Ramat Gan, Israel*

Objective: To determine whether the use of telemedicine (web-based downloading data software for blood glucose and insulin pump data) for insulin dose adjustment is safe and effective as routine treatment in adults with type 1 diabetes mellitus.

Methods: In a randomized, non-inferiority clinical trial, a total of 67 subjects treated with insulin pump with T1D for ≥1 year (mean duration 23.5±11.6 years) and HbA1c ≥6.5% were included. Subjects were randomized to the telemedicine intervention group (n=31) or routine care group (n=36). Subjects in intervention group were instructed to download data from insulin pump and glucometer monthly by CareLink Professional Software. For a period of 12 months they received immediate phone feedback and recommendation for insulin dose adjustment if needed. In addition, they came in for face-to-face visits once in 6 months (total 3 visits in 12 months). Control group did not submit web results and kept routine follow-up visits once every 3 months (total 5 visits in 12 months).

Results: Of 67 randomized patients (47.8% male; age 43.7±14.1; mean HbA_{1c} 7.76±0.7% [61±7.7 mmol/mol], 36 were allocated to intervention group and 31 to control group. At 6 months, HbA_{1c} changes were -0.07% in intervention group and -0.06% in control group (p=0.99). At 12 months, HbA_{1c} changes were -0.14% in intervention group and 0.04% in control group (p=0.71). Treatment satisfaction (DTSQ) and Quality of life (ADDQoL19) scores were similar in both groups (0.3±0.1 vs. 0.0±0.07, p=NS and 1.2±0.6 vs. 0.4 ±1; p=NS, respectively), although a positive trend was seen in intervention group.

Conclusions: Use of internet-based BG monitoring and insulin dose adjustment is safe and effective as routine care in adults with T1D treated by insulin pump and reduces the need for face-to-face visits by 40%. The time consuming regular routine visits may be replaced in a certain subgroup of diabetic subjects by easy available digital medicine.

Supported By: Maccabi Healthcare Services

113-LB

Effectiveness of DPP-4 Inhibitors on Blood Glucose Variability in Type 2 Diabetes Patients Undergoing Hemodialysis

TOMOMI ISHIKAWA, MICHIHIRO HOSOJIMA, HIDEYUKI KABASAWA, RYOHEI KASEDA, SHOJI KUWAHARA, NORIAKI IINO, TAKAHIRO TANAKA, NOBUTAKA KITAMURA, YOSHIKI SUZUKI, ICHIEI NARITA, AKIHIKO SAITO, *Niigata, Japan*

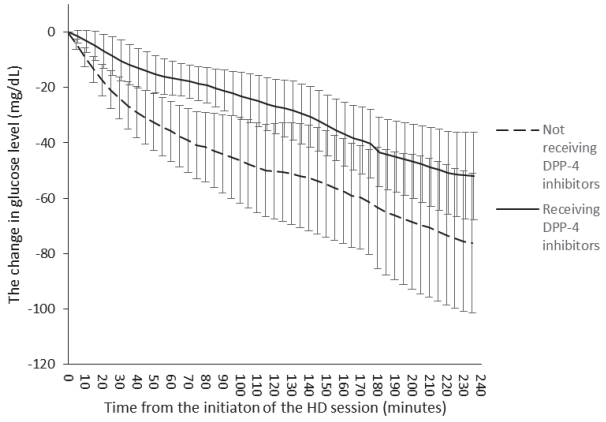
Background: Patients with end-stage renal disease are at great risk of asymptomatic hypoglycemia. It is also well known that hemodialysis (HD) patients often have pronounced blood glucose (BG) variability during HD. However, precise BG profiles of HD patients are unclear, and the effectiveness of dipeptidyl peptidase-4 (DPP-4) inhibitors in HD patients with diabetes is unknown.

Methods: We examined BG profiles using continuous glucose monitoring during an HD session and in the subsequent nighttime in 31 patients with type 2 diabetes. Differences between the groups receiving and not receiving DPP-4 inhibitors (n=16 vs. n=15, respectively) were analyzed using the linear mixed-effects model to assess change in glucose level every 5 minutes.

Results: Analysis revealed a significant interaction between receiving DPP-4 inhibitors and change in glucose level from the HD start time, with a significant difference in the slope of 0.1 mg/dL per minute during HD (Figure). Moreover, a significant interaction was noted between receiving DPP-4 inhibitors and change in glucose level in the subsequent nighttime, with a significant difference in the slope of 0.05 mg/dL per minute.

Conclusion: DPP-4 inhibitors can potentially suppress BG variability during HD sessions and in the subsequent nighttime in patients with type 2 diabetes.

Figure. Change in Glucose Level in Patients with Type 2 Diabetes Receiving or Not Receiving DPP-4 Inhibitors during the HD Session.



114-LB

Reducing A1C Levels in Individuals with High-Risk Diabetes Using the Mobile Glucose Meter Technology

MOSHE KAMAR, YIFAT HERSHCOVITZ, DROR BACHER, EITAN FENIGER, *Holon, Israel, Caesarea, Israel*

The aim of glucose meters technology is to improve treatment and glucose level control for people with diabetes. Frequent self-testing has long been advocated to improve glucose level control. The Dario™ Blood Glucose Meter connects directly to a smart mobile device and automatically logs blood glucose measurements into designated app. Data is transmitted to a cloud based database.

Methods: We selected a group of high-risk Dario™ users (with baseline A1C > 8 percent). A retrospective analysis of change in A1C levels for users measuring at least three times a day over a period of 3 and 6 months was performed, with sub-analysis stratifying by baseline A1C (>8, >9 and >10).

Results: 276 high risk subjects were selected with levels of A1C >8 (mean baseline A1C 9.1±1.1) and with greater than three blood glucose measurements taken per day. After 3 months of use 178 (64%) users who started with A1C > 8 (mean baseline 9.3±1.2) improved by 1 percent on average (mean of 8.3±1.1 percent). 90 out of 120 (75%) with A1C > 9 (baseline 10.1±1.1) improved by 1.3 (8.8±1.1) percent on average and 36 out of 47 (77%) with A1C > 10 (baseline 11.1±1.2) improved by 1.7 (9.4±1.3) percent on average. The users with a baseline A1C greater than 8, 9 and 10 were analyzed after 6 months. 174 users had improved by 1.1 percent (8.2±1.1), 89 users by 1.4 percent (8.7±1.3) and 39 users by 2 percent (9.1±1.5) on average, respectively.

Conclusions: The use of digital smartphone based blood glucose monitoring systems in high risk patients has the potential to increase patients' engagement and awareness for routine self-testing, thus improving their glucose levels and A1C over time.

115-LB

Continuous Glucose Monitoring for 90 Days: How Stable Are Time-in-Range and Glucose Patterns?

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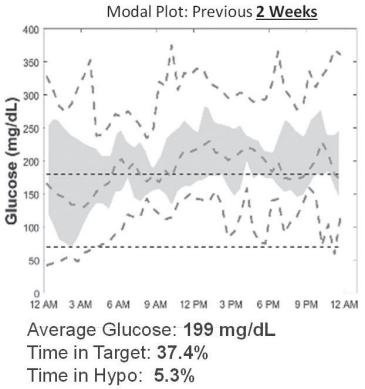
To help guide personalized diabetes management, clinicians need access not only to HbA1c, but also to glucose monitoring metrics and glycemic patterns in a patient's history. Glycemic variability was analyzed from the previously reported PRECISE II trial, a blinded prospective, single-arm study with 90 subjects using the Eversense® CGM System (90 day implantable, subcutaneous glucose sensor with an MARD of 8.8%). This analysis aimed to determine the utility and representativeness of the Ambulatory Glucose Profile (AGP) plots for different measurement periods consisting of median glucose, 25^{th}-75^{th} percentile (interquartile range) and 10^{th}-90^{th} percentile lines as well as variability metrics, for 14, 30 and 90 days of integrated data (Figure 1).

With longer data periods integrated, there were fewer acute, short term data fluctuations in the interquartile and 10^{th}-90^{th} percentile ranges enabling more representative of the glycemic pattern corresponding to the 90 day AGP. Figure 1 also illustrates the variability of the metrics. In terms of accuracy of the metrics, to achieve 20%, 10% and 5% of the chronic values, for >80% of the subjects, 14, 43 and 71 days, respectfully, of monitoring were needed for integration.

Analyzing the full dataset, we concluded that the clinical assessment for the AGP patterns at 14, 30, and 90 days would result in similar decisions about treating the low (3AM) and high (10PM) daily glucose trends.

Figure 1.



116-LB

CGM Is Safe for Making Treatment Decisions in Type 1 Diabetes: Evidence from an In Silico Trial

MARTINA VETTORETTI, ANDREA FACCHINETTI, GIOVANNI SPARACINO, CLAUDIO COBELLI, *Padova, Italy*

Recently, in silico clinical trials (ISCTs) based on a type 1 diabetes patient decision-making (T1D-DM) simulation model provided evidence that CGM can be safely used to make treatment decisions. This modelling helped support FDA approval of the Dexcom G5 Mobile for insulin dosing decisions. Here, an ISCT based on an improved T1D-DM simulation model is presented providing a more comprehensive treatment assessment. Specifically we compared treatments based on SMBG only, CGM with confirmatory SMBG (adjunctive CGM) and CGM alone (nonadjunctive CGM). The T1D-DM model includes four components: the UVA/Padova T1D model, which describes the kinetics of glucose, insulin and glucagon in T1D subjects; a model describing the functioning of SMBG and CGM glucose monitoring devices; a model of the patient's behavior in making treatment decisions based on SMBG and/or CGM; and a model of insulin administration via insulin pump. The model was used to perform a two-week ISCT in 100 adult virtual subjects with three treatment scenarios: SMBG, adjunctive and nonadjunctive CGM use. Simulation parameters for the three scenarios were determined based on literature data and Dexcom G5 Mobile users' data. Treatments were then compared based on time spent in euglycemia (i.e., between 70 and 180 mg/dl), hypoglycemia (i.e., below 70 mg/dl) and hyperglycemia (i.e., above 180 mg/dl). Compared to SMBG, nonadjunctive CGM use increases median time in euglycemia from 14.92 h/day to 15.70 h/day, reduces median time in hypoglycemia from 42.15 min/day to 28.07 min/day and lowers median time in hyperglycemia from 8.56 h/day to 7.83 h/day. In the adjunctive CGM scenario, median time in eu/hypo/hyperglycemia are 15.78 h/day, 33.33 min/day and 7.69 h/day, respectively, and thus similar to the metrics achieved by nonadjunctive CGM use.

In conclusion, the two-week ISCT based on the T1D-DM model suggests that nonadjunctive CGM use is as safe as adjunctive CGM use and thus CGM can be safely used to replace SMBG in making T1D treatment decisions.

117-LB

Performance Evaluation of Five Blood Glucose Monitoring Systems in the Hands of Intended Lay Users following ISO 15197:2013

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The standard for blood glucose meters for self-monitoring (BGMS) ISO 15197:2013 specifies an evaluation of BGMS accuracy when operated by intended lay-users.

In this study, such an evaluation was performed with 5 BGMS, applying the accuracy criteria: ≥95% of the BMGS results have to be within ±15 mg/dl or ±15% of comparison results at glucose concentrations < or ≥100 mg/dl, respectively. Additionally, Consensus Error Grid (CEG) analysis was performed.

100 diabetic subjects that had not used the evaluated BGMS before performed measurements with the 5 BGMS (Accu-Chek Aviva Connect [A], Contour Next One [B], FreeStyle Freedom Lite [C], GlucoMen areo [D] and OneTouch Verio [E]). Afterwards, study personnel performed 2 additional BGMS measurements as well as measurements with a comparison method (glucose oxidase or hexokinase).

Accuracy results are shown in the Table. Frequently observed lay-user errors were not checking the test strip's expiry date, incorrect blood application and mistakes in device handling.

Four of the five BGMS fulfilled user performance criteria of ISO 15197:2013, but differences in the percentages of results within the accuracy limits and in the relative bias were observed. No BGMS showed clinically inacceptable results. To achieve comparable performance in hands of intended users and professionals, BGMS should be easy to use and resistant to errors.

Table.

System	Comparison method	% of results within ±15 mg/dl/ 15%	Bias [%]	CEG Zone A [%]	CEG Zone B [%]
		Lay-users			
A	HK	**96**	-6.3	99	1
B	GOD	**100**	-2.9	100	-
C	GOD	**95**	-6.7	98	2
D	GOD	**95**	4.2	99	1
E	GOD	**93**	4.8	100	-
		Study personnel			
A	HK	**100**	-4.8	100	-
B	GOD	**100**	-1.1	100	-
C	GOD	**99.5**	-6.1	100	-
D	GOD	**100**	1.4	100	-
E	GOD	**88.5**	6.5	99.5	0.5

Supported By: Ascensia Diabetes Care

118-LB

Design and Evaluation of Diabetes Self-Management mHealth Apps

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While the pervasiveness of mobile phones has resulted in a consumer-driven market for diabetes-focused mHealth applications, the majority of these apps are not evidence-based or rigorously evaluated. The main objectives of this research were to design, develop and evaluate, a consumer-focused, behavioural app for the self-management of diabetes. Following a knowledge translation framework, existing evidence around behaviour change theory, diabetes self-management, and mHealth was reviewed, and informed the conceptualization of the app features. The app was developed following user-centered design principles, where iterative feedback was obtained from patients throughout the process. The resulting intervention,

For author disclosure information, see page LB107.

bant2, was a consumer-focused app for the self-management of type 2 diabetes, focused on the contextualization of blood glucose readings with personalized lifestyle behaviours. While a 12-month RCT was designed to evaluate the impact of bant2 on clinical outcomes, findings from recent studies led to reconsider both the intervention the evaluation approach. The bant RCT (n=96) and <30 Days study demonstrated that traditional evaluation of apps cannot keep pace with the rapidly evolving consumer expectations or technological landscape. The <30 Days study, a pragmatic evaluation of a consumer-focused chronic disease self-management app among 70,000 users, demonstrated how population-level data can power robust evaluations of apps. Traditional RCTs are lengthy, high cost, do not consider practical implementation, and assume that all users require the same behavioural intervention. The next generation of apps must consider strategies that integrate with information systems to optimize the use of patient data, through approaches like precision medicine, to provide patients with dynamic, adaptive and personalized diabetes interventions. Shifting focus to population-level approaches will enable the rapid optimization and scalability of diabetes self-management apps.

Supported By: Canadian Institutes of Health Research

119-LB

Linking Real-Time Blood Glucose to Driver Risk in Diabetes

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This pilot study addresses real-world driver safety in diabetes mellitus (DM). Low or high blood glucose (BG) can impair driver performance, thereby increasing the risk of crashes. We collected continuous data (over 4 weeks; 3,687 drives) from sensors installed in 35 drivers' own vehicles (19 with DM; 16 without DM) and measured real-time BG levels in DM drivers using CGM. We tested the hypothesis that real-world DM driver risk is linked to at-risk BG levels (<70; >300 mg/dL). DM drivers had at-risk BG 17.96% of total study time, elevating risk of driving while impaired. DM subjects took 1,940 drives. DM drivers had at-risk BG 13% of time during driving (<70 mg/dL, 3.4%; >300 mg/dL, 9.6%) showing insufficient self-restriction. DM driver behavior, linked to erratic driving based on accelerometer profiles, increased relative to controls even during eu- to moderate hyperglycemia (β=0.14, SE=0.04, p=<0.001). At-risk DM driver behavior in impaired BG states, particularly hypoglycemia, further increased relative to controls in high-speed environments (β=0.01, SE=<0.01, p=<0.001). At BG levels of 70-300 mg/dL, DM drivers showed the same degree of at-risk behavior across speed as controls (β=-0.001, SE=<0.001, p=0.27). Models within individual DM drivers showed greater at-risk behavior with BG <70 mg/dL (β=-0.38, SE=0.07, p=<0.0001) and >300 mg/dL (β=-0.17, SE=0.05, p=<0.001), particularly on high-speed roadways, mirroring between group analyses. State DMV records of the subjects showed DM drivers accounted for all crashes (N=3) and 85% of citations (N=13). These novel results show that real-time BG, particularly hypoglycemia, is related to real-world, real-time changes in DM driver behavior. Findings demonstrate that vehicle sensor and BG data can be used to quantify individual driver risk in DM. Combining sensor data and phenotypes of driver behavior can inform patients, caregivers, interventions (education, training, medical), policy, and design of supportive in-vehicle technology responsive to driver state.

Supported By: Toyota Collaborative Safety Research Center

120-LB

Lactate and Cortisol Levels during Exercise under Closed-Loop Control

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A multi-variable artificial pancreas (AP) uses biosensor signals and blood glucose (BG) from continuous glucose monitors to inform the pump of insulin decisions and provide warning for low BG, meal detection for delivery of insulin, and detection of exercise. To understand what affects BG during exercise, we measured salivary cortisol and lactate during different exercises under AP conditions. We hypothesize both lactate and cortisol vary according to exercise. If so, we can develop an indicator for these factors to provide feedback to the AP to help BGs remain in target. Thirteen males and females (ages 19-26 yrs) were studied in a CRC for 60 hrs under AP control. Day 1 consisted of an aerobic session with goal to achieve 80% of target heart rate range (THRR) based off maximal exercise test, followed by a resistance exercise based on number of repetitions (reps) subjects were able to complete. Goal was two sets of 10 reps with first based on subject self-reporting difficulty; if <8 reps were completed, weight was decreased, if >12 reps were completed weight was added. Day 2, resistance training was identical to day 1 followed by aerobic interval exercise based off of the maximal exercise test. The aerobic interval training protocol was four bouts of high intensity (90-95% of THHR) exercise, four minutes in duration. Between each high intensity bout, a 3 minute bout of moderate intensity (60-80% THHR) exercise was completed, in a 4x3 interval. Day 3 was identical to day 1. Results showed, in general lactate levels went up and cortisols went down during exercise. Specifically, lactate did not differ across exercise bouts but there was a statistically significant difference in cortisol across exercise sessions by repeated measures ANOVA analysis (p=0.03). The interval session led to significantly lower cortisols than the other two sessions (p=0.01 for both comparisons). Lactate and cortisols vary during various exercises, particularly cortisol. Understanding these patterns will enhance an AP's ability to keep BG in target range.

Supported By: National Institutes of Health; JDRF

121-LB

Clinical Comparison of iWel and Medtronic Continuous Glucose Monitoring (CGM) Devices

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Background: Continuous glucose monitoring (CGM) devices are increasingly being used by diabetes patients today as a result of both convenience and improved accuracy. All CGM devices on the market require an insertion device with a relatively large needle sleeve for sensor placement. The iWel CGM device does not need an inserter due to its short and small sensor. The device has been used by more than 36,000 patients/sensors in several countries around the world and will be launched in Europe in 2017.

Study Design: A clinical study was conducted to compare the performance of the iWel and Medtronic 530G CGM devices in 24 Asian female/male, 16-68 years old of type 1, type 2 and other diabetic patients. The study was conducted using open labels in a single study site in China. All patients had both devices on at the same time with the iWel CGM device located in the side of an arm (above the elbow) and the Medtronic CGM device located in the abdominal area. Self-monitoring blood glucose (SMBG) using finger pricking kits were used for calibration (one and four times per day for the iWel and Medtronic devices, respectively). The glucose values from SMBG were also paired with CGM values as reference for determination of accuracy. The mean absolute relative difference (MARD) relative to SMBG was calculated for each device.

Results: The MARD relative to SMBG was 11.1% for iWel and 15.9% for Medtronic. The data were also analyzed with the Clarke Error Grid method, with a region A area of 86.73% and 71.67% for the iWel and Medtronic devices, respectively.

Conclusion: A side-by-side clinical study of the iWel and Medtronic 530G CGM devices shows a higher degree of accuracy for the iWel device compared to the Medtronic device when it comes to continuously assessing blood glucose level.

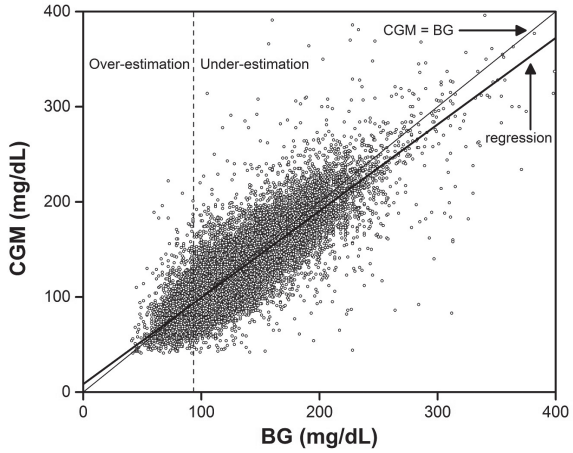
122-LB

Effectiveness of Continuous Glucose Monitoring and Detecting Hypoglycemia in Critically Ill Children

GARRY M. STEIL, KYLE F. HUGHES, JAMIN L. ALEXANDER, NATALIE HASBANI, VINAY M. NADKARNI, DAVID WYPIJ, MICHAEL S.D. AGUS, *Boston, MA, Philadelphia, PA*

Hyperglycemia and blood glucose (BG) variability are associated with poor outcomes in critically ill children. When treating hyperglycemia, continuous glucose monitoring (CGM) can alert providers of impending hypoglycemia, however, false alarms can impose unnecessary burden on clinicians. To assess the effectiveness of CGM in critically ill children, we analyzed 28,600 paired point-of-care (POC; Nova Biomedical) blood glucose (BG) values and CGM (Dexcom G4 Platinum, Software 505) values in 364 children enrolled in the multicenter Heart and Lung Failure-Pediatric Insulin Titration trial (HALF-PINT; NCT01565941). Additionally, 131 confirmed hypoglycemia adverse events, defined as BG (POC or laboratory) <60 mg/dL and ending when BG is ≥ 60 mg/dL, in 65 children were individually reviewed. Mean absolute relative difference (MARD) of the paired values was 11.8% with a strong linear relationship between CGM values and BG (r=0.86; p<0.001). With the CGM alarm set to 70 mg/dL and hypoglycemia defined as BG <60 mg/dL, sensitivity was 71.6% and specificity was 97.0%. At the start time of each adverse event, the CGM read ≤ 70 mg/dL in 110 events (84%). CGM can accurately and effectively alert providers of impending hypoglycemia, but at a cost of a false alarm rate of 11:1, checking confirmatory BG represents a burden to bedside clinicians.

Figure 1. CGM-BG Paired Values (N=28,600).



*Regression line: CGM = 0.91(BG) + 8.41, Point of intersect: 93.4 mg/dL

Supported By: National Institutes of Health

123-LB

The Effect of Acetaminophen on Continuous Glucose Monitoring in Critically Ill Children

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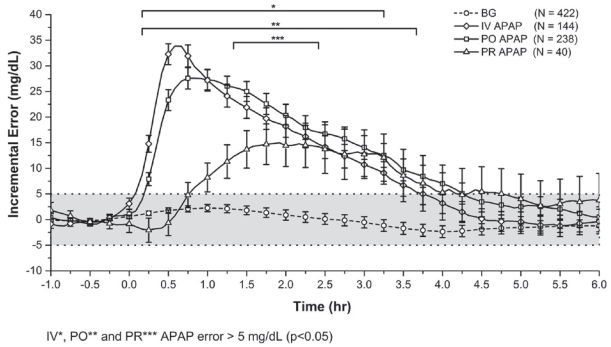
Continuous glucose monitoring (CGM) is a useful method to manage blood glucose (BG) levels in critically ill children, although measurement interference by medications is a known complication. We recently completed a multicenter study, Heart and Lung Failure-Pediatric Insulin Titration (HALF-PINT; NCT01565941), using Dexcom's G4 Platinum sensor (Software 505); this sensor falsely recognizes acetaminophen (APAP) as glucose. Our objective was to quantify the magnitude and duration of APAP's effect on CGM. BG was assessed by point of care blood glucose meters (Nova Biomedical). BG and CGM were interpolated to 5 minute intervals from 1 hour prior to 6 hours following administration of 15 mg/kg of APAP either intravenously (IV), enterally (PO) or rectally (PR) (N=422). Peak concentrations reported by CGM but not BG for IV, PO and PR APAP were 33.9 ± 2.2, 27.6 ± 2.0 and 15.0 ± 4.1 mg/dL, respectively, with peak concentration of IV APAP being higher than both PO and PR APAP. The duration of PR APAP's effect on the CGM was shorter than both IV and PO APAP.

In conclusion, when using CGM on critically ill children, clinicians should wait approximately 3.3., 3.7 and 2.4 hours after administering IV, PO, and PR APAP, respectively, to avoid treating false elevations of CGM glucose attributable to APAP's effect.

Figure 1. Mean ± SE Every 15 Minutes.



IV*, PO** and PR*** APAP error > 5 mg/dL (p<0.05)

Supported By: National Institutes of Health

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULINS

124-LB

Patient-Reported Outcomes (PROs) in Insulin Degludec/Liraglutide (IDegLira) vs. Basal-Bolus (BB) Therapy in Patients (Pts) with Type 2 Diabetes (T2D): DUAL VII Trial

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In a 26-wk open-label trial, 506 adult pts with T2D, A1C 7-10% on Metformin (met) and 20-50 units insulin glargine U100 (IGlar) were randomized 1:1 to once-daily IDegLira or BB (IGlar + insulin aspart ≤4 times a day) and met. Pts' perceived health status and treatment experience were quantified using PROs.

Treatment Related Impact Measure-Diabetes showed greater improvements in favor of IDegLira vs. BB in all domains (Table) and Total Score (estimated treatment difference [ETD] 6.50 [95% CI 4.44; 8.57] p<0.0001). The greatest improvements were in diabetes management (likely driven by items on avoiding hypoglycemia/weight gain), treatment burden and compliance. Short Form Health Survey 36 v2 (SF-36) ETD was in favor of IDegLira vs. BB for the mental component summary (1.83 [95% CI 0.26; 3.40] p=0.023), driven by mental health (ETD 2.29 [95% CI 0.62; 3.96] p=0.0074). Other SF-36 ETDs were not significant. In a motivation survey 26 wks after randomization, 84.5% of IDegLira pts were willing to stay on study therapy vs. 68.1% of BB pts (odds ratio 2.54 [95% CI 1.63; 3.98] p<0.0001).

Thus, IDegLira induced greater improvements in PROs, mainly in diabetes management and treatment burden, vs. BB in pts with A1C 7-10% switched from met and IGlar. Pts on IDegLira had an equal reduction in A1C, lower burden of hypoglycemia, fewer injections/day, and weight loss vs. BB.

Table: Change from baseline to week 26 in TRIM-D domain scores. DUAL VII trial: NCT02420262

	IDegLira + met Observed mean change (n=252)*	IGlar + IAsp + met Observed mean change (n=254)*	Estimated treatment difference (ETD) [95% CI]	*p*-value
Diabetes management	16.7	6.8	10.76 [7.62; 13.90]	<0.0001
Treatment burden	12.4	4.3	10.50 [7.34; 13.67]	<0.0001
Compliance	9.1	3.9	6.25 [3.82; 8.69]	<0.0001
Daily life	3.5	–0.4	4.23 [1.09; 7.37]	0.0083
Psychological health	5.7	3.0	2.77 [0.32; 5.21]	0.0268

Observed data; MMRM with treatment, region and visit as fixed factors, and baseline value as covariate. Interactions between visit and all other factors and covariate are included. TRIM-D questions available at https://eprovide.mapi-trust.org/instruments/treatment-related-impact-measure-for-diabetes.

*Positive number denotes improvement in parameter being measured.

CI, confidence interval; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide; IGlar, insulin glargine 100 units/mL; met, metformin; MMRM, mixed-model repeat measurement; TRIM-D, Treatment Related Impact Measure–Diabetes.

Supported By: Novo Nordisk

125-LB

Patients Preferred Different Insulin Glargine Titration Algorithms from Physicians: A Real-World Survey

LI WANGEN, *Guangzhou, China*

Background: Patient-directed basal insulin titration have similar efficacy and safety with physician-directed titration. However, all the titration algorithm are decided by physicians.

Hypothesis: Patients prefer different basal insulin titration algorithms with physicians.

Methods and Design: If type 2 diabetes patients fail to reach their hemoglobin A1c target using oral antidiabetic drugs, physicians were asked to choose their preferred insulin glargine titration algorithms from 5 candidates and give the reasons. Algorithm 1: increased 2-8U weekly based on 3-day mean FPG levels; algorithm 2:2U increased every 3 days; algorithm 3:1U increased once daily; algorithm 4: increased 3U every 3 days; algorithm 5: titration every 3 days, increased 1U, 10%-20% of TDD. Then, we began to survey patient's preferred algorithms by providing the same 5 candidates.

Results: A total of 210 physicians participate the survey. 195(92.9%) preferred algorithm 2, 11(5.2%) preferred algorithm 3, and 5(2.4%) preferred algorithm 4. No physicians preferred other two algorithms. 198 patients were willing to self-titrated their insulin glargine. Of which, 18(9.1%) patients

For author disclosure information, see page LB107.

preferred algorithm 2 and 180(90.9%) preferred algorithm 3. No patients preferred other three algorithms. There were four reasons for most physicians preferred algorithm 2. First, it was recommended by several guidelines (89.5%). Second, the titrating dose and frequency were moderate (56.2%). Third, I don't know other algorithms (15.7%). Forth, it was better than other algorithms (9.0%). In contrast, there were also four reasons for most patients preferred algorithm 3. First, it was simple (97.5%). Second, titrating 1U once is safe (13.6%). Third, titrating every day reached target faster (2.5%). Forth, it does not need calculating mean FBG (1.0%).

Conclusion: Patients prefer different insulin glargine titration algorithms with physicians. We should pay more attention to 1U increased once daily algorithm.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULIN DELIVERY SYSTEMS

126-LB

Maintaining Glucose Control at One+ Year of MiniMed® 670G System Home Use: Single Center Experience

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The safety and effectiveness of 3-month in-home use of the MiniMed 670G hybrid closed-loop (HCL) system has been reported. 19/24 of patients (mean±SD 28.4±14.6 yrs) continued to use the system for > 1 year at the Barbara Davis Center for Diabetes, via the Continued Access Program (CAP). To the best of our knowledge this is the first report of in-home use of the system at 1 yr.

The Table in the Figure (1a) shows mean A1c and % of sensor use and HCL control (or Auto Mode), over time. Improvements observed at 3-month (time in target, 70-180 mg/dL; hypoglycemia, ≤70 mg/dL, ≤50 mg/dL; hyperglycemia, >180 mg/dL, >300mg/dl; and CV, were maintained at 1 yr. The Figure (1b-d) also shows sensor glucose over the 24-hour day, for the 2-week run-in and combined 3-month study and 9-month CAP periods for all, adolescent and adult patients. The mean bolus insulin dose in units/day at baseline was lower than at 1 yr (24.7±12.2 vs. 26.7±10.7), while total daily insulin dose in units/day was essentially unchanged (50.0±16.8 vs. 50.3±17.4). There were no serious adverse device-related events throughout the study at our site.

At our center, use of the MiniMed 670G HCL system for up to 1 yr was safe and improvements in glycemia were maintained. Our findings suggest that long-term use of the system may benefit patients with type 1 diabetes.

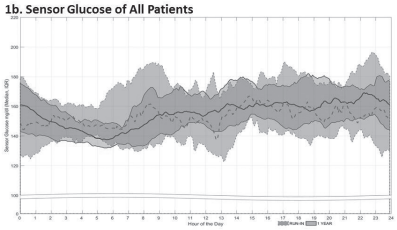
Figures.

1a.

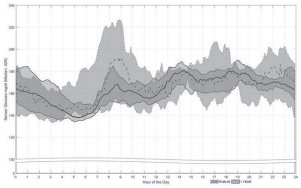
		Baseline Mean±SD	3 Months Mean±SD	1 year Mean±SD
A1c(%)		7.7±0.9	7.0±0.5	7.2±0.9*
Sensor Usage(%)			88.2±7.0	80.5±12.4
HCL Control Usage(%)			73.8±10.7	68.2±16.4
Time in Range (%)	SG ≤50 mg/dL	0.8±0.8	0.6±0.5	0.6±0.5
	SG ≤70 mg/dL	4.7±3.8	3.2±1.5	3.5±1.7
	70< SG <180 mg/dL	63.9±11.3	70.4±7.5	68.0±9.4
	SG >180 mg/dL	31.5±13.3	26.4±7.5	28.5±9.8
	SG >300mg/dL	3.2±4.7	2.0±1.8	3.0±3.1
Coefficient of Variation-CV		34.1±4.1	31.7±3.0	32.1±2.7

Note: Summary baseline and 3-month data are based on 24 subjects (28.5±13.6 yrs of age). Summary 1-year data are based on 19 subjects, except A1c at 1 year (* 13 subjects).

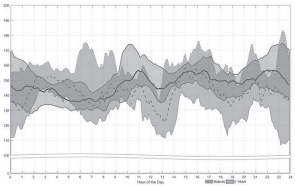
1b. Sensor Glucose of All Patients



1c. Sensor Glucose of Adolescent Patients



1d. Sensor Glucose of Adult Patients



The 1 year duration includes the 3-month study and 9-month CAP periods.

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Automatic Estimation of Basals, ISF, and Carb Ratio for Sensor-Augmented Pump and Hybrid Closed-Loop Therapy

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Summary: A tool for automatically tuning insulin pump basal rates, ISF, and carb ratios has been developed by patients in the open source community. Insulin dosing and carb data, glucose data from CGM, and pump profile settings are used to calculate expected blood glucose impact (BGI) for each glucose value. Each glucose value is then categorized as being most attributable to basal, ISF, or carb sensitivity factor (CSF=ISF/carb ratio), and used to calculate adjustments to basals, ISF, and CSF. For each hour, total BGI deviations and necessary adjustment in basal to bring deviations to 0 are calculated; 20% is applied to the previous 3 hours' basals. Median deviation for entire day's ISF-attributed data and necessary adjustment in ISF to bring the median deviation to 0 are calculated; 10% is applied. Total BGI deviations during observed carb absorption are calculated and compared to total carb intake to calculate new CSF; 10% is applied to the carb ratio. (n=1)*16 users reported feedback about how well this tool ("autotune") works.

Outcomes: 75% of surveyed users made changes to their insulin pump settings after running autotune. 100% of people felt basal suggestions were accurate: 83% changed their basal rates. They were less sure of carb ratio estimations (only 69% felt the estimates were accurate): 58% changed their carb ratios. 88% of people felt ISF suggestions were accurate: 67% changed their ISF. On average in the surveyed population, autotune estimated a needed 10.24% average change in hourly basal rates (net 4.54% increase overall); 29% increase needed in carb ratios; and 19% increase needed in ISF. Patients felt strongly that using data to assess changes to pump settings should be the norm rather than relying on the current methods of guessing or weight-based estimations.

Conclusion: These data show many patients are using non-optimal settings. Pump users and HCPs could benefit from using this type of tool to help make ongoing changes to ratios and basals.

128-LB

Metabolic Differences between CSII and MDI in Type 1 Diabetes Mexican Patients from the Multicentric Study RENACED

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Introduction: There is limited information regarding differences in metabolic control in patients with type 1 diabetes (T1D) treated with CSII or MDI in Mexico. RENACED, a longitudinal online system, was created to have a real-life data registry of T1D patients.

Methods: Bivariate analysis (alfa=0.05) of 464 T1D patients registered in RENACED system up to 2/22/2017.

Results: Of the 464 patients, 135 (29%) are on CSII and 329 (71%) on MDI. Patients on CSII had lower HbA1c levels (7.9%; CI 95% 7.6-8.1) than those on MDI (8.8%; CI 95% 8.6-9.1) ($p<0.05$). The total insulin daily dose was lower on CSII (0.58 IU/kg; CI 95% 0.52-0.64), than on MDI (0.82 IU/kg; CI 95% 0.69-0.96) ($p<0.05$), (Table 1). CSII was associated with higher SMBG per day ($p<0.01$). Almost no patients on MDI used CGM. A significantly higher event rate of mild/moderate hypoglycemia/week was observed in the CSII group 4.2 (3.0-5.3) vs. the MDI group 2.5 (2.3-2.7) ($p<0.01$). Patients on CSII that used CGM had lower HbA1c levels (7.7%; CI95% 7.4-8.0) than those that did not (8.0%; CI95% 7.7-8.4) ($p=.22$). An interesting finding is that those patients on CSII exercise more.

Conclusions: According to the literature, CSII use and higher number of SMBG/day are associated with better glycemic control. It is interesting that

those on CSII exercise more, a finding that will need to be confirmed with higher number of patients in the registry.

Table 1. Bivariate analysis of T1D patients that are on CSII or MDI therapy

	MDI (CI 95%)	CSII (CI 95%)	p
HbA1c (%)*	8.8 (8.6 - 9.1)	7.9 (7.6 – 8.1)	< 0.01
Mean daily insulin dose (kg/day)	0.82 (0.69 - 0.96)	0.58 (0.52 - 0.64)	< 0.01
Age (years)*	24.7 (23.4 - 26.1)	27.4 (25.1 - 29.8)	0.04
SMBG per day*	3.2 (3.0 - 3.4)	4.2 (3.7 - 4.6)	< 0.01
Exercise (%)*	38.9 (33.5 - 44.3)	76.2 (68.6 - 83.9)	< 0.01
Count Carbohydrates (%)*	62.6 (57.3 - 68.9)	93.2 (88.9 - 97.6)	< 0.01
Mild/Moderate hypoglycemia per week (events)*	2.5 (2.3 - 2.7)	4.2 (3.0 - 5.3)	< 0.01

*p< 0.05

129-LB

Behind Closed Doors: Technology and Intimacy in Type 1 Diabetes

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Introduction: Intimacy is an important determinant of quality of life. External technologies such as insulin pumps (CSII) and continuous glucose monitors (CGM) have the potential to impact intimacy and this may impact their uptake. We aimed to explore the association between external technologies and sexual activity.

Methods: An invitation to complete an online survey was sent to 3500 type 1 diabetes patients aged 16-60 years living in Western Australia. We used a mixed method approach with quantitative and qualitative responses.

Results: Of the 289 respondents (mean age 34.3 years, range 16-60 years, female 53%), 129 (45%) used CSII and 101 (35%) used CGM. Most respondents were sexually active (92%). Of CSII users, 48% reported that CSII interferes with sex. Common problems cited were; interrupts the moment, tangles and pulls. As a result, 75% of patients disconnect their pump to avoid this. The preferred CSII insertion site with respect to sexual activity was the abdomen, and 22% of patients reported that comfort during sex influenced the location of the site. One in four non-CSII users cited concerns about intimacy as a factor for not adopting the technology. In contrast, CGM was reported to interfere with sexual activity in only 20% of respondents, sexual activity did not commonly affect CGM placement (18%), and just one in ten non-CGM users cited intimacy as a factor for not adopting the technology. There were no differences between CSII and non-CSII respondents in body dissatisfaction using the Stunkard Figure rating scale (p=0.664) or anxiety the state-trait anxiety inventory (p=0.344).

Conclusion: CSII has a significant impact on intimacy and these concerns may significantly influence their uptake, but is less of an issue with respect to CGM. With increasing use of diabetes technologies, it is important for health care professionals to be aware of these potential concerns and address strategies to mitigate these.

Supported By: University of Western Australia

130-LB

WITHDRAWN

131-LB

Device-Supported vs. Routine Titration of Insulin Glargine 300 U/mL (Gla-300) in T2DM: Efficacy and Safety

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Insulin self-titration may help people with T2DM reach glycemic targets. MyStar DoseCoach™, a combined titration device/blood glucose meter, aids self-titration by providing automated insulin glargine dosing suggestions. AUTOMATIX, a randomized, parallel-group, multicenter treat-to-target trial, evaluated the efficacy and safety of device-supported vs. routine (investigator recommended) Gla-300 titration regimens. In total 151 participants with T2DM (insulin naïve/insulin pre-treated) were randomized 1:1 to device-supported or routine titration with Gla-300. Primary endpoint: percentage of participants reaching fasting SMPG (FSMPG) target 90-130 mg/dL at week 16 without severe hypoglycemia. Secondary endpoints included: percentage of participants reaching target FSMPG at week 16 without confirmed or severe hypoglycemia; change in mean FSMPG, HbA_{1c} and daily insulin dose (baseline to week 16). Number of participants experiencing hypoglycemia and adverse events were also reported. Although not significant, a higher proportion of participants using device-supported vs. routine titration achieved the primary endpoint (Table). Between titration arms, comparable numbers of participants experienced hypoglycemia and TEAEs/SAEs (Table). The results show that device-supported titration with Gla-300 has a good efficacy/safety profile and may aid glycemic target achievement.

Table. Outcomes from the AUTOMATIX study

	Device-supported titration (on-treatment period) (n=75)	Routine titration (on-treatment period) (n=76)
Participants[a] reaching mean FSMPG target range (90–130 mg/dL) at week 16, estimated[b] %		
Without severe hypoglycemia	45.9	36.8
Estimated weighted difference (95% CI)[c]	9.04 (−6.748 to 24.829)[NS]	
Without confirmed (≤70 mg/dL) or severe hypoglycemia	34.3	14.5
Estimated weighted difference (95% CI)[c]	19.75 (6.284 to 33.207)[ND]	
Change in mean FSMPG from baseline to week 16, mg/dL[a]	−45.21 (42.24)	−40.96 (41.23)
Change in mean HbA_{1c} from baseline to week 16, %[a]	−1.16 (0.84)	−1.01 (0.88)
Change in average daily Gla-300 dose from baseline to week 16, U/kg[d]	0.213 (0.185)	0.157 (0.153)
Hypoglycemia, number of participants (%)[d]		
Any time of day (24 h)		
Any event	26 (34.7)	29 (38.2)
Confirmed (≤70 mg/dL) or severe hypoglycemia	22 (29.3)	27 (35.5)
Nocturnal (00:00–05:59 h)		
Any event	8 (10.7)	11 (14.5)
Confirmed (≤70 mg/dL) or severe hypoglycemia	7 (9.3)	10 (13.2)
TEAEs, n (%)[d]	34 (45.3)	29 (38.2)
SAEs, n (%)[d]	2 (2.7)	3 (3.9)

[a]mITT population.
[b]Estimated proportion of participants obtained by averaging all the imputed proportions of participants reaching the endpoint (a multiple imputation method was used to address missing values in the mITT population).
[c]Estimated difference of proportions obtained by combining the difference in percentage, weighted by the randomization stratum of previous use of insulin (insulin naive, insulin pre-treated), between titration groups of all different imputed data sets, using Rubin's formula.
[d]Safety population.
[NS]Not statistically significant (superiority testing).
[ND]Superiority not determined.
Values are expressed as mean (SD) unless otherwise stated.
CI, confidence interval; SAE, serious adverse event; SD, standard deviation; FSMPG, fasting self-monitored plasma glucose; mITT, modified intent-to-treat; TEAE, treatment-emergent adverse event

Supported By: Sanofi (NCT02585674)

132-LB

Safety and Feasibility of Omnipod Hybrid Closed-Loop in Children Aged 6-12 Years with Type 1 Diabetes Using a Personalized Model Predictive Control Algorithm

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Children have enhanced insulin sensitivity compared to adolescents and adults with type 1 diabetes. We investigated the performance of an automated glucose control algorithm using the Omnipod® Insulin Management System in children with type 1 diabetes. The system included a modified version of Omnipod, Dexcom® G4 sensor and a personalized model predictive control algorithm. The study consisted of a 36-hour inpatient closed-loop assessment with announced meals ranging from 30-90 g of carbohydrates and limited physical activity. Subjects aged 6-12 y and A1C between 6.0-10.0% were eligible. Endpoints included sensor glucose percentage of time <70, 70-180, >180, >250 mg/dL and mean glucose. Clinical demographics for 12 subjects included (mean±SD): age 8.9±1.6 y, diabetes duration 4.3±2.3 y, A1C 7.8±0.8% and TDD 0.8±0.1 U/kg. Glycemic outcomes are reported in the Table. The mean percentage of time in range, 70-180 mg/dL, was 69.2% overall and 82.0% overnight. The mean fasting glucose following overnight closed-loop was 136±24 mg/dL. The Omnipod automated glucose control algorithm performed well and was safe during day and night use in children with type 1 diabetes.

Table. Glycemic Outcomes during Hybrid Closed-Loop.

Glycemic outcomes	Overall	Night (23:00 - 07:00)
Mean glucose (mg/dL)	157±20	149±24
Percentage time between 70-180 mg/dL (%)	69.2±12.6	82.0±19.9
Percentage time between 70-140 mg/dL (%)	38.2±16.1	32.8±30.6
Percent time <70 mg/dL (%)	2.0±2.6	0.1±0.3
Percent time >180 mg/dL (%)	28.8±13.5	22.0±30.0
Percent time >250 mg/dL (%)	6.7±5.5	2.1±5.8

For author disclosure information, see page LB107.

133-LB

Safely Eliminating Sliding Scale through a Hospital-Wide Conversion to Basal/Bolus Insulin vs. Implementation of an Electronic Glycemic Management System

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Background: Hyperglycemia occurs in >40% of our hospitalized patients and is associated with poor outcomes, including mortality, length of stay and surgical site infections. The standard of care in non-critical patients is subcutaneous (SubQ) basal bolus insulin (BBI). Despite best practice recommendations, sliding scale insulin (SSI) persisted across our hospital due to many challenges, including lack of diabetes and endocrinology expertise. An electronic glycemic management system (eGMS) was selected to facilitate the conversion of our system to BBI.

Methods: This Retrospective Quality Improvement Study describes the journey of clinicians at a 400-bed hospital to convert from high usage of SII to BBI. Clinical efforts through the support of hospital leadership included improving education for clinicians; increased utilization of BBI order sets, analysis of inpatient glucometrics, and safer insulin management. Inclusion: hyperglycemic adult patients prescribed insulin, with/without a diagnosis of diabetes. Education campaign: nursing/provider administered in collaboration with the vendor for Glucommander (GM), Glytec with hands-on classroom based training.

Results: Prior to implementation of eGMS, SSI was close to 95%, BBI at 5%. Within the first month of use, 96% usage of BBI was achieved. Baseline hypoglycemic events (% of BG <70mg/dL) were 7% compared to post eGMS implementation with GM at 1.74%. Baseline Hypoglycemia (% of BG <70mg/dL) in the ICU was 3% compared to GM at 1.5%. At the end of the 10-month duration of this case study, the number of patients that had received BBI was 4,804 at an average duration of treatment of 4.31 days on GM.

Conclusion: Improved education, order sets and the use of an eGMS significantly increased the percent of patients prescribed best practice BBI over SSI. GM also improved patient safety by reducing hypoglycemia 50-75% hospital wide.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—NONINSULIN INJECTABLES

134-LB

iGlarLixi Fixed-Ratio Combination vs. Insulin Glargine and Lixisenatide in Patients with T2DM Treated Previously with Two Oral Antidiabetics: LixiLan-O Subgroup Analysis

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If HbA_{1c} is uncontrolled after adding a 2nd oral antidiabetic (OAD) to Metformin, intensification strategies include: triple therapy with a 3rd OAD, a GLP-1 RA, or basal insulin (ADA/EASD); and non-insulin triple therapy or starting insulin-based combination treatment (NICE). iGlarLixi is a fixed-ratio combination of insulin glargine (iGlar) + lixisenatide (Lixi). The 30-week LixiLan-O trial (NCT02058147) treated patients (pts) with T2DM uncontrolled on Metformin ± a 2nd OAD with iGlarLixi, iGlar, or Lixi (OADs besides Metformin were stopped at study entry). Here we report a subgroup analysis of pts on 2 OADs according to randomization strata at screening for this trial. We assessed whether intensification to iGlarLixi was an effective treatment option following failure of 2 prior OADs (as approved in EU but not in U.S.). In each study arm, ~60% of pts had received a 2nd OAD (~86% of whom received sulfonylurea). In pts on 2 OADs at screening, significantly greater HbA_{1c} reductions were seen and significantly more pts achieved HbA_{1c} <7% with iGlarLixi than with iGlar or Lixi alone (Table). HbA_{1c} improvements did not come at the expense of additional hypoglycemia risk or body-weight gain (Table). In this LixiLan-O subanalysis, iGlarLixi was more effective than iGlar or Lixi in achieving HbA_{1c} <7% in pts requiring 2nd treatment intensification.

Table. Efficacy of iGlarLixi compared with iGlar and Lixi in LixiLan-O patients on 2 OADs according to randomization strata at screening

	iGlarLixi	iGlar	Lixi
LixiLan-O, n	469	467	234
Second OAD use at screening,* n (%)	291 (62.0)	288 (61.7)	146 (62.4)
Sulfonylurea, n (%)	257 (88.3)	247 (85.8)	122 (83.6)
DPP-4 inhibitor, n (%)	12 (4.1)	11 (3.8)	5 (3.4)
Glinide, n (%)	3 (1.0)	10 (3.5)	5 (3.4)
SGLT-2 inhibitor, n (%)	2 (0.7)	2 (0.7)	0
2 OADs received prior to screening			
Baseline demographics,* n	291	288	146
Age, mean ± SD	59.1 ± 9.9	59.2 ± 9.0	59.8 ± 7.4
Female, n (%)	154 (52.9)	144 (50.0)	65 (44.5)
White n (%)	260 (89.3)	260 (90.3)	134 (91.8)
Baseline characteristics,* n	291	288	146
HbA_{1c} % (Week −1), mean ± SD	8.0 ± 0.6	8.1 ± 0.7	8.1 ± 0.7
BMI (kg/m^2), mean ± SD	31.5 ± 4.4	31.3 ± 4.3	32.0 ± 4.3
Duration of diabetes (years), mean ± SD	9.2 ± 5.3	9.2 ± 5.8	9.1 ± 5.8
HbA_{1c} %,† n	290	285	145
Change from baseline (LOCF)	−1.5 ± 0.1	−1.2 ± 0.1	−0.7 ± 0.1
Difference (95% CI)		0.3 ± 0.1 (0.2, 0.4) p<0.0001	0.8 ± 0.1 (0.7, 1.0) p<0.0001
Patients reaching HbA_{1c} target,† n	290	287	145
<7%, n (%)	210 (72.4)	166 (57.8)	40 (27.6)
Proportion difference (95% CI)		−14.6 (−22.3, −6.9) p=0.0002	−44.8 (−53.7, −35.9) p<0.0001
Weight,† n	290	286	145
Change from baseline (LOCF)	−0.1 ± 0.3	1.3 ± 0.3	−2.3 ± 0.4
Difference (95% CI)		1.3 ± 0.3 (0.7, 1.9) p<0.0001	−2.3 ± 0.4 (−3.0, −1.5) p<0.0001
Hypoglycemia,‡§ n	291	288	145
Patients with events, n (%)	77 (26.5)	74 (25.7)	10 (6.9)
Events per patient per year, n	1.4	1.3	0.4

Data are LS mean ± SE unless noted otherwise.
*Randomized population; †mITT population; ‡Safety population; §Documented symptomatic hypoglycemia; symptoms typical of hypoglycemia accompanied by plasma glucose ≤70 mg/dL.
CI, confidence interval; HbA_{1c}, glycated hemoglobin; LOCF, last observation carried forward; LS, least squares; mITT, modified intent to treat; SD, standard deviation; SE, standard error.

Supported By: Sanofi

135-LB

A Hydrogel-Microsphere Drug Delivery System that Supports Once-Monthly Administration of a GLP-1 Receptor Agonist

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GLP-1 receptor agonists have emerged as a standard-of-care treatment for type 2 diabetes. Currently, available agonists can be administered subcutaneously once or twice daily, or once weekly. The longer-acting agonists show improved glucose control, decreased incidence of side effects and improved patient compliance. Nevertheless, poor medication adherence and persistence lead to failure of glycemic control in almost 50% of patients. With chronic diseases, compliance improves as the dosing interval increases.

We have developed an ultra-long acting delivery system to support once-monthly administration of a peptidic GLP-1R agonist. In preliminary studies, the GLP-1R agonist exenatide was covalently attached to hydrogel microspheres by a self-cleaving β-eliminative linker; after subcutaneous injection in rats the peptide was slowly released into the systemic circulation. However, the serum exenatide had a shorter half-life than expected, suggesting degradation of the peptide while in the subcutaneous depot. We unexpectedly found that exenatide undergoes spontaneous deamidation at Asn^{28} with an in vitro and in vivo half-life of approximately two weeks. The variant [Gln^{28}]exenatide shows stability for long periods, while having GLP-1R agonist activities as well as pharmacokinetic and pharmacodynamic effects in rodents indistinguishable from exenatide. Two different hydrogel-[Gln^{28}]exenatide conjugates were prepared using β-eliminative linkers with different cleavage rates. After subcutaneous injection in rodents, the serum half-lives for the released [Gln^{28}]exenatide from the conjugates were about two weeks and one month. Two monthly injections of the latter in the ZDF rats showed pharmacodynamic effects indistinguishable from two-months of continuously infused exenatide. Pharmacokinetic simulations indicate that the delivery system should serve well as a once-monthly GLP-1R agonist for treatment of type 2 diabetes in humans.

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136-LB

Arachidonic Acid and Lipoxin A4 Have Antidiabetic Actions

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ω-3 eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids and their metabolites: resolvin E1 and protectin D1 possess insulin-sensitizing and anti-steatotic actions in the ob/ob mice. High pancreatic n-3 fatty acids prevent streptozotocin-induced diabetes in fat-1 mice. In the present study, we noted that ω-6 and ω-3 fatty acids prevent alloxan and streptozotocin (STZ)-induced apoptosis of rat-insulinoma (RIN) cells in vitro. Of all the fatty acids tested, arachidonic acid (AA) is the most potent in preventing alloxan and STZ-induced apoptosis of RIN5F (rat insulinoma) cells and alloxan-induced type 1 diabetes and STZ-induced type 1 and type 2 DM in Wistar rats. This beneficial action of AA was not blocked by cyclo-oxygenase and lipoxygen-

ase inhibitors suggesting that prostaglandins and leukotrienes do not have a role in this process. This was confirmed by the observation that various prostaglandins, and leukotrienes did not prevent alloxan and STZ-induced apoptosis of RIN cells. Lipoxin A4 (LXA4), an antiinflammatory product of AA, prevented alloxan and STZ-induced apoptosis of RIN cells in vitro and type 1 and type 2 diabetes mellitus in experimental animals. AA enhanced LXA4 formation in RIN cells in vitro and enhanced plasma LXA4 levels in alloxan and STZ-treated animals. In addition, we noted that oral AA abrogated high-fat-STZ-induced type 2 DM in Wistar rats. AA treated HFD animals showed enhanced plasma LXA4 levels that coincided with reduced plasma glucose levels. Both oral and intraperitoneal routes of AA administration showed similar beneficial action in reducing hyperglycemia. Furthermore, AA and LXA4 enhanced the formation of BDNF that is known to have antidiabetic action. Plasma phospholipid content of AA was decreased in alloxan-treated animals and patients with type 2 DM. Plasma LXA4 levels are low in patients with type 2 DM. These results suggest that AA and its product LXA4 function as endogenous antidiabetic molecules.

Supported By: Indian Council of Medical Research

137-LB

iGlarLixi Fixed-Ratio Combination in Patients with HbA1c >9%: LixiLan-O Subgroup Analysis

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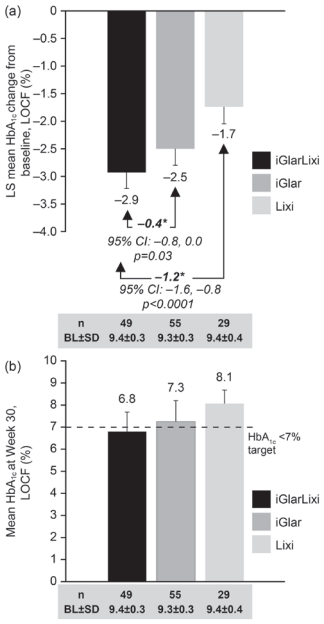
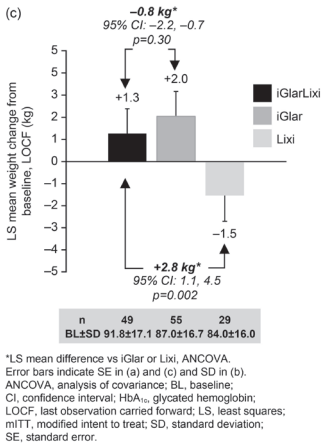
In patients (pts) with T2DM and HbA_{1c} ≥9% (75 mmol/mol), the ADA/EASD guidelines recommend considering a dual combination of Metformin + oral antidiabetics (OADs), a glucagon-like peptide-1 receptor agonist (GLP-1 RA), and/or basal insulin; NICE recommends premixed insulins. Both guidelines suggest that pts with high HbA_{1c} may require basal ± prandial insulin replacement to expedite reaching target HbA_{1c}. The 30-week randomized LixiLan-O trial (NCT02058147) treated pts with T2DM uncontrolled on Metformin ± another OAD with iGlarLixi (insulin glargine [iGlar] + lixisenatide [Lixi] fixed-ratio combination), iGlar, or Lixi. This LixiLan-O exploratory subgroup descriptive analysis, assessed whether iGlarLixi, which improves fasting and postprandial glucose, demonstrated findings consistent with the primary trial results in pts with baseline HbA_{1c} ≥9% (iGlarLixi, n=49; iGlar, n=55; Lixi, n=29). iGlarLixi showed greater HbA_{1c} reductions (–2.9%) at Week 30 vs. iGlar (–2.5%; least squares [LS] mean difference, –0.4%; p=0.03) and Lixi (–1.7%; LS mean difference, –1.2%; p<0.0001); only the iGlarLixi group achieved a mean HbA_{1c} <7.0% (Figure a, b). iGlarLixi also mitigated weight gain with iGlar (Figure c). In pts with HbA_{1c} ≥9%, iGlarLixi provided benefits generally consistent with the primary LixiLan-O analysis. These findings support iGlarLixi as part of stepwise intensification in pts with high HbA_{1c}.

Figures. (a) LS Mean HbA_{1c} Change from Baseline, (b) Mean HbA_{1c} Overall, and (c) LS Mean Weight Change from Baseline at Week 30 in LixiLan-O Patients with Baseline HbA_{1c}c ≥9% (mITT Population).





*LS mean difference vs iGlar or Lixi, ANCOVA.
Error bars indicate SE in (a) and (c) and SD in (b).
ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; HbA_{1c}, glycated hemoglobin; LOCF, last observation carried forward; LS, least squares; mITT, modified intent to treat; SD, standard deviation; SE, standard error.

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138-LB

Comparable Glycemic Control, Greater Weight Loss, and Lower Hypoglycemia with Once-Weekly Dulaglutide vs. Insulin Glargine, Both Combined with Lispro, in Type 2 Diabetes and Moderate-to-Severe Chronic Kidney Disease (AWARD-7)

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This phase 3 study compared once weekly dulaglutide (DU) to titrated daily insulin glargine, both combined with insulin lispro, in people with type 2 diabetes (T2D) and chronic kidney disease (CKD) stages 3-4. Participants were randomized (1:1:1) to DU 1.5 mg or DU 0.75 mg or titrated insulin glargine. The objective was to demonstrate DU noninferiority for A1c change after 26 weeks.

Baseline characteristics (N=576) included: [mean±SD] age 64.6±8.6 years, A1c 8.6±1.0%, eGFR 38.3±12.8 mL/min/1.73m^2, BMI 32.5±5.2 kg/m^2, daily insulin dose 58.2±31.8 U. DU was non-inferior to insulin glargine for A1c change (Table). Body weight decreased with DU, whereas it increased with insulin glargine. The hypoglycemia rate (≤70 mg/dL) was lower for DU 1.5 mg and 0.75 mg vs. insulin glargine (5.5, 7.8 and 17.1 events/participant/year; p<0.001). Nausea, vomiting and diarrhea were more common with DU 1.5 mg (19.8%, 12.0%, 15.6%) and DU 0.75 mg (11.1%, 5.8%, 13.7%) vs. insulin glargine (2.6%, 3.1%, 3.1%).

In conclusion, DU produced comparable glycemic control, greater weight loss, and lower hypoglycemia rate vs. insulin glargine in people with T2D and CKD stage 3-4.

Table.

Primary Endpoint (26 wk, mITT population (safety population for weight))	DU 1.5 mg (N=183)	DU 0.75 mg (N=180)	Insulin Glargine (N=186)
A1c change, % (primary)	-1.2 (0.1)†††***	-1.1 (0.1)***	-1.1 (0.1)**
Percentage of pt with A1c <7% / A1c <8%	37.5 / 78.3	31.7 / 72.6	34.6 / 75.3
Weight change, kg	-2.8 (0.4)**##	-2.0 (0.4)**##	1.1 (0.3)*

Data are reported as LSM (SE) unless otherwise indicated. †, †† multiplicity adjusted 1-sided p<0.001 for noninferiority versus insulin glargine with a 0.4% margin or 0.3% margin, respectively, *2-sided p<0.05 and **2-sided p<0.001 change from baseline, ##2-sided p<0.001 versus insulin glargine. Abbreviations: BMI=body mass index; CI=confidence interval; eGFR=estimated glomerular filtration rate (CKD-EPI creatinine equation); mITT=modified intent-to-treat; LSM=least squares mean; SE = standard error; pt=participant(s)

Supported By: Eli Lilly and Company

For author disclosure information, see page LB107.

139-LB

WITHDRAWN

140-LB

A Pilot Study in Adults with T1DM to Examine the Efficacy of Stable Nonaqueous Glucagon for Treatment of Severe Hypoglycemia

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Severe hypoglycemia remains a significant problem in patients with diabetes. Currently approved rescue products are based on lyophilized formulations, which require reconstitution at time of use, complicating administration in emergency situations. Xeris is developing a pre-mixed, ready-to-use, soluble liquid glucagon formulation in a pre-filled syringe and auto-injector. This glucagon injection formulation (G-Pen™) is expected to be stable for at least 24 months at room temperature. A pilot study was conducted in adults with T1DM to explore whether subcutaneously injected G-Pen™ glucagon (0.5 or 1 mg) could rescue subjects from insulin-induced hypoglycemia. After an overnight fast, subjects were given IV insulin in clinic to induce plasma glucose < 50 mg/dL for 5 minutes. Across 13 hypoglycemia induction procedures, IV insulin resulted in a mean plasma glucose of 44.8 ± 3.3 mg/dL just prior to treatment with glucagon. Following the 1 mg glucagon dose, 7/7 subjects achieved primary response with plasma glucose > 70 mg/dL in an average time of 11.3 minutes (range: 10-20 minutes). Following the 0.5 mg dose, 6/6 subjects achieved plasma glucose > 70 mg/dL in an average time of 13.6 minutes (range: 10-20). Symptomatic relief began within 5 minutes of dosing, and all subjects experienced complete resolution of hypoglycemia symptoms in a median time of 20 minutes (range 10-30). Overall, no significant safety concerns were noted in this pilot study. For the 1 mg dose, 3/7 subjects reported a total of 8 mostly mild treatment-emergent adverse events, including 3 cases of nausea/vomiting.

The results of this study provide support for Phase 3 clinical development of the G-Pen™ single-use auto-injector as a rescue treatment for severe hypoglycemia.

141-LB

DURATION-8 Randomized Controlled Trial 1-Year Results: Efficacy and Safety of Once-Weekly Exenatide (ExQW) Plus Once-Daily Dapagliflozin (DAPA) vs. ExQW or DAPA Alone

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In patients with T2D uncontrolled by Metformin (baseline HbA_{1c} 8-12%), dual therapy for 28 weeks with ExQW + DAPA reduced glycemia, weight and systolic blood pressure (SBP) significantly more than with ExQW + placebo (PBO) or DAPA + PBO alone with no unexpected safety signals (DURATION-8 trial: NCT02229396). Here, we examined these outcomes after a further 24 weeks of double-blind therapy. Of 695 patients randomized, 548 (78.8%) completed 52 weeks with only 3.6% discontinuing due to adverse events (AEs). At Week 52, greater reductions in HbA1c, FPG, 2-h PPG, body weight and SBP were observed with ExQW + DAPA vs. ExQW + PBO or DAPA+ PBO. Compared with Week 28, reductions in HbA1c in all treatment groups and treatment differences were maintained at Week 52. Reductions in estimated glomerular filtration rate at Week 1 with ExQW + DAPA and DAPA + PBO returned to baseline by Week 52 (Table). AEs occurring in ≥5% of patients were diarrhea, headache, injection site nodule, nausea, upper respiratory tract infection, and urinary tract infection. Serious AEs occurred in 4.8%, 5.2%, and 5.2%, respectively. Minor hypoglycemia occurred in 1.3%, 0%, and 0.4%. No major hypoglycemia was recorded.

In conclusion, ExQW + DAPA was well tolerated with no unexpected AEs, and the glycemic, weight, and SBP effects observed at Week 28 were maintained over 52 weeks.

Table.

	ExQW+DAPA N=228 n=184	ExQW+PBO N=227 n=174	DAPA+PBO N=230 n=190	ExQW+DAPA versus ExQW+PBO	ExQW+DAPA versus DAPA+PBO
HbA_{1c}, %					
BL mean (SD)	□	□	□	□	□
28w LSM change	9.34 (1.07)	9.30 (1.06)	9.30 (1.03)	□	□
from BL (SE)	–1.95 (0.09)	–1.58 (0.09)	–1.37 (0.09)	–0.37 (0.13)**	–0.58 (0.13)***
52w LSM change from BL (SE)	–1.72 (0.10)	–1.33 (0.10)	–1.19 (0.10)	–0.39 (0.14)**	–0.53 (0.14)***
FPG, mg/dL					
BL mean (SD)	□	□	□	□	□
28w LSM change	198.2 (54.2)	192.0 (50.4)	190.4 (47.3)	□	□
from BL (SE)	–65.0 (3.0)	–45.0 (3.0)	–48.5 (2.9)	–20.0 (4.0)***	–16.4 (4.0)***
52w LSM change from BL (SE)	–61.0 (3.0)	–43.8 (3.2)	–37.9 (3.1)	–17.2 (4.2)***	–23.1 (4.2)***
2h-PPG, mg/dL					
BL mean (SD)	□	□	□	□	□
28w LSM change	270.7 (66.4)	269.3 (66.6)	262.5 (60.8)	□	□
from BL (SE)	–87.0 (4.1)	–59.6 (4.3)	–61.4 (4.2)	–27.4 (5.2)***	–25.7 (5.2)***
52w LSM change from BL (SE)	–79.6 (5.1)	–64.6 (5.4)	–60.1 (5.2)	–15.1 (6.6)*	–19.6 (6.5)**
Body weight, kg					
BL mean (SD)	□	□	□	□	□
28w LSM change	91.8 (22.2)	89.8 (20.2)	91.1 (19.7)	□	□
from BL (SE)	–3.4 (0.3)	–1.5 (0.3)	–2.2 (0.3)	–1.9 (0.4)***	–1.2 (0.4)**
52w LSM change from BL (SE)	–3.2 (0.4)	–1.5 (0.4)	–2.2 (0.4)	–1.7 (0.5)**	–0.9 (0.5)
Systolic BP, mmHg					
BL mean (SD)	□	□	□	□	□
28w LSM change	130.1 (12.7)	129.1 (13.1)	130.0 (12.9)	□	□
from BL (SE)	–4.2 (0.8)	–1.3 (0.8)	–1.8 (0.8)	–2.9 (1.1)**	–2.4 (1.1)*
52w LSM change from BL (SE)	–4.5 (0.8)	–0.7 (0.9)	–2.6 (0.8)	–3.8 (1.1)***	–1.9 (1.1)
eGFR (CKD-EPI), ml/min/1.73m²					
BL mean (SD)	□	□	□		
1w mean change	98.0 (17.2)	97.7 (17.5)	97.1 (17.4)		
from BL (SD)	–3.8 (9.2)	–1.0 (10.6)	–3.9 (8.7)		
28w mean change	–1.0 (9.5)	–0.1 (8.4)	–1.3 (8.6)		
from BL (SD)	–1.9 (8.8)	–1.5 (8.8)	–0.9 (10.3)		
52w mean change from BL (SD)					

*p<0.05, **p<0.01, ***p<0.001 (p-values at 52w are nominal). BL, baseline, BP, blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; LSM, least-squares mean; N, number comprising the intention-to-treat analysis set; n, number completing 52 weeks of treatment; 2h-PPG, 2-hour post-prandial glucose; SD, standard deviation; SE, standard error; w, week.

142-LB

Dulaglutide vs. Glargine, Both Combined with Lispro, Mitigated eGFR Decline in People with Type 2 Diabetes and Moderate-to-Severe Chronic Kidney Disease (AWARD-7)

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In short-term studies, dulaglutide (DU) reduced albuminuria and did not change estimated glomerular filtration rate (eGFR) in people with type 2 diabetes (T2D) and normal kidney function. This phase 3 study compared weekly DU 1.5 mg or 0.75 mg to daily titrated insulin glargine (IG), both combined with insulin lispro, in people with chronic kidney disease (CKD) stages 3-4 and T2D. The study met its primary objective of DU noninferiority to IG in A1c reduction at 26 weeks. This pre-specified secondary analysis was designed to determine effects of DU on eGFR and albuminuria.

Baseline characteristics were similar between treatment groups ([mean±SD] eGFR (CKD-EPI): 38.3±12.8 mL/min/1.73m², A1c: 8.6±1.0%, age: 64.6±8.6 years, duration of T2D: 18.1±8.7 years, 30% (n=174/576) had eGFR <30 mL/min/1.73m², 45% (n=258/575) had urine albumin-to-creatinine ratio (UACR) >300 mg/g. At 26 weeks, eGFR remained stable with DU, but significantly decreased with IG (Table). UACR was lowered in all treatment groups. Results were driven by participants with UACR >300 mg/g who had less decline in eGFR with both DU doses and greater reduction in UACR with DU 1.5 mg.

In conclusion, DU mitigated eGFR decline in people with T2D and moderate to severe CKD. The DU effect to lessen loss of kidney function and reduce albuminuria was most evident in people with UACR >300 mg/g.

Table. Effects of dulaglutide and glargine on eGFR and albuminuria in the overall study participants and by UACR> 300 mg/g and UACR ≤300 mg/g at 26 weeks

Treatment arm	All Participants (N=576)		Participants with UACR >300 mg/g (n=258)		Participants w ith UACR ≤300 mg/g (n=317)	
	Δ eGFR, mL/min/1.73m²	Δ UACR, %	Δ eGFR, mL/min/1.73m²	Δ UACR, %	Δ eGFR, mL/min/1.73m²	Δ UACR, %
DU 1.5 mg (N=192)	-0.1# (-1.2, 1.0)	-27.7** (-38.7, -14.8)	-1.9*# (-3.5, -0.4)	-43.1**# (-54.7, -28.6)	0.3 (-1.0, 1.7)	-0.4 (-19.2, 22.8)
DU 0.75 mg (N=190)	-0.4# (-1.4, 0.7)	-26.7** (-37.9, -13.5)	-2.6*# (-4.2, -1.1)	-25.3* (-40.2, -6.8)	0.3 (-1.0, 1.7)	-18.0 (-33.6, 1.3)
Glargine (N=194)	-1.9** (-3.0, -0.9)	-16.4* (-29.0, -1.5)	-4.8** (-6.3, -3.4)	-14.3 (-30.9, 6.3)	-0.7 (-2.0, 0.7)	-5.7 (-23.2, 15.8)

Data presented as change from baseline LSM (95% CI); safety population. *2-sided $p < 0.05$ and **2-sided $p < 0.001$ change from baseline, #2-sided $p < 0.05$ and **2-sided $p < 0.001$ versus insulin glargine. Abbreviations: CI=confidence interval; DU=dulaglutide; eGFR=estimated glomerular filtration rate; IG=insulin glargine; LSM=least squares mean; UACR=urine albumin/creatinine ratio

Supported By: Eli Lilly and Company

Clinical Diabetes/ Therapeutics POSTERS

143-LB

The MetAP2 Inhibitor ZGN-1061 Improves Glycemia and Has Weight Loss Efficacy with an Improved Safety Profile in Preclinical Models

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Methionine aminopeptidase 2 inhibitors (MetAP2i) are a promising new therapeutic approach for the treatment of obesity, diabetes and associated metabolic complications. Beloranib is a prototype MetAP2i which, when tested in obese type 2 diabetes subjects, resulted in 13% weight loss and 2.0% reduction in HbA1c from baseline following 26 weeks of treatment. Beloranib development was discontinued due to an imbalance of venous thromboembolism events in the treated groups. A second generation MetAP2i, ZGN-1061, has been developed and is in Phase 1 clinical testing. ZGN-1061 shows similar effects on diabetes and metabolic endpoints as beloranib in animal models, but has greatly improved safety profiling in model systems of thrombotic risk. In rodent models of obesity and diabetes ZGN-1061 (0.1 to 0.3 mg/kg, QD, subcutaneous dosing up to 5 wk) showed potent reductions of HbA1c (-2% ± 0.19% from baseline) along with improved OGTT glucose AUC (-11%), peak glucose (-57 mg/dl), weight loss (-28% at week 4) via reduced body fat (-36%) in addition to plasma LDLc (-34%) and triglyceride (-46%) improvements. In dog toxicology models which exhibit signs of coagulopathy, ZGN-1061 has a margin of >150 fold compared to only ~4 fold for similarly effective doses of beloranib. This improvement appears to be explained by a differential endothelial cell (EC) activity that shows beloranib having a rapid and lasting effect on proliferation and thereby promoting a procoagulant increase of plasminogen activator inhibitor-1 and decrease of thrombomodulin in ECs with as little as 4-hour exposure. ZGN-1061, however, requires prolonged exposure of ECs (>24h) to induce such a state. The in vivo pharmacokinetic profile of ZGN-1061 has a much shorter duration of exposure and is undetectable less than 10 hours after administration.

144-LB

Single and Multiple Dose Evaluation of a Novel MetAP2 Inhibitor: Results of a Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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The methionine aminopeptidase 2 (MetAP2) inhibitor beloranib resulted in 13% weight loss and 2.0% reduction in A1C from baseline in obese T2DM subjects but development was halted due to its pro-thrombotic effect. Nonclinical studies of a 2nd generation MetAP2 inhibitor, ZGN-1061 (1061), showed a superior safety profile with a shorter half-life ($t_{½}$) that is hypothesized to reduce endothelial cell exposure and limit thrombosis. This Phase 1 clinical trial of 1061 assessed safety, pharmacokinetics (PK), and preliminary efficacy. The clinical trial included a single ascending dose (SAD) phase in healthy subjects (BMI 23-<30) and a multiple ascending dose (MAD) phase in subjects with BMI 27-40. SAD phase doses were 0.2, 0.6, 1.2, 2.4, 3.6, and 4.8 mg, and MAD phase evaluated 0.2, 0.6, and 1.8 mg twice weekly for 4 wks. SAD included 39 subjects (1061 N=28, placebo N=11), 90% male and BMI 26. 1061 maximum plasma concentrations (C_{max}) increased linearly with dose and occurred within 30 min, with $t_{½}$ less than 1 hr. 1061 was well tolerated across all doses with most frequent adverse events of mild headache and procedural site irritation. There were no severe or serious events and no events of venous thromboembolism. MetAP2 binding and evidence of MetAP2 inhibition increased with dose; maximal values were observed at doses ≥1.2 mg. MAD included 29 subjects (1061 N=22, placebo N=7), 76% male and BMI 33. PK and target engagement results were consistent with SAD findings although C_{max}, overall exposure, MetAP2 binding and MetAP2 inhibition increased after repeat dosing. Safety observations were comparable to the SAD phase. Efficacy measures indicated trends for greater weight loss and favorable biomarker changes with 1061 vs. placebo. Safety results indicate that 1061 was well tolerated with no safety signals or venous thromboembolic events in all doses tested, together with the PK profile and efficacy trends, support the evaluation in larger and longer clinical trials.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—ORAL AGENTS

145-LB

Satiety and Glycemic Control Enhancing Properties Vary between Functional Fibers, Mixed Salad, and a Novel Hydrogel (Gelesis100)

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Background: Viscoelastic properties of fibers confer benefits in satiety, weight management, and glycemic control. We compared these properties between common processed functional fibers, vegetables rich with natural fibers, and a novel hydrogel (Gelesis100) constructed from modified cellulose and citric acid to mimic ingested vegetables.

Methods: Equal amounts of pre-hydrated processed functional fibers (psyllium, guar gum, glucomannan), masticated mixed green salad, and Gelesis100 were subjected to sequential in vitro digestion in simulated gastric (SGF), small intestine (SIF), and colonic (SCF) fluids. Following digestion for 30-180 min in each simulated gastrointestinal (GI) fluid, samples were transferred to a rheometer (TA Instruments) for measurement of elastic modulus (G') and viscosity (η) in triplicate.

Results: During 30-180 min digestion in SGF, G' of Gelesis100 (594-950 Pa) approached those of mixed salad remnants (697-2,074 Pa), and both were several magnitudes higher than glucomannan (27-49 Pa), which had the highest elastic modulus among processed functional fibers tested. This pattern was maintained during a subsequent 120 min digestion in SIF (257-302 Pa, 105-543 Pa and 42-50 Pa, respectively). During the final 30 min digestion in SCF, Gelesis100 and mixed salad remnants lost their elastic component (G'~1 Pa), which is consistent with degradation by colonic esterases, while G' of glucomannan remnants was maintained. Loss moduli and viscosities were also measured and results were consistent with the elasticity pattern in the simulated GI transit.

Conclusions: In this in vitro model of GI digestion, Gelesis100 demonstrated a viscoelastic profile similar to masticated vegetables, and orders of magnitude superior to that of common processed functional fiber supplements. These data provide further evidence to explain the weight-loss and glycemic-control properties of this novel hydrogel.

146-LB

24-Week Efficacy and Safety of Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct Therapy to Insulin in Type 1 Diabetes (inTandem2)

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Sotagliflozin (SOTA) is a dual SGLT1 and SGLT2 inhibitor in Phase 3 development for type 2 diabetes (T2D) and as adjunct therapy to insulin in type 1 diabetes (T1D). SGLT1 inhibition delays and reduces glucose absorption in the proximal intestine, improving postprandial glycemic control. SGLT2 inhibition reduces renal glucose reabsorption.

Methods: In a double-blind, 52-week international Phase 3 trial, 782 adults with T1D treated with MDI or pump therapy, with A1C 7.0-11.0% at screening, were randomized 1:1:1 to placebo, SOTA 200 or 400 mg after a 6-week insulin optimization period. Baseline characteristics were comparable among groups. The primary outcome was change from Baseline in A1C at 24 weeks.

Results: SOTA 200 and 400 mg were statistically significant vs. placebo in lowering A1C and achieving the prespecified net benefit[a] endpoint. Overall incidences of TEAEs[b] were similar across groups. There were 2 deaths on placebo. There were more genital mycotic infections, diarrhea events, and DKA in the SOTA arms.

Conclusion: The international inTandem2 trial of SOTA as adjunct therapy to insulin met its primary endpoint with a statistically significant and clinically meaningful A1C reduction after 24 weeks, while demonstrating the general safety and tolerability of dual SGLT1 and SGLT2 inhibition in T1D. These results confirm the findings of inTandem1.

Table.

Efficacy and Safety Results from Randomization to Week 24 on a Background of Optimized Insulin Therapy			
	Placebo n = 257	SOTA 200 mg n = 261	SOTA 400 mg n = 263
Efficacy			
A1C at Screening, %	8.43	8.35	8.38
A1C at Baseline, after 6-week insulin optimization, %	7.80	7.74	7.71
A1C at Week 24, %	7.79	7.36	7.35
A1C at Week 24 LSM Change from Baseline, % (*p*-value)	-0.03 (p=0.54)	-0.39 (p<0.001)	-0.37 (p<0.001)
A1C at Week 24 LSMD vs. placebo[c], % (*p*-value)	N/A[e]	-0.36 (p<0.001)	-0.35 (p<0.001)
Patients with Safety Event			
Any TEAE, n (%)	132 (51.4)	146 (55.9)	143 (54.4)
AE as primary reason for early discontinuation of Core Treatment Period, n (%)	4 (1.6)	5 (1.9)	8 (3.0)
Serious adverse events, n (%)	9 (3.5)	11 (4.2)	11 (4.2)
Death, n (%)	2 (0.8)	0 (0)	0 (0)
DKA, n (%)	0 (0)	1 (0.4)	3 (1.1)
Severe hypoglycemia, n (%)	7 (2.7)	10 (3.8)	6 (2.3)
Diarrhea[d], n (%)	10 (3.9)	14 (5.4)	19 (7.2)
Genital mycotic infection, n (%)	4 (1.6)	19 (7.3)	22 (8.4)
Efficacy and Safety			
Net benefit [A1C < 7.0% at Week 24 and no SH and no DKA Randomization to Week 24], n (%)	39 (15.2)	83 (31.8)	85 (32.3)
Net benefit difference, % responders vs. placebo[c], n (*p*-value)	N/A[e]	16.6 (p<0.001)	17.1 (p<0.001)

LSM, least squares mean; LSMD, least squares mean difference; SH, severe hypoglycemia. [a]Net benefit: A1C <7.0% at Week 24 and no SH and no DKA from Randomization to Week 24. [b]TEAE: Treatment-emergent adverse event. [c]Statistical comparisons of each SOTA arm to placebo were preplanned and performed using a generalized linear model with repeated measures statistics. [d]Discontinuation of drug due to diarrhea was: 0.4% placebo, 0.4% SOTA 200 mg, and 0.8% SOTA 400 mg. [e]N/A: Not applicable.

[4]The Sotagliflozin inTandem2 Writing Group: Michael Brandle, Helmut Brath, Roger Davies, Edward Franek, Diane Gesty-Palmer, Jake A. Kushner, Darren K. McGuire, Heena Pandya, Anne L. Peters, and David R. Powell.

147-LB

12-Week Efficacy and Safety of Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct Therapy to Insulin in Young Adults with Poorly Controlled Type 1 Diabetes (JDRF Study)

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Sotagliflozin (SOTA) is a dual SGLT1 and SGLT2 inhibitor in Phase 3 development for type 2 diabetes (T2D) and as adjunct to insulin in type 1 diabetes (T1D). SGLT1 inhibition delays and reduces glucose absorption in the proximal intestine, improving postprandial glycemic control. SGLT2 inhibition reduces renal glucose reabsorption.

Methods: In a double-blind Phase 2 trial of young adults (age 18-30 years) with poorly controlled T1D (A1C ≥9.0%), 87 patients were randomized 1:1 to placebo or SOTA 400 mg once daily for 12 weeks. The primary outcome was change from Baseline in A1C at 12 weeks.

Results: SOTA decreased A1C by 0.35% compared with placebo (p=0.10). SOTA treatment resulted in lower postprandial glucose (PPG), higher net benefit[a], lower body weight, and lower A1C in a prespecified subgroup analysis (9.0% ≤ screening A1C ≤ 10.0%) than placebo. Overall incidences of treatment-emergent adverse events (TEAEs) were similar across groups. There were more genital mycotic infections and diarrhea events on SOTA. There was no DKA on SOTA.

Conclusion: In young adults with poorly controlled T1D, SOTA for 12 weeks as adjunct therapy to insulin, was well tolerated with evidence of improvements in glycemic control and weight reduction consistent with dual SGLT1 and SGLT2 inhibition.

Table.

Efficacy and Safety Results from Randomization to Week 12		
	Placebo (n = 42)	SOTA 400 mg (n = 43)
Efficacy		
A1C at Screening, % (SD)	10.3 (0.95)	10.6 (1.3)
A1C at Baseline, after 2-week screening + 2-week run-in, % (SD)	9.7 (0.93)	9.9 (1.4)
A1C at Week 12, % (SD)	8.7 (1.0)	8.4 (1.5)
A1C at Week 12, LSM Change from Baseline, % (SE, *p*-value[c])	-0.99 (0.15, p<0.001)	-1.33 (0.14, p<0.001)
A1C at Week 12, LSMD vs. placebo[b], % (SE, *p*-value[c])	N/A[f]	-0.35 (0.21, p=0.10)
A1C at Week 12, LSMD vs. placebo[b] with 9.0% ≤ screening A1C ≤10.0% , % (SE, *p*-value)	N/A[f]	-0.75 (0.26, p=0.006)
2-hr PPG LSMD vs. placebo[b], mg/dL (SE, *p*-value[c])	N/A[f]	-56.6 (16.6, p=0.001)
Daily CGM time in range 70-180 mg/dL vs. placebo[c] % (SE, *p*-value[c])	N/A[f]	+7.7% (3.9, p=0.057)
Daily CGM time in range 70-180 mg/dL vs. placebo, hours[g]	N/A[f]	+1.8 hours
Body weight LSMD vs. placebo[b], kg (SE, *p*-value[c])	N/A[f]	-2.4 (0.6, p<0.001)
Patients with Safety Events		
Any TEAE, n (%)	26 (61.9)	25 (58.1)
AE as primary reason for early discontinuation of treatment period, n (%)	2 (4.8)	0 (0)
Serious adverse event, n (%)	3 (7.1)	2 (4.7)
Diabetic ketoacidosis (DKA), n (%)	1 (2.4)	0 (0)
Severe hypoglycemia (SH), n (%)	2 (4.8)	1 (2.3)
Nausea[e], n (%)	3 (7.1)	1 (2.3)
Diarrhea[e], n (%)	0 (0)	2 (4.7)
Genital mycotic infection[e], n (%)	0 (0)	2 (4.7)
Efficacy and Safety		
Net benefit [A1C <7.0% at Week 12 and no SH and no DKA Randomization to Week 12], n (%)	1 (2.4)	7 (16.3)
Net benefit difference, % responders vs. placebo[b], n (*p*-value[c])	N/A[f]	13.9 (p=0.026)

CGM, continuous glucose monitoring; LSM, least squares mean; LSMD, least squares mean difference; PPG, postprandial glucose [a]Net benefit: A1C <7.0% at Week 12 and no SH and no DKA from Randomization to Week 12. [b]Statistical comparisons of each SOTA arm to placebo were preplanned and performed using a generalized linear model with repeated measures statistics. [c]Because the primary endpoint was not significant, *p*-values attached to nonprimary/secondary endpoints are descriptive and cannot be used to declare statistical significance. [d]Mild to moderate with no discontinuations. [e]N/A: Not applicable. [f]Estimated by assuming 100% of daily CGM data available for analysis; therefore, 1.0% of daily CGM time = 0.24 hours.

The Sotagliflozin JDRF Study Writing Group: Kathleen Bethin, Eda Cengiz, Thomas Danne, Diane Gesty-Palmer, Jake A. Kushner, Darren K. McGuire, Heena Pandya, Anne L. Peters, David R. Powell, Lisa Sherman, and R. Paul Wadwa.

Supported By: JDRF

148-LB

DS-8500a, a GPR-119 Agonist, Showed a Significant Glucose-Lowering Effect in Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control with Sitagliptin Therapy

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DS-8500a is an agonist of the G-protein coupled receptor 119 (GPR119). The efficacy and safety of DS-8500a as add-on therapy to sitagliptin in Japanese type 2 diabetes mellitus (T2DM) patients were evaluated in a 4-week, phase 2, multicenter, randomized, double-blind, placebo-controlled trial. Eligible participants were aged ≥20 years with HbA1c ≥7.0% and <9.0% and inadequate glycemic control with sitagliptin 50 mg monotherapy. Patients received 25 mg or 75 mg of DS-8500a, or placebo, orally. The primary endpoint was change from baseline at day 28 in 24-hr weighted mean glucose (WMG). Secondary endpoints included change from baseline in the following: fasting plasma glucose (FPG), 2-hr postprandial PG (PPG), total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides. Eighty-five patients were randomized (mean age 62.0 ± 9.4 years; mean HbA1c 7.58 ± 0.53%). Overall, 29, 28, and 27 patients in the placebo, 25-mg, and 75-mg groups, respectively, were analyzed. A significant dose-dependent reduction was observed in 24-hr WMG compared with placebo (–12.77 mg/dL, p=0.0044 and –15.71 mg/dL, p=0.0006 for the 25-mg and 75-mg groups, respectively). A significant reduction in FPG at 75 mg compared with placebo was observed (p=0.0003). At both 25 mg and 75 mg, significant reductions of 2-hr PPG (p=0.0018, p=0.0126, respectively), total cholesterol (p=0.0012, p<0.0001), and LDL-cholesterol (p=0.0022, p<0.0001) were observed, with a tendency to increase HDL-cholesterol and decrease triglycerides. Both doses of DS-8500a were well tolerated, and there were no significant treatment-emergent adverse events (AEs) or AEs leading to discontinuation during the study period. DS-8500a was well tolerated, and showed significant glycemic benefits and favorable changes in lipid profile over 28 days of administration in Japanese T2DM patients who have inadequate glycemic control with sitagliptin therapy.

Supported By: Daiichi Sankyo Company, Limited

149-LB

Estimated Glomerular Filtration Rate Corrected by HbA1c Determines Effects of SGLT2 Inhibitor Empagliflozin on Glycaemic Control and Renal Function in Type 2 Diabetes

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Aim: Glycemic control affects the assessment of glomerular filtration rate (GFR) in diabetic patients. To accurately assess GFR in diabetic patients, we have to take into account recent glycemic control state. Recently, the calculation formulae to assess estimated GFR (eGFR) corrected by HbA1c (eGFR(c)) have been reported (Diabetes Care 2014). In the present study, we evaluated the influence of eGFR(c) before the start of treatment in the effects of sodium glucose transporter-2 inhibitor, empagliflozin, on glycaemic control and renal function in Japanese type 2 diabetic patients.

Methods: Forty eight Japanese out-patients with type 2 diabetes treated with empagliflozin, were included in this analysis. All patients were divided into three groups by eGFR(c) before the start of treatment: Group 1; eGFR(c) < 60 ml/min (52.85 ml/min (eGFR: 60.28 ml/min)), Group 2; 60 ≤ eGFR(c) < 90 min/ml (72.94 ml/min (eGFR: 82.42 ml/min)), Group 3; ≥ 90 ml/min (101.58 ml/min (eGFR: 105.68 ml/min)). Changes of HbA1c, eGFR, and eGFR(c) were evaluated before and at 3 months after the start of empagliflozin.

Results: Empagliflozin significantly reduced HbA1c in Group 1 and 2. Improvement of HbA1c tended to be higher in Group 2 (-0.96%), than in Group 1 (-0.66%), and 3 (-0.40%), but the difference was not significant. eGFR(c) was significantly increased only in Group 2. Changes of eGFR(c) (eGFR) for 3 months were -1.76 ml/min (-4.60 ml/min), 4.88 ml/min (-0.72 ml/min), -6.35 ml/min (-9.32 ml/min) in Group 1, 2, and 3, respectively. Change of eGFR(c) was significantly higher in Group 2 than in Group 1 and 3, although there were no differences in change of eGFR for 3 months among three groups. Serum creatinine levels significantly increased in Group 3.

Conclusion: Improvement of glycaemic control by empagliflozin may be affected by eGFR(c) before the start of empagliflozin, and eGFR(c) improved in the patients with eGFR(c) from 60 ml/min to 90 ml/min.

150-LB

Effects of Canagliflozin (CANA) on Biomarkers of Cardiovascular (CV) Stress in Older Patients with Type 2 Diabetes Mellitus (T2DM)

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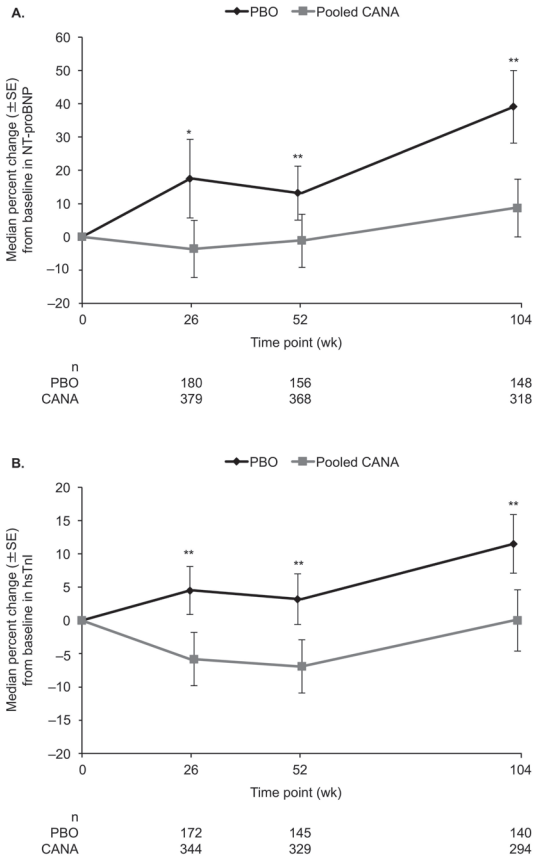
SGLT2 inhibitors may reduce CV risk in T2DM patients. In an exploratory analysis of a subset of T2DM patients (age 55-80 y, mean=64 y; 56% male, T2DM duration=12 y) randomized to placebo (PBO; N=216), CANA 100 mg/d (N=229) or CANA 300 mg/d (N=221) for 104 wks, serum levels of the CV stress biomarkers N-terminal pro-B type natriuretic peptide (NT-proBNP; Roche) and high sensitivity troponin I (hsTnI; Abbott) were measured. Median percent change from baseline (BL) was compared at wks 26, 52, and 104. For these analyses, CANA groups were pooled. BL characteristics were similar between groups. From a BL median of ≈50 pg/mL, NT-proBNP increased with PBO, but changed minimally with CANA over 104 wks (Figure). From a BL median of ≈3.3 pg/mL, hsTnI also increased with PBO, but was reduced or unchanged with CANA. Hodges-Lehmann estimates (95% CI) of the median percent differences between CANA and PBO at wks 26, 52, and 104, respectively, were -13.2% (-25.4, -1.7), -16.3% (-28.9, -4.0), and -27.6% (-43.2, -11.5) for NT-proBNP; and -8.3% (-14.0, -2.5), -11.9% (-18.0, -5.6), and -10.0% (-17.3, -2.6) for hsTnI (p<0.05 for each between-group difference).

In summary, CANA delayed rise in NT-proBNP and hsTnI over 2 y compared with PBO in older T2DM patients. These results suggest attenuation in CV stress with CANA, consistent with the anticipated CV protective effect of SGLT2 inhibitors.

Figure. Median Percent Change in (A) NT-proBNP and (B) hsTnI from Baseline to 26, 52, and 104 Weeks.



*Nominal p<0.05; **Nominal p<0.01. Nominal p values for the difference in median percent change between the CANA and PBO groups are based on the Wilcoxon rank sum test. SEs for the median percent change were estimated using the bootstrap technique by simulated repeated samples for each biomarker and treatment group. Results are data as observed for patients with values at baseline and at each specific time point.

Supported By: Janssen Global Services, LLC

151-LB

Discovery of ID11014A as a Novel GPR40 Agonist for the Treatment of Type 2 Diabetes

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GPR40 (G protein-coupled receptor 40) is involved in regulation of insulin secretion and agonistic activity of GPR40 enhances antidiabetic effect by increasing insulin in a glucose-dependent manner. While there have been multiple studies on the discovery of GPR40 agonists to target type 2 diabetes, most have ended in failed clinical trials. Here we identified ID11014A as a potent, selective, and novel GPR40 agonist which has been shown to significantly increase potency, with EC_{50} of 20 nM in Ca^{2+} influx assay (hGPR40). In an Oral glucose tolerance test (OGTT) using GK rat models, ID11014A (1-10 mg/kg) showed blood glucose-lowering effect dose-dependently without any risk of hypoglycemia. In addition, results from in vitro study of glucose-stimulated insulin secretion (GSIS) showed statistically significant correlation with results from in vivo evaluation. ID11014A increased insulin levels (1.53-fold at 5 μM), compared to DMSO vehicle in HIT-T15 cells, and also exhibited a significantly improved insulinotropic effect with increased relative blood insulin levels (3.55-fold), compared to vehicle group in SD rats. The leading compound TAK-875 was discontinued during its phase III clinical trial, most likely due to liver safety concerns. In response to this, we conducted in vitro studies to verify liver safety profiles. It was proven that ID11014A was less likely to induce drug-induced liver injury (DILI) in 3D hepatotoxiciy assay using human hepatic carcinoma cell lines with minimum effect concentration (MEC)'s scope of over 10 μM, based on the predicted approximated clinical C_{max} of 1.8 μM. Additionally, in transporter inhibition assays, ID11014A showed low risk of inhibitory effects. Results from these assays thus far have shown that ID11014A is safe in terms of liver toxicity. Overall, ID11014A exerts great efficacy with no known safety issue so far, and this compound will continue to be tested for a long-term efficacy and further toxicity evaluations.

Supported By: Ildong Pharmaceutical Co., Ltd.

152-LB

Pilot Testing of a Nurse-Facilitated Intervention "mWellcare": mHealth-Based Clinical Decision Support System for Management of Diabetes and Hypertension at Primary Care Settings in India

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Cardiovascular diseases (CVD) and diabetes are among the leading causes of premature adult deaths in India. Innovative approaches such as Clinical Decision Support System (CDSS) could play a major role in improving the quality and access to diabetes/hypertension care in primary care settings. In order to evaluate acceptability and feasibility of mWellcare intervention (nurse facilitated tablet computer based CDSS for management of diabetes and hypertension), pilot testing was done in the 5 Community Health Centres (CHCs) in 2 states of India. The mWellcare intervention was rolled out in 3 stages: 1.) setting up the intervention: provided mWellcare CDSS and equipment to each pilot CHC; 2.) orientation and training: conducted 5 day training of nurses and a 1 day on-site orientation of physicians on the use of mWellcare CDSS; 3.) observation and support: provided by study team during initial 3 days in each pilot CHC. During the 2 months pilot phase, a total of 631 patients diagnosed with diabetes and/or hypertension, were registered using mWellcare CDSS. Out of which, 65.6% of patients had hypertension, 14.7% had diabetes and 19.7% had both hypertension and diabetes. Physician agreement with the mWellcare generated Decision Support Recommendations (DSR) for diabetes and hypertension were 70% and 61%, respectively. The most common reason for disagreement was unavailability of mWellcare CDSS recommended drugs at the CHC. Nurses reported that the mWellcare intervention was helpful in performing their duties and improved their knowledge, skills and ability to manage their workload. Physicians reported that the DSR was useful as it reduced time spent and improved quality of patient assessment. Pilot testing of mWellcare intervention demonstrated that a nurse-facilitated, CDSS enabled intervention is feasible and acceptable at primary care settings in India.

Supported By: Wellcome Trust UK

For author disclosure information, see page LB107.

153-LB

Sitagliptin Improves Glucose Tolerance and Serum Triglyceride Levels in Overweight, Prediabetic Caucasian Men

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Objectives: The DPP-4 inhibitor sitagliptin inhibits the degradation of GLP-1 thereby ameliorating glucose intolerance, dyslipidemia and fat accumulation in type 2 diabetes patients. Since the effect of sitagliptin in prediabetes is unclear, the aim of this study was to evaluate the effect of sitagliptin on glucose tolerance, plasma lipids, energy expenditure and brown fat, white fat and skeletal muscle metabolism in overweight prediabetic men.

Methods: A randomized double-blinded placebo-controlled study was conducted in overweight, prediabetic white Caucasian men (aged 45.9±6.2 years; BMI 28.6±2.7 kg/m^2). Subjects received sitagliptin (100 mg/day) (n=15) or placebo (n=15) for twelve weeks. Before and after treatment, fasting venous blood samples were obtained, and brown and white fat volume and activity (cold-induced [^{18}F]FDG PET-/CT), resting energy expenditure (indirect calorimetry), and body composition (DXA) were assessed. In addition, skeletal muscle biopsies were obtained and an OGTT was performed.

Results: Sitagliptin, but not placebo, improved glucose excursion (AUC -14%; p<0.001) after OGTT and lowered serum triglycerides (-29%; p=0.054) without altering body composition, energy expenditure, substrate preference, or skeletal muscle mRNA expression of genes involved in glucose and lipid metabolism or mitochondrial function. Although sitagliptin did not influence [^{18}F]FDG uptake by brown fat, interestingly sitagliptin increased [^{18}F]FDG uptake in subcutaneous white adipose tissue (+45%; p<0.05).

Conclusion: Twelve weeks of sitagliptin treatment in overweight prediabetic white Caucasian men improves glucose tolerance, lowers serum triglyceride levels and might induce browning of subcutaneous white adipose tissue. Studies on the effect of sitagliptin on preventing or delaying the progression of prediabetes and dyslipidemia in individuals at risk for developing type 2 diabetes are warranted.

Supported By: Merck Sharp & Dohme Corp.

154-LB

DS-8500a, a GPR-119 Agonist, Enhanced Insulin Secretory Capacity in a Hyperglycemic Clamp Study in Patients with Type 2 Diabetes Mellitus

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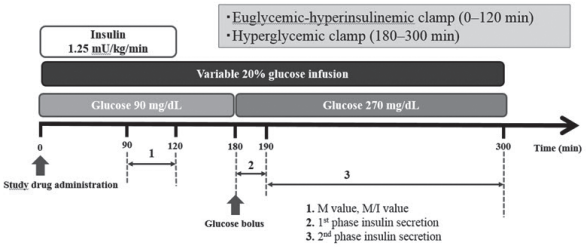
DS-8500a is an agonist of the G-protein coupled receptor 119 (GPR119). Effects of DS-8500a on insulin secretory capacity and its safety were evaluated in a 4-week, phase 2, randomized, double-blind, crossover study in 21 type 2 diabetes mellitus (T2DM) patients in Japan. T2DM patients aged ≥20 years with HbA1c ≥7.0% and <9.0% were enrolled. At each period, the patients received 75 mg of DS-8500a or placebo orally daily for 4 weeks in random order. A combined euglycemic-hyperinsulinemic and hyperglycemic clamp test was performed to assess insulin secretion before and after each 4-week treatment period (Figure 1). The primary endpoint was 1st-phase secretion (insulin $AUC_{180\text{-}190\ min}$ and C-peptide $AUC_{180\text{-}190\ min}$) and 2nd-phase secretion (insulin $AUC_{190\text{-}300\ min}$ and C-peptide $AUC_{190\text{-}300\ min}$). The secondary endpoints were insulin sensitivity (M value) from 90 to 120 min, and disposition index (DI). DS-8500a significantly increased 1st- and 2nd-phase insulin AUC (p=0.0011, p=0.0112) and C-peptide AUC (p=0.0012, p<0.0001) compared with placebo. At the end of the treatment period, M values were comparable with those of placebo, while the DI for insulin and C-peptide were significantly increased (p=0.0108, p=0.0002). No significant treatment-emergent adverse events were observed. DS-8500a enhanced insulin secretory capacity but not insulin sensitivity in the study period.

Figure 1. Combined Euglycemic-Hyperinsulinemic and Hyperglycemic Clamp Procedure.



155-LB

Therapeutic Utility of Liver-Specific Acetyl-CoA Carboxylase Inhibition for the Treatment of NAFLD

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Pharmacologic inhibition of the acetyl-CoA carboxylase (ACC) enzymes, ACC1 and ACC2, offers an attractive therapeutic strategy to simultaneously inhibit fatty acid synthesis and stimulate fatty acid oxidation, favorable outcomes in treating obesity, nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2D). In this regard, our lab and others have previously shown that inhibition of hepatic ACC1 and ACC2 improves dyslipidemia and reduces hepatic steatosis in rodent models of obesity. However, the effects of ACC inhibition on hepatic mitochondrial oxidation, anaplerosis, and ketogenesis in vivo are unknown. Here, we evaluated the impact of a novel liver-directed allosteric inhibitor of ACC1 and ACC2 on these parameters, as well as glucose and lipid metabolism, in control and diet-induced rat models of NAFLD. Specifically, we demonstrate that acute treatment of chow-fed rats with 10 mg/kg of the inhibitor preferentially inhibits enzymatic activity in the liver and significantly reduces hepatic malonyl-CoA levels. Using stable isotope tracer methods, we show that acute treatment enhances hepatic ketogenesis by 50% (P=0.001), indicative of increased hepatic fat oxidation. Furthermore, administration (10 mg/kg/day x 6 days) to high-fructose fed rats results in a 20% reduction in hepatic de novo lipogenesis (P=0.01). Collectively, these studies warrant further investigation into the therapeutic utility of liver-directed inhibition of ACC for the treatment of NAFLD and hepatic insulin resistance.

Supported By: National Institutes of Health

156-LB

Efficacy of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors in Type 1 Diabetes: A Systematic Review and Meta-analysis

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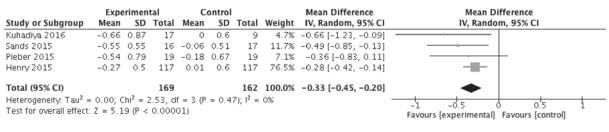
Sodium-glucose cotransporter 2 (SGTL2) inhibitors are currently FDA approved for the management of type 2 diabetes. The primary objective of this study was to systematically review the available evidence of their effects on glycemia and body weight (BW) in patients with type 1 diabetes by performing a meta-analysis of randomized-controlled trials (RCTs). A systematic search from PubMed, Embase, Web of Science, Scopus, and Cochrane Library databases was conducted through January 2017. We identified four RCTs examining the effects of SGLT2 inhibitors as add-on therapy on A1c and BW in patients with type 1 diabetes. We calculated weighted mean differences (WMDs) and 95% confidence intervals (CIs) using a random-effects model. Compared to placebo, SGLT2 inhibitors showed significant improvement in A1c (WMD -0.33; 95% CI -0.45, -0.20), but not in BW (Figure). Subgroup analysis of high-dose SGLT2 inhibitors showed significant improvement in BW (WMD -3.70; 95% CI -6.91, -0.48). In evaluating the pre- and post-effects of SGLT2 inhibitors, there was a significant improvement in both A1c (WMD -0.63; 95% CI -0.76, -0.49) and BW (WMD -1.77; 95% CI -2.38, -1.15).

In conclusion, this study demonstrates that various SGLT2 inhibitors significantly lower A1c and may be a viable option for patients with type 1 diabetes.

Figure. Effects of SGLT2 Inhibitors on A1c.



157-LB

Delayed-Release Metformin Targeting the Lower Bowel Elicits Sustained Improvements in A1c and Fasting Glucose with Minimal Systemic Exposure

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Delayed-release Metformin (Met DR) is being developed for T2DM patients with chronic kidney disease (CKD 3B/4). This blinded study evaluated 571 subjects over 16 weeks of double-blind Met DR (600, 900, 1200, 1500 mg QD) or Placebo (PBO) in subjects with T2DM; unblinded 2000 mg (1000 mg BID) immediate-release Metformin (Met IR; 1000 mg QD for first week) was included as a reference. Due to Met IR restrictions of use/contraindication

For author disclosure information, see page LB107.

in CKD 3B/4, only CKD 1/2 subjects were enrolled. Data are LS mean±SE change from baseline in the mITT population (≥1 post-baseline A1c).

542 subjects (56 y; 53% male; 7.9±6.7 y T2DM; BMI 32±5 kg/m^2; A1c 8.6±0.9%) were included in the mITT population. Met plasma exposure with Met DR was ≤37% of Met IR. Met DR resulted in a significant ($p<0.05$) dose-dependent A1c reduction with no plateau (1200 mg: -0.49±0.13%; 1500 mg: -0.62±0.12%; PBO: -0.06±0.13%). Met IR 2000 mg elicited a -1.10±0.13% A1c improvement. Fasting plasma glucose (FPG) improvement ($C_{average\ Week\ 4\text{-}16}$) was significantly greater with 900-1500 mg Met DR vs. PBO, and the effect with 1500 mg Met DR approached that of 2000 mg Met IR (-25.1±4.1 vs. -32.6±4.2 mg/dL, respectively; ns). Thus, 1500 mg Met DR exhibited 1.5-fold (A1c) and 2.1-fold (FPG) greater relative efficacy than Met IR when adjusting for plasma met exposure. Adverse events were primarily gastrointestinal and incidence was lower with Met DR (<16% at all doses) vs. Met IR (28%). Nausea incidence was markedly lower with Met DR (1-3% vs. 10% Met IR), likely due to Met DR bypassing the stomach.

The improved efficacy relative to plasma exposure with Met DR may result in an improved benefit/risk profile for patients with CKD 3B/4 for whom minimizing exposure is desirable. Delivery of Met DR at higher doses may result in greater efficacy but at the expense of increased systemic exposure. Importantly, reducing current Met dosage in an attempt to achieve the low exposure of Met DR would result in a disproportionate loss in efficacy.

158-LB

Inhibition of IKKε and TBK1 Improves Glucose Control in Patients with Type 2 Diabetes

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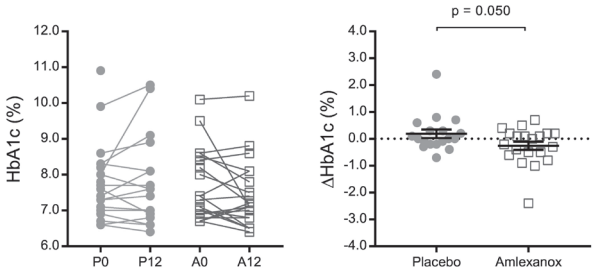
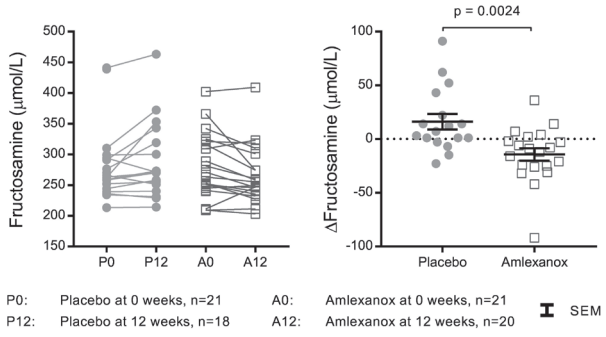
The inflammatory kinases IKKε and TBK1 are over-expressed in obesity. Amlexanox (A; an approved treatment of asthma in Japan and for aphthous ulcers in the U.S.) was shown to be a potent inhibitor of IKKε/TBK1 and corrected hyperglycemia, obesity and fatty liver in mice. We therefore tested the metabolic effects of oral A therapy in patients with these conditions. 42 patients (22M/20F, age: 58±1, mean±SEM) with T2DM on oral medications, on a stable regimen >12 weeks with HbA1c 6.5-10.5%, BMI (34.3±0.7) kg/m^2 and NAFLD (confirmed by U.S.) were randomized to receive either placebo (P) or 50 mg amlexanox (A), t.i.d. for 12 weeks (NCT01842282). The primary end point was improvement in HbA1c. 38 patients completed the study (18 P, 20 A). The reduction of HbA1c was significantly different with A at 12 weeks (P: 0.19 ± 0.16%, A: -0.26 ± 0.15%, p=0.050). 7 patients in the A group had a clinically meaningful 0.5% decrease in HbA1c vs. only 1 in the P group (p=0.02). Fructosamine levels were also reduced (P: 16±7 ± 0.16 µmol/L, A: -14±6 µmol/L, p=0.0024). In post-hoc analyses, the patients who had a clinically meaningful response to A showed a distinct inflammatory gene expression signature from biopsied subcutaneous fat at baseline. They also exhibited a unique pattern of changes in response to A consistent with increased energy expenditure. These data suggest that IKKε/TBK1 inhibitors may hold promise for treatment of metabolic disease in humans.

Figure. Change in Glucose Control in the Trial.





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159-LB

Assessment of Therapeutic Effects of Acarbose and Metformin under Different β-Cell Function Status in Chinese Patients with Newly Diagnosed Type 2 Diabetes: Based on MARCH Trial

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The data of MARCH (Metformin and acarbose in Chinese as the initial hypoglycaemic treatment) trial demonstrated that acarbose and Metformin have similar efficacy as initial therapy for HbA1c reduction in Chinese patients with newly diagnosed type 2 diabetes. We investigated whether the therapeutic efficacy was diversified under different β-cell function status. All 784 subjects were divided into better β-cell function group, medium β-cell function group and poor β-cell function group [median HOMA-β 88.18(74.38-114.62)], 47.61(41.22-55.62) and 21.91(16.47-27.71), respectively]. Patients were assigned to 48 weeks of therapy with acarbose or Metformin, respectively. Both acarbose and Metformin significantly decreased HbA1c levels similarly after 48 weeks in all groups. In poor β-cell function group, the decreases of weight and BMI after acarbose treatment were significant compared to Metformin group [-2.80 (-3.53 to -2.07) vs. -1.78 (-2.39 to -1.17), and -1.02 (-1.30 to -0.75) vs. -0.65 (-0.87 to -0.42), both $P < 0.05$, respectively]. Moreover, in poor β-cell function group, the decreases of FBG, PBG and HbA1c% after acarbose or Metformin treatment were significant compared to better β-cell function group at 48 weeks [-1.87 (-2.13 to -1.61) vs. -1.37 (-1.57 to -1.18), $P < 0.01$, -3.19 (-3.68 to -2.70) vs. -2.14 (-2.54 to -1.75), $P < 0.01$, and -1.22 (-1.41 to -1.03) vs. -0.97 (-1.12 to -0.82), $P < 0.05$, respectively]. Thus, acarbose treatment may contribute a similar effect to plasma glucose control compared to Metformin, even under the pathologic condition of β-cell.

160-LB

A Comparative Assessment of CNX-013-B2 (B2), a Selective Rexinoid, and Pioglitazone (PIO) in the Control of Hyperglycemia, Body Weight, and Hemodynamic Parameters in mZDF Rats

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We have previously reported that B2, a selective, small molecule rexinoid, demonstrated robust anti-hyperglycemic, anti-lipidemic, anti-obesity effects in various animal models of T2DM, improved exercise endurance in Diet Induced Obese mice on high fat diet (HFD) and did not cause hepatomegaly, edema or decrease hematocrit in treated animals. In this study 6 week old male Zucker Diabetic Fatty (mZDF) rats (N= 6), with ad libitum access to food (Purina, Research Diet) and water, were treated with either 10mg/kg B2 or 10mg/kg Pio for 18 weeks. Compared to the Zucker lean control rats the mZDF rats displayed significant increase in serum fasting (95.8 vs. 498.83 mg/dl) and fed glucose levels (141.1 vs. 531.50 mg/dl) and HbA1c at the end of the study.

Compared to mZDF control animals: Treatment with Pio displayed robust control of fasting (498.8 vs. 142.5 mg/dl) and fed (531.5 vs. 140.3 mg/dl) glucose and HbA1c (9.35 vs. 4.03%), but resulted in a drastic increase in body weight (408 vs. 868 g) while treatment with B2 significantly controlled fasting (498.8 vs. 242.4 mg/dl) and fed (532.5 vs. 330.5 mg/dl) glucose levels and HbA1c (9.35 vs. 6.32%), but unlike Pio caused only a modest increase in body weight (408 vs. 576 g).

Treatment with B2 and Pio displayed differential effects on visceral (3.7X vs. 7.3X), inguinal (1.9X vs. 2.96X) adipose tissue weight and heart weight (1.2X vs. 1.6X).

Treatment with B2 significantly increased end diastolic volume (Ved: 153 vs. 229.6µl) and significantly reduced end diastolic pressure (Ped: 8.67 vs. 6.57 mmHg) and systolic pressure (Pes: 101.39 vs. 88.07mmHg). In contrast Pio treatment did not either improve Ved or reduce Pes and Ped.

Study supports hypothesis that improved hemodynamic parameters in B2 treated mZDF rats could be due to a combination of glycemic and body weight control and independent action on cardiac tissue. Histopathological observations of cardiac tissue will be discussed.

161-LB

Effects of DA-1241, a Novel GPR-119 Agonist, on Lipid Control in Disease Models Mediated by Regulating an AMPK/SREBP1c Signaling Path

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DA-1241 is a novel, potent and selective GPR119 agonist under early clinical development, which was reported to have sustained antidiabetic effects in diabetic animal models. The purpose of the herein study is to investigate the lipid-lowering effects of DA-1241 in disease models and to explore the underlying mechanisms.

Chronic administration of DA-1241 completely normalized the plasma triglycerides (TG) levels and thereby decreased hepatic TG accumulation in dyslipidemic mice. The lipid lowering effect of DA-1241 was comparable to GSK-263A and synergistically augmented by combination therapy with sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, through enhancing the incretin effects. DA-1241 treatment also significantly alleviated plasma cholesterol levels in a same mice model and attenuated the disease progression with a comparable efficacy to atorvastatin in high cholesterol-fed rats. When DA-1241 was acutely given to normal mice by oral gavage prior to corn oil loading, the postprandial TG excursion was dose-dependently suppressed, which seemed to partly contribute to the chronic lipid control in high fat-fed mice. In cell-based experiments using human hepatoma cells, DA-1241 treatment activated AMP-activated protein kinase (AMPK), increased phosphorylation of sterol regulatory element-binding transcription factor (SREBP)1c, an inhibitory form of SREBP1c, decreased total SREBP1c expression, and hereby suppressed the downstream lipogenic signals. Moreover, we found that DA-1241 modulated the protein expression of SREBP1c and phospho-p38 kinase levels altered by a liver X receptor (LXR) agonist in an opposite way.

Our findings suggest i) the therapeutic potential of DA-1241 for the treatment of dyslipidemia, ii) further metabolic benefits other than glucose control when co-treated with DPP-4 inhibitors, and iii) the further elucidation for the potential underlying mechanisms of GPR119 agonist in lipid control.

162-LB

Endogenous Glucose Production Increase with SGLT2 Inhibition Is Unchanged by Denervation in Renal Transplant Patients

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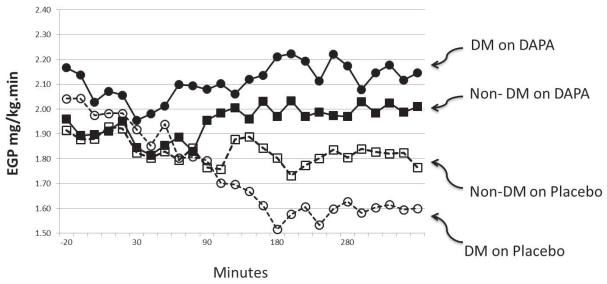
SGLT2 inhibition causes a "paradoxic" increase in EGP, indicating the presence of a "reno-hepatic axis." However, the mechanism(s) behind the increase in EGP has yet to be elucidated.

The aim of the study was to assess the effect of SGLT2 inhibition on EGP and hormone substrate response in type 2 diabetic (DM) and nondiabetic (non-DM) subjects after renal transplantation. After an overnight fast, DM and non-DM renal transplant subjects underwent measurement of EGP with 8 hour 3-3Hglucose infusion on 2 separate days. Each subject received dapagliflozin (DAPA) 10mg or placebo (PBO) in random order, followed by serial measurement of fasting plasma insulin (INS), C-peptide, glucagon (GNG) and glucose (FPG) concentration. Eight subjects were enrolled (DM=3, non-DM=5); Age= 47±5; BMI= 30.4±2.1; A1c= 7.2±0.1 vs. 5.4±0.1%; FPG= 132±3 vs. 98±2 mg/dl, respectively. During the EGP test, the DM group on DAPA had a significant decrease in FPG (132±3 to 107±3 mg/dl) and INS (14±1 to 10±1), while GNG (66±4 to 77±1) increased compared to PBO. In non-DM group on DAPA there was a significant decrease in FPG and INS compared to PBO and no change in GNG. After 30 min of DAPA administration, EGP significantly increased in both groups whereas there was the expected decrease in EGP with placebo during fasting.

Conclusion: Renal denervation in transplanted patients did not obliterate the EGP response to dapagliflozin.

Figure. Effect of DAPA and PBO in Diabetic (DM) and Nondiabetic Renal Transplant Subjects.



163-LB

Linagliptin Exerts an Antiinflammatory and Insulin Signaling Promoting Effects in Well Controlled Patients with Type 2 Diabetes

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We have previously shown an acute and a long term antiinflammatory effect of sitagliptin, a DPP-4 inhibitor, in patients with type 2 diabetes. We have now investigated the potential antiinflammatory effects of linagliptin in patients with well controlled type 2 diabetes. Twenty-four patients with well-controlled type 2 diabetes were divided into 2 groups of 12 patients each. One group was treated with linagliptin 5 mg daily and the other was treated with placebo. Blood samples and adipose tissue biopsies were collected prior to and 12 weeks after treatment. Blood samples were also collected following a high fat high calorie (HFHC) meal administered before and after 12 weeks of treatment. At 12 weeks, HbA1c had fallen significantly from 6.8±0.2% to 6.5±0.2%. Reactive oxygen species (ROS) generation by polymorphonuclear cells (PMN) was significantly lower by 21±7%, plasma lipid peroxide levels measured as TBARS had fallen by 18±7% as had intranuclear NFκB binding by mononuclear cells (MNC) fell by 16±6% in fasting blood samples. The expression of IL-1β and JNK-1 in MNC had also diminished significantly by 29±7% and 24±10%, respectively at 12 weeks. In the adipose tissue, the expression of TNF-α and JNK-1 was significantly lower (by 24±10% and 26±12%, respectively) while that of insulin receptor, IRS-1 and GLUT-4 was significantly higher (by 41±18%, 57±16% and by 62±15%, respectively) in the fasting state following 12 weeks of treatment. Following the administration of a HFHC meal, ROS generation by PMN and MNC was diminished, as was the expression of JNK-1 in the linagliptin treated group in addition to a significantly diminished glucose excursion and a trend towards increased GLP-1 and insulin secretion.

We conclude that linagliptin exerts antiinflammatory and insulin signal transduction promoting effects even in well controlled patients with type 2 diabetes.

Supported By: Boehringer Ingelheim

164-LB

GOAL-RCT: A Randomized Trial Comparing Colesevelam vs. Ezetimibe in Type 2 Diabetes

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Lipid-lowering therapies are often added to statin drugs in patients with type 2 diabetes (T2D) who fail to achieve target LDL. Our objective was to compare the efficacy and safety of two second-line LDL lowering options: colesevelam (COL) vs. ezetimibe (EZE) in T2D.

GOAL-RCT is the first randomized controlled trial comparing open-label COL vs. EZE in T2D patients with uncontrolled A1c (7-10%) and LDL cholesterol (>77.2 mg/dl) (NCT02682680). T2D medications were unchanged during the trial. The primary outcome was the proportion of patients achieving A1c ≤7.0% and LDL ≤77.2 mg/dl (≤2 mmol/L).

GOAL-RCT enrolled 200 subjects with comparable baseline characteristics: mean age 59 ± 10 years, mean A1c 8.0%, mean LDL 97.2 mg/dl with 97% subjects on statin drugs. 3-month data was available for 85 COL patients and 98 EZE patients. The proportion of patients achieving A1c ≤7.0% and LDL ≤77.2 mg/dl by 3 months in the COL arm (14%) was non-inferior to the proportion in the EZE arm (9%) (Table 1). The COL arm had a smaller reduction in LDL (-10.8 vs. -25.2 mg/dl; p<0.01), and a greater reduction in A1c (-0.4% vs. 0%; p<0.01) compared to EZE. Fifteen COL patients and 6 EZE patients discontinued study treatment (7 and 5 subjects due to adverse effects, respectively).

When used in combination with statin therapy in patients with T2D, ezetimibe produced greater reductions in LDL cholesterol whereas colesevelam produced greater reductions in A1c at 3 months.

Table 1. Comparison of Clinical Efficacy Parameters at 3 Months between Colesevelam and Ezetimibe among Subjects with Type 2 Diabetes.

	colesevelam (n=85)		ezetimibe (n=98)		Between-group difference (95% CI) (ezetimibe as reference)
Proportion achieving A1c ≤ 7.0 and LDL ≤2.0	14.0%		9.2%		-5.1% (-13.8 to 3.6%)
Proportion achieving A1c ≤ 7.0%	35.3%		14.3%		-20.0% (-33.7% to -7.8%)
Proportion achieving LDL ≤ 77.2 mg/dl (≤2 mmol/L)	43.5%		69.4%		25.9% (10.8% to 39.7%)
	Baseline	**3 month Δ**	**Baseline**	**3 month Δ**	**Between-group difference (95% CI)**
A1c (%)	8.0 ± 0.9	-0.4 ± 0.92	8.0 ± 0.8	0.0 ± 0.7	-0.4* (-0.6 to -0.1)
A1c (mmol/mol)	63.9 ± 9.9	-4.0 ± 10.1	64.0 ± 9.1	0.1 ± 7.6	-4.1* (-6.7 to -1.6)
LDL (mg/dl)	97.8 ± 24.3	-10.8 ± 33.1	96.6 ± 21.3	-25.2 ± 31.1	14.4* (4.9 to 23.8)
Non-HDL (mg/dl)	127.8 ± 29.0	-12.6 ± 37.9	123.2 ± 27.6	-28.6 ± 38.3	16.0* (4.7 to 27.3)

* significant difference between groups (P<0.05).
Data is presented either as a proportion, or as mean ± standard deviation.

Supported By: Valeant Pharmaceuticals International

165-LB

Dapagliflozin Is Associated with Lower Risk of Hospitalization for Kidney Disease, Heart Failure, and All-Cause Death Compared to DPP-4i: CVD-REAL Nordic

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Main goals of T2D management is to prevent morbid complications, including renal and cardiovascular disease (CVD). We aimed to investigate associations of hospitalization for kidney disease (HKD), hospitalization for heart failure (HHF) and all-cause death (ACD) between new users of either dapagliflozin or DPP-4i in T2D patients.

All patients dispensed with glucose lowering drugs during 2013-2016 were identified in nationwide registries in Norway and Sweden. Patients were divided in two groups; new users of dapagliflozin and new users DPP-4i, matched 1:3 by propensity score of dapagliflozin use calculated by using extensive data on patient characteristics, co-morbidities and drug treatment. Cox survival models estimated hazard ratio per country and weighted averages are presented.

A total of 34,328 T2D patients were identified as new users of dapagliflozin (n=8582) or DPP-4i (n=25,746). The groups were well balanced at baseline; 61 years, 41% women, 21% CVD, 19% microvascular disease, 1% kidney disease, mean follow-up 0.98 years, a total of 33,612 patient-years. Dapagliflozin was associated with lower risk of HKD, HHF and ACD compared to the DPP-4i group (Table).

In T2D patients, dapagliflozin was associated with lower risks of hospitalization for kidney disease, hospitalization for heart failure and all-cause death when compared to DPP-4i.

Table.

	Dapagliflozin N=8582		DPP-4i N=25,746		Weighted average estimates N=34,328		
	No. events	Rate/100 PYR	No. events	Rate/100 PYR	Hazard ratio	95% CI	p-value
Hospitalization for kidney disease*	52	0.64	417	1.64	**0.38**	(0.29-0.51)	<0.001
Hospitalization for heart failure	77	0.95	375	1.47	**0.63**	(0.50-0.81)	<0.001
All cause death	106	1.04	468	1.44	**0.73**	(0.59-0.91)	0.004

*Any hospitalization with main diagnosis for chronic-, acute- or unspecified kidney disease

166-LB

Transition of Diabetes Care in Surgery Patients with Type 2 Diabetes (T2D) Using an HbA1c-Based Algorithm

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Limited data is available on the optimal transition of diabetes care from inpatient to outpatient setting in surgical patients with T2D. We prospectively studied the efficacy and safety of using an algorithm based on admission HbA1c to guide outpatient therapy in 224 surgery patients with T2D (age 57±11 yrs, BMI 34±8 kg/m^2, duration of T2D: 8.5±8 yrs). Patients who were on incretin based therapy or insulin >0.5 units/kg prior to hospitalization were excluded. The algorithm recommended starting linagliptin 5 mg/day for drug naïve patients or continuing home regimen for patients with HbA1c <7%; adding linagliptin to home regimen of oral antidiabetic agents (OAD) plus insulin glargine at 50% of the inpatient dose for HbA1c 7-9%, and adding linagliptin to home regimen of OAD plus glargine at 80% of the inpatient dose for HbA1c >9% group. Treatment was adjusted to achieve a target HbA1c <7%. Mean HbA1c at admission was 6.4±0.4%, 7.8±0.6% and 11.4±2.1% (p <0.001) for groups with HbA1c <7% (n=92), 7-9% (n= 93) and >9% (n=39), respectively. In the entire cohort, HbA1c decreased from 7.9±2.0% at admission to 7.1±1.5% at 3 months after discharge (p <0.001). HbA1c did not change in HbA1c <7% group but decreased by 0.8±0.9% in HbA1c 7-9% and 3.2±2.5% in HbA1c >9% (both p <0.001). There was a lower rate of mild hypoglycemia (BG <70 mg/dL) in patients with HbA1c <7% as compared to those with HbA1c 7-9% and >9%, (10% vs. 19% vs. 31%, respectively; p=0.03). A BG <40 mg/dL was reported in only 2 patients, one in HbA1c <7% and the other in the HbA1c >9% group. The rate of severe hyperglycemia (>300 mg/dL) was not different in patients with HbA1c <7% as compared to those with HbA1c 7-9% and >9% (8% vs. 14% vs.22%, respectively; p=0.12). HbA1c and hypoglycemia rate were similar in patients treated with linagliptin vs. comparators.

Conclusion: The proposed HbA1c-based algorithm with linagliptin (±OAD), with or without basal insulin, is safe and effective for transitioning of care in general surgery patients with T2D.

Supported By: Boehringer Ingelheim

167-LB

Effect of Combination SGLT2i and GLP-1RA Therapy on Glycemic Control, Body Weight, and Beta-Cell Function in Type 2 Diabetic (T2D) Subjects

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To examine whether SGLT2 inhibition plus GLP-1RA combination therapy provides superior clinical and metabolic benefit compared to monotherapy with each agent, we randomized 24 inadequately controlled (A1c=8.2±0.2%) T2D patients (treated with MET or MET/SU) to receive either canagliflozin (300 mg/d; n=8, CANA), liraglutide (1.8 mg/d; n=8, LIRA) or both (n=8, COMBO). Baseline characteristics were similar across all groups. After a baseline OGTT and clinical measurements (systolic blood pressure [SBP], body weight [BW], A1c and fasting plasma glucose [FPG]), a 16-wk treatment period was started. Clinical parameters and OGTT were repeated at study end. Matsuda [MI]* for insulin sensitivity, insulinogenic index [ΔI/ΔG] and insulin secretion/insulin resistance [disposition] index [IS/IR=ΔI/ΔG X MI*] were calculated.

Combination therapy with canagliflozin and liraglutide provides a greater than additive effect on body weight and systolic blood pressure and an additive effect on glycemic control and beta cell function. These findings provide a strong rationale for the use of combined SGLT2i/GLP-1 RA therapy in poorly controlled T2D patients to reduce A1c (8.2% to 6.2%), improve beta cell function, and promote weight loss.

Table.

	LIRA	CANA	COMBO	p-value
Body Weight (kg)**	-2.6 ± 1.4	-3.4 ± 0.6	-7.2 ± 1.2	0.01
SBP (mmHg)**	0 ± 7	-6 ± 3	-16 ± 3	0.04
HbA1c (%)	-1.59 ± 0.54	-1.10 ± 0.32	-1.94 ± 0.49	0.39
FPG (mg/dl)†	- 44 ± 15	- 32 ± 13	- 76 ± 24	0.18
Mean OGTT PG (mg/dl)†	-84 ± 15	-75 ± 14	-134 ± 23	0.04
Insulinogenic Index [ΔI/ΔG]†	+0.58 ± 0.18	+0.17 ± 0.11	+0.93 ± 0.40	0.05
Ins. Sec./Ins. Resist. [=ΔI/ΔG X MI*]†	+0.73 ± 0.20	+0.67 ± 0.25	+1.26 ± 0.26	0.05

*Corrected for glycosuria; **COMBO is more than additive; †COMBO is additive; ANOVA method used to calculate p-value; SBP=systolic blood pressure; FPG=fasting plasma glucose; OGTT=oral glucose tolerance test; PG=plasma glucose.

Supported By: Janssen

For author disclosure information, see page LB107.

168-LB

Is Less More? Learning to Dose the Oral, Nonpeptide GLP-1R Agonist, TTP273 in Type 2 Diabetics

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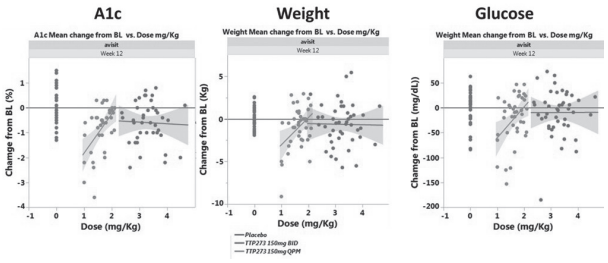
In a 12-week Phase 2 study, TTP273, an oral, non-peptide GLP-1R agonist, at doses of 150mg QPM and 150mg BID showed highly statistically significant reductions in A1c of 0.9 ($p<0.001$) and 0.7% ($p<0.01$), respectively. Subsequent concentration/effect analysis revealed an unexpected result: lower doses showed more pronounced effects for key efficacy endpoints. This observation is confirmed when correlating TTP273 plasma concentration with efficacy. The analysis of the current data reveals that doses lower than 1.35mg/kg may translate into reductions of A1c, weight, and FPG of 1.7% ($p<0.001$), 3.7 kg ($p<0.01$), and 56mg/dL ($p<0.05$), respectively. Similar findings were observed in the Phase 2 study with our predecessor agonist (TTP054) and phase 1 studies for both TTP273 and TTP054. TTP273 differs from GLP-1 in two significant ways that may reduce its effect/increase tolerance at higher exposure levels: 1.) TTP273 can signal directly in the intestine (a response known to desensitize over time), and 2.) TTP273 has a differential signaling pattern that does not signal through β-arrestin and seems to have sustained activation relative to GLP in vitro. These characteristics of TTP273 provide a potential scientific rationale for the observations described herein and support the conduct of additional clinical investigation using lower doses to confirm that for TTP273, less is more.

Figure.



169-LB

The Efficacy and Safety of SGLT2 Inhibitor vs. Placebo as Add-on Therapy in Patients with T2DM and Inadequate Glycemic Control with Metformin and a DPP-4 Inhibitor: Systematic Review and Meta-analysis

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Dual therapy with Metformin and a Dipeptidyl Peptidase-4 (DPP-4) inhibitor is often insufficient to achieve or sustain glycemic targets among patients with type 2 diabetes mellitus (T2DM). In this meta-analysis, we evaluated the efficacy and safety of Sodium Glucose Co-transporter 2 (SGLT2) inhibitor vs. placebo as add-on therapy in patients with T2DM and inadequate glycemic control with Metformin and a DPP-4 inhibitor. Randomized controlled trials (RCTs) comparing SGLT2 inhibitor vs. placebo as add-on therapy to Metformin and a DPP-4 inhibitor were searched using PubMed, Cochrane, and EMBASE database. Outcomes of interest were HbA1c, fasting plasma glucose (FPG), weight, urinary tract infection, genital infection, hypoglycemia, and discontinuation due to adverse events.

Four RCTs met the inclusion criteria. In comparison with placebo, add-on therapy with a SGLT2 inhibitor to existing Metformin and a DPP-4 inhibitor therapy was associated with a significant improvement in HbA1c (mean difference [MD]: -0.68%; 95% CI: -0.93, -0.43; $p<0.01$), FPG (MD: -1.88mmol/L; 95% CI: -2.16, -1.60; $p<0.01$) and weight (MD: -1.86kg; 95% CI: -2.25, -1.47; $p<0.01$). There was no significant statistical difference in the relative risk (RR) for urinary tract infections (RR: 1.01; 95% CI: 0.63, 1.62; $p=0.97$), genital infections (RR: 3.73; 95% CI: 0.62, 22.62; $p=0.15$), hypoglycemia (RR: 1.25; 95% CI 0.62, 2.54; $p=0.53$), or discontinuation due to adverse events (RR: 0.95; 95% CI: 0.37, 2.45; $p=0.91$), between the SGLT2 inhibitor and placebo groups.

In comparison with placebo, add-on therapy with a SGLT2 inhibitor is significantly more effective in lowering HbA1c, FPG, and weight in patients with T2DM and inadequate glycemic control with dual therapy with Metformin and a DPP-4 inhibitor. This is achieved with a similar safety profile.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—PHARMACOLOGIC TREATMENT OF COMPLICATIONS

170-LB

SGLT2 Inhibition via Dapagliflozin Improves Generalized Vascular Dysfunction in Type 2 Diabetic Mice

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Sodium glucose cotransporter 2 inhibitors (SGLT2i) have recently been shown to reduce mortality in diabetic patients. Improvements in vascular function may underlie this protection. The aim of this study was to examine if dapagliflozin, a widely prescribed STLT2i, improves generalized vascular dysfunction in type 2 diabetic (T2D) mice. Male T2D mice (Db) and control littermates received either a low fat diet or a low fat diet containing dapagliflozin (60mg dapagliflozin/kg diet) for 8 weeks. Arterial stiffness was assessed by aortic pulse wave velocity (aPWV); endothelial function and vascular smooth muscle function were assessed by dilatory responses to acetylcholine and sodium nitroprusside, respectively. Compared to untreated Db mice, Db mice treated with dapagliflozin displayed significantly ($p<0.05$) lower aPWV (Db=469cm/s vs. Db+dapa=435cm/s), and improvements in endothelial dysfunction (AUC, Db=57.2 vs. Db+dapa=117.0) and vascular smooth muscle dysfunction (AUC, Db=201.7 vs. Db+dapa=285.5). These vascular improvements were accompanied by reductions in hyperglycemia and circulating markers of inflammation.

In conclusion, dapagliflozin treatment improves generalized vascular dysfunction in T2D mice. These improvements may represent an important mechanism underlying the cardiovascular benefits of SGLT2i therapy.

VARIABLE	Con	Con+dapa	Db	Db+dapa
aPWV, cm/s	426±11	433±10	469±9*	435±11
ACh dilation, AUC	352±24	348±21	57±20*	117±21#
SNP dilation, AUC	386±12	373±26	202±24*	286±20#
Fasting glucose, mg/dl	146±5	152±15	672±26*	321±16#
IL-6, pg/ml	3.8±0.5	9.8±3.1	26.3±12.6*	2.9±0.5
IL-1β, pg/ml	7.1±2.7	2.5±2.2	208.9±92.8*	10.1±8.4
MCP-1, pg/ml	10.5±4.1	6.8±1.9	138.4±64.1*	4.9±1.5
IL-17, pg/ml	ND	ND	60.3±4.3	ND
CCL5, pg/ml	ND	ND	10.10±2.8	ND
IL-10, pg/ml	ND	ND	41.0±16.8	ND

*=$p<0.05$ vs. all other groups; #=$p<0.05$ vs. Con and Con+dapa.

Supported By: AstraZeneca

171-LB

Effects of NS-0200, a Leucine-Metformin-Sildenafil Combination, on Nonalcoholic Fatty Liver Disease (NAFLD)

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NAFLD and nonalcoholic steatohepatitis (NASH), its progressive subtype, is closely associated with obesity and/or diabetes. Sirt1 is suppressed in NAFLD, while its' stimulation or overexpression results in reduced disease severity in experimental systems. We have shown leucine to allosterically activate Sirt1 and synergize with other Sirt/AMPK/NO pathway activators. Thus, we developed a triple combination of leucine, Metformin and sildenafil (NS-0200), which effectively reversed steatosis, inflammation and fibrosis in a mouse model of NASH. We conducted a placebo-controlled Phase 2 randomized clinical trial of 91 obese or overweight subjects with NAFLD (liver fat ≥15% by MRI). Subjects were randomized to placebo, low-dose (2.2 g Leu/1.0 g Metformin/1.0 mg sildenafil) or high-dose NS-0200 (2.2 g Leu/1.0 g Metformin/2.0 mg sildenafil) for 16 weeks; change in hepatic fat was assessed via MRI-proton density fat fraction (MRI-PDFF), and lipid metabolism was further assessed via changes in lipidomic signature. 70 subjects completed the trial and met a priori compliance criteria. Analyses were conducted on the full cohort and on those with ALT values above median (50 U/L; n=35). The high ALT group also exhibited significant elevations in other hepatic biomarkers. High dose NS-0200 reduced MRI-PDFF by 15.7% in the high ALT group ($p<0.005$) while there was no significant effect in the low dose or placebo arms. In the full cohort, however, treatment did not separate from placebo due to an unusually high placebo response. Lipidomic analysis showed dose-responsive treatment effects in both full and high ALT cohorts, with significant decreases in metabolically active lipids and up-regulation of fatty acid oxidation. Other metabolic parameters exhibited

dose-responsive improvements. NS-0200 was well tolerated and there was no difference in adverse events in treatment vs. placebo groups. These data suggest NS-0200 should be further studied as a therapy for NASH.

Supported By: NuSirt Biopharma

172-LB

SGLT2 Inhibitors Inhibit Cardiac NHE and Lower Cardiomyocyte $[Na^+]_c$, but Only Empagliflozin (EMPA) Improves Oxygen Consumption of Isolated Mouse Hearts

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Background: EMPA is the first diabetes drug that reduces cardiovascular diseases in T2D patients. However, the cardioprotective mechanisms are unknown. We recently reported that EMPA reduces cardiac $[Na^+]_c$, $[Ca^{2+}]_c$ and increases mitochondrial $[Ca^{2+}]_m$ through inhibition of the myocardial sodium/hydrogen exchanger (NHE-1). Inhibition of NHE-1 has been shown to reduce hypertrophy and heart failure. This suggests that NHE-1 inhibition contributes to EMPA-induced cardioprotection. We examined whether other SGLT2 inhibitors (dapagliflozin (DAPA) and canagliflozin (CANA)) also inhibit cardiac NHE and reduce $[Na^+]_c$, and whether SGLT2 inhibitors affect performance of isolated-perfused mouse hearts.

Methods/Results: Molecular docking simulations on a homology model of the NHE-1 protein structure predicted all three compounds to bind with relatively high binding affinity to the extracellular Na^+-binding site of NHE-1. Subsequently, isolated mouse cardiomyocytes were loaded with the pH probe SNARF to detect NHE-1 activity following a $NH4^+$-pulse, or with the SBF1 probe to monitor myocardial sodium $[Na^+]_c$. EMPA (1 μM) demonstrated strongest inhibition of NHE as reflected by less pH recovery compared to DMSO control (6.69±0.03 vs. 7.09±0.04, $p<0.001$); DAPA (1 μM; 6.79±0.03, $p<0.001$) and CANA (3 μM; 6.87±0.06, $p=0.015$) also inhibited NHE. EMPA, DAPA and CANA, significantly lowered $[Na^+]_c$ (from 13.0±0.4 mM to 9.9±0.3, 10.7±0.3 and 11.0±0.5 mM, respectively). Only EMPA significantly increased oxygen consumption (from 36.1±2.0 to 42.4±1.3 μmol/min/g_{dw}; $p=0.027$), with non-significant trend for increased glucose consumption (from 9.4±2.7 to 18.4±3.1 μmol/min/g_{dw}; $p=0.127$) of the isolated mouse heart. Mechanical performance was unaffected by all three SGLT2 inhibitors.

Conclusions: EMPA, DAPA and CANA inhibit cardiac NHE and lower $[Na^+]_c$, albeit to different degrees, but only EMPA increased cardiac oxygen consumption.

HEALTH CARE DELIVERY—ECONOMICS

173-LB

Retrospective Analysis: Malnutrition on Survival and Health-Care Costs in Medicare Beneficiaries with Diabetes

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Patient nutritional status is important in the context of an aging population with diabetes. Despite a high prevalence of overweight/obesity, malnutrition can result from e.g., dietary restriction, depression, polypharmacy. However, the association of malnutrition on outcomes in these patients has not been studied. This was a retrospective observational study to examine the impact of malnutrition and other significant health conditions on survival time and health care costs using Centers for Medicare Services (CMS) data from 1999 to 2014 for beneficiaries who had a confirmed first date of initial diabetes diagnosis (n=15,121,131). The primary outcome was survival time. Healthcare utilization was a secondary outcome. The results revealed that n=801,272 beneficiaries had a malnutrition diagnosis. These beneficiaries had decreased survival when malnutrition was analyzed adjusting for age, gender, race, and other disease conditions (Table). In addition, a simple means comparison of spending for beneficiaries with malnutrition was $26,353 greater than annual spending for beneficiaries with diabetes alone.

Table. Hazard Ratio (99.9% Confidence Interval) for Each Health Condition from Twenty Propensity Matched Samples.

	For Health Condition	For Malnutrition within Health Condition
Ischemic Heart Disease	0.93 (0.92, 0.94)	1.61 (1.60, 1.63)
Stroke / Transient Ischemic Attack	1.20 (1.18, 1.22)	1.54 (1.52, 1.55)
Acute Myocardial Infarction	1.21 (1.20, 1.23)	1.45 (1.44, 1.46)
Chronic Obstructive Pulmonary Disease	1.42 (1.40, 1.43)	1.59 (1.57, 1.60)
Chronic Kidney Disease	1.50 (1.47, 1.52)	1.52 (1.51, 1.53)
Heart Failure	1.53 (1.50, 1.55)	1.51 (1.50, 1.53)
Malnutrition	1.70 (1.68, 1.72)	—

In conclusion, malnutrition is a significant comorbidity affecting survival and health care costs in CMS beneficiaries with diabetes. Aggressive identification and treatment of malnutrition in these patients is warranted.

174-LB

One-Year Time Analysis in an Academic Diabetes Clinic: The Burden of Diabetes Care

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Non-reimbursed time utilization to support staff is a growing concern for all diabetes practices yet we are not aware of any recent quantification. We collected time data for 1 month and extrapolated to 1 year to estimate the annual time spent on telephone calls, emails, and faxes addressed per year, in an academic diabetes clinic with 3727 patients, 10,332 visits per year, and 3.6 MD/NP (P). We describe how much time in one year is required for RN/RD/MA/PharmD (S) to support one P.

There were 1945 yearly triage interactions (telephone, fax, or email) in 2016. Medication questions, prescriptions, and medication prior authorizations by S comprise 674 hours per P and 46 percent of these interactions. Most intensive time utilizations are noted in the Table. The 10,332 patient visits required 1984 hours for clinic personnel, while the non-billable time by staff required 1461 hours/provider (28 hours/week). This non-billable time grossly underestimates actual total time since P time was not captured.

In conclusion, non-billable time required for an academic diabetes clinic is significant with interactions for prescriptions comprising almost half of the time. When including providers, more time is spent caring for patients with no reimbursement than time spent for actual patient care. This is not sustainable and given the explosion of diabetes, new systems are required to ease the burden of patient care.

Table.

Issue	Median Time/ contact/min	Mean Time/ contact/min
Health Challenges	15	16.78
Medication Questions	10	13.271
Prior Authorizations	10	15.22
Hyper/Hypoglycemia	15	15.63
Coordination of Care	10	12.52
Diabetes Education	15	17.38
Pump Questions	15	16.61
CGM questions	10	12.78
Referrals	15	16.42
Nutrition	15	15.10
Steroid Induced Hyperglycemia	20	22.66
Walk-ins	10	11.66
Travel	13	15
Colonoscopy	12.5	12.33

175-LB

The Disruption Continues: Negative Impact of Medicare Competitive Bidding Program

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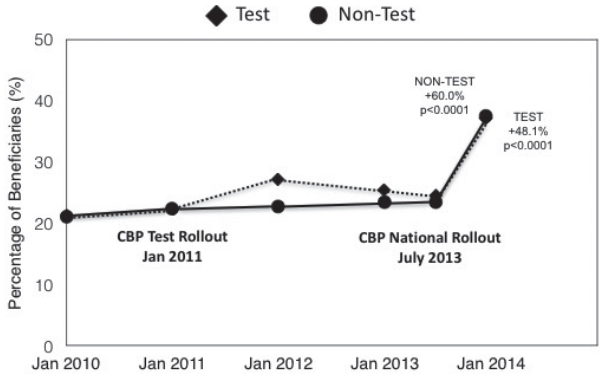
The impact of the Medicare Competitive Bidding Program (CBP) 2011 rollout in 9 test markets revealed substantial disruption of beneficiary access to testing supplies and significant increases in the percentage of beneficiaries with reduced or no acquisition of diabetes testing supplies. This was significantly associated with increased mortality, hospitalizations and costs. We evaluated the impact of the national CBP rollout in July 2013, which now covers both mail order and retail channels with lower reimbursement, to determine if the outcomes seen in 2011 continued. This longitudinal study followed 529,627 insulin-treated beneficiaries from 2009-2013 to assess changes in testing supply acquisition by beneficiaries in the initial 9 test markets (TEST, n=43,939) and beneficiaries not affected by the 2011 rollout (NON-TEST, n=485,688). The percentages of beneficiaries with Partial/No SMBG acquisition were significantly higher in both the TEST (37.4%) and NON-TEST (37.6%) groups following the first 6 months of the national CBP rollout, showing increases of 48.1% and 60.0%, respectively (both p<0.0001). (Figure 1) The negative impact of CBP has persisted and worsened. Our data suggest that the additional changes in CBP may have exacerbated disruption of beneficiary access to their prescribed testing supplies, further usurping the clinician-patient relationship and threatening public health safety.

Figure 1. Change in Percentage of Beneficiaries with Full Insulin Acquisition and Partial/No SMBG Acquisition.



176-LB

Impact of Digital Remote Coaching Program on Health Disparities among Patients with Type 2 Diabetes

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The ADA's recent release of the 2017 Standards of Medical Care in Diabetes recommends self-management support as a strategy to reduce health disparities. In this study, we investigate the impact of a remote digital coaching program on health disparities as part of a behavioral counseling intervention for management of type 2 diabetes. Patients (n=213) with a recent HbA1c of 6.5% and higher opted into the study and gave consent and received a 12-week coaching intervention.

Patients were divided into two groups: those who live in zip codes where the median household income is below the national median of $51,939 (n=111) and those above (n=102). Patients in the lower income group were more likely (p <0.001) to be in a rural area (37%) than those in the higher income group (1%). At baseline, those in the lower income group had higher HbA1c than those in the higher income group (8.72 vs. 8.11, p=0.007), however BMI and medication adherence were not significantly different between groups. Post intervention, both groups saw a statistically significant reduction in HbA1c (-1.33 and -0.96, p < 0.001) and BMI (-1.1 and -0.7, p < 0.001) and increase in adherence (22% and 20%, p < 0.001). Results suggest that a remote patient centered engagement intervention is an effective solution in reducing health disparities and improving outcomes associated with type 2 diabetes.

Table. Results (All within Group Comparisons are p < 0.001).

	Lower Income Group n = 111	Higher Income Group n = 102	Across Groups p-value
HbA1c Pre	8.72	8.11	0.007
HbA1c Post	7.39	7.15	0.130
BMI Pre	35.8	34.5	0.202
BMI Post	34.7	33.8	0.349
Percent Adherent Pre	66%	74%	0.260
Percent Adherent Post	88%	94%	0.138
Percent in Rural Area	37%	1%	<0.001

177-LB

Predictive Analytics and Managing Type 2 Diabetes

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Objective: To identify factors predicting transition of type 2 diabetes patients (T2DM) with good hemoglobin A1c control (HbA1c 5.5-6.9%) at baseline to poor control (HbA1c ≥ 8%) 12-15 months later.

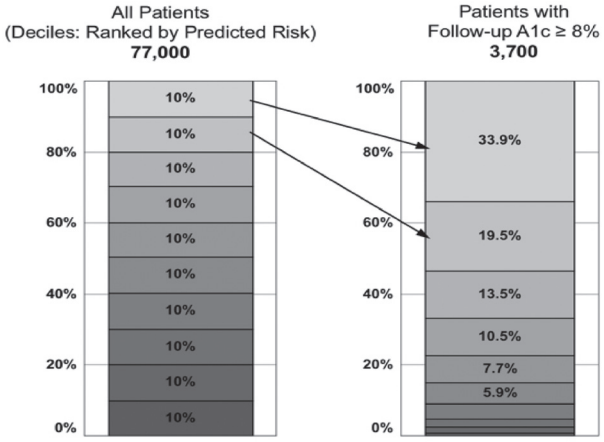
Study Design: Multivariable logistic regression models predicted poor control (HbA1c ≥ 8%) at follow-up. Predictors included baseline health status, medications, and patient demographics. Predicted vs. observed risk was calculated.

Population Studied: Longitudinal electronic medical record data from 29 U.S. health care organizations representing 144,644 adult patients were examined.

Principal Findings: Older age and baseline medications strongly predicted poor outcomes (P < .0001). Other predictors included male sex, low-income insurance, obesity diagnosis, and LDL cholesterol ≥ 100 mg/dL (P < .001); and baseline systolic blood pressure ≥ 160 mm Hg, hypoglycemia, and ≥ 1 microvascular complication (P < .05). Comparing predicted with observed risk, the 10% of patients at greatest predicted risk represented 34% of patients with subsequent poor glycemic control (Figure 1).

Conclusion: Five percent of T2DM patients with HbA1c < 7% will transition out of control (≥ 8%) within 12-15 months offsetting efforts to control patients' HbA1c, resulting in little observed population level improvement. Study models provide opportunities to stratify "well-controlled' patients by risk of future poor outcome facilitating targeted outreach and intervention.

Figure 1. Predicted vs. Observed Risk of Poor Glycemic Control.



178-LB

Are Providers and Staff an Additional Barrier to Insulin Initiation? Results of a Survey in a Safety-Net Primary Care Clinic

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Insulin therapy in diabetes is generally initiated in primary care (PrC), where resistance to its use is commonly encountered, especially in low-income, minority patients. To assist PrC with insulin initiation, we surveyed clinic providers/staff (PS) to examine their preconceived notions of barriers experienced by patients (P). We compared results of PS to the same survey of P's perceptions in the same PrC clinic. Design of surveys used literature-based factors associated with psychological insulin resistance and tested for language and cultural sensitivity. Surveys were performed at a safety-

net clinic in Los Angeles County Dept. of Health Services, in 55 PS and 150 diabetic P. Clinic P were low-income, 75% Hispanic, 23% African American. The results demonstrated marked discrepancies in the PS and P perceptions of barriers. PS overestimated many P's concerns: fear of needles (85 vs. 56%), understanding how to use insulin (87 vs. 52%), insulin interference with daily life/work (74 vs. 44%), feelings of negative judgment by others (54 vs. 21%), and loss of independence (54 vs.27%) in PS and P, respectively (all p<0.001). This may have been part of a general overestimation of clinic barriers, such as perceived difficulty communicating with PrC providers (58 vs. 14%), and difficulty coming to clinic (54 vs. 15%) (both p<0.001). Yet the surveys also showed underestimation by PS of P concerns: feelings of personal failure managing diabetes (58 vs. 78%; p=0.03), the idea that significant diet changes are required with insulin (54 vs. 86%; p<0.001) and high cost of insulin despite subsidies or insurance coverage (36 vs. 56%; p=0.02).

We conclude that an additional barrier to initiation of insulin may be lack of appreciation by PS that their perceptions of P barriers are incorrect. We suggest that, considering time pressured PS-P interactions in PrC, focused targeting of P-perceived barriers (not PS notions) can lead to a more efficient discussion of insulin initiation to allay P concerns.

Supported By: California Community Foundation

179-LB

WITHDRAWN

180-LB

Impact of a Pharmacist-Led Diabetes Management on Outcomes, Utilization, and Cost

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Objective: To evaluate the impact of a pharmacist-lead medication therapy and disease management (MTDM) program implemented by a large integrated healthcare system among patients with type 1 or type 2 diabetes mellitus (DM) on clinical outcomes, care utilization, and cost.

Methods: 2,750 DM patients who were enrolled in MTDM between February 2011 and September 2014 were identified from Geisinger Health System's electronic health records and were compared to a propensity score matched cohort of 2,750 DM patients who had not enrolled in MTDM. The primary endpoint for this study was a composite endpoint of target glycemic control (HbA1c <8%), blood pressure control (<130/80 mmHg) and low density lipoprotein cholesterol control (<70 mg/dL, or <100 mg/dL for patients with coronary heart disease or chronic kidney disease). Healthcare resource utilization was also studied.

Results: Matched cohorts were well-balanced across all characteristics. At 12 months after the first MTDM encounter, there were no significant difference between the MTDM and the non-MTDM cohorts in the composite primary endpoint. Patients in the control group were more likely to reach HbA1c goal (57% vs. 51% p < 0.001). However, the MTDM cohort was associated with a reduction in the rate of all-cause hospitalizations (-19.3%; p=0.01) as well as increased primary care provider (PCP) visits (18.5%; p<0.001). The MTDM cohort was also associated with lower total healthcare cost of care (-13.7%; p=0.03).

Conclusion: Despite the lack of MTDM impact on the clinical outcomes, MTDM is associated with an overall lower cost of care and fewer hospitalizations. This could be due to avoidance of adverse events such as hypoglycemia, but future studies are warranted to determine the reasons behind the reduction in healthcare resource use in this patient population.

Supported By: GlaxoSmithKline

181-LB

Review of Type 1 Diabetes Service Delivery Models and Governance for the Poorest Billion

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Objectives: The goal of this study was to review modalities of service delivery and country-level health system governance for type 1 diabetes (T1D) among the world's poorest billion people.

Methods: We conducted a literature search to identify articles concerning T1D in the 45 countries that contained 96 percent of world's poorest billion people in 2011. We also reviewed national policy documents from a purposive sample of 11 of these countries. This analysis was supplemented by interviews with government officials and T1D program implementers in Haiti, Rwanda, Malawi, Ethiopia, Tanzania, Kenya, India, Mozambique, and Nepal.

Results: Of the 552 papers initially identified, only 61 described T1D service delivery strategies in 30 countries with a high prevalence of severe poverty. The T1D services described were largely organized at the referral-level and were supported primarily by T1D donor programs. T1D was only referenced specifically in national policy documents in 2 of these 11 countries.

Conclusions: At present, many T1D programs for the world's poorest populations are externally supported and limited to referral facilities in regional or national centers. There may be a need to better integrate and decentralize T1D services in order to make them a more routine part of universal health coverage in the poorest countries.

182-LB

Real-World Progression in Diabetes (RAPIDS) Model

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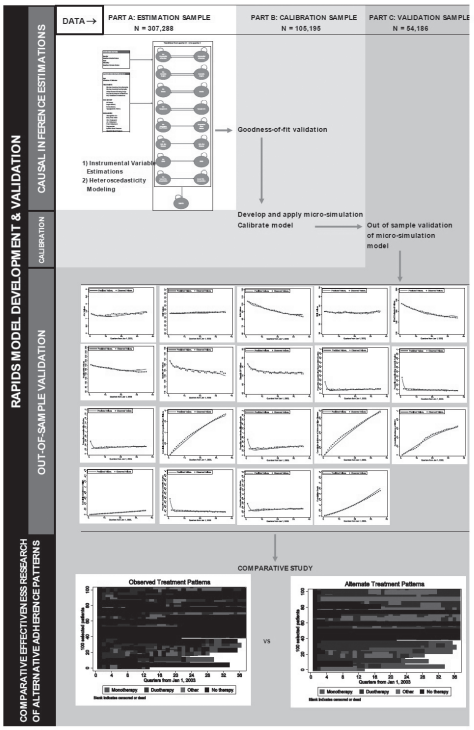
Aim: To develop and validate a real-world-data based type 2 diabetes progression model that can study the comparative effects of complex dynamic patterns of glucose-lowering drug use.

Methods: The Veterans Affairs EMR and claims databases were used to identify diabetes patients in 2003-2010 with up to 9-year follow-up. The RAPIDS model contains a series of first-order Markov processes over quarters, for micro and macro-vascular events, hypoglycemia, and death. The transitions are modeled to vary by static demographic risk factors, and also dynamic factors, such as age, treatments, and eight biomarker levels (Figure 1). A simple comparative study was set up to compare observed treatment use patterns to alternate patterns if perfect adherence is assumed among patients who initiate use of new medications.

Results: The full data were randomly split into three parts of 307,288, 105,195, and 54,186 patients respectively to perform out-of-sample calibration and validation. Model predictions in the hold-out sample closely aligned with observed longitudinal trajectory of biomarkers and outcomes. Perfect adherence does not lead to changes in most outcomes over the 9-year period, except for a slight increase in hypoglycemia.

Conclusion: The RAPIDS model was developed by applying causal inference econometrics and a micro-simulation model to real-word data. It has the potential to carry out many complex CER studies of dynamic glucose-lowering drug regimens.

Figure 1.



Supported By: Agency for Healthcare Research and Quality; National Institutes of Health

For author disclosure information, see page LB107.

PEDIATRICS—OBESITY AND TYPE 2 DIABETES

183-LB

Insulin Sensitivity across the Life Span from Obese Adolescents to Obese Adults with Impaired Glucose Tolerance (IGT): Who Is Worse Off?

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Youth type 2 diabetes occurs decades earlier than adult type 2 diabetes and is characterized by high therapeutic failure rates and decreased response to insulin sensitizers suggesting a more severe disease process than in adults. To explain these observations, we investigated if insulin sensitivity (IS) is worse in obese youth than adults with IGT at high risk for type 2 diabetes. Obese IGT youth (age 14.5 ± 0.5 yrs [SE]; 71% Tanner stage V) were matched 2:1 for BMI, sex and race to obese IGT adults (age 44.7 ± 1.7 yrs). Fasting lipids, fasting hepatic IS ([6,6-$^2H_2$]glucose), peripheral IS (hyperinsulinemic-euglycemic clamp) and body composition (DEXA) were examined. Despite similar % body fat, HbA1c and 2-hr OGTT glucose, IGT youth had lower hepatic and peripheral IS, higher fasting insulin, and lower HDL compared with IGT adults (Table). However, adults had higher total, LDL and non-HDL cholesterol. Obese youth with IGT are more insulin resistant, ~ 50%, and worse off than obese adults with IGT in spite of similar adiposity. This could potentially explain the earlier onset of type 2 diabetes in youth and their lower therapeutic response to insulin sensitizers through an early and amplified burden on a β-cell destined to decompensate. However, obese adults with IGT manifest worse atherogenic lipid profile than youth with IGT highlighting an enhanced risk of CVD in adults.

Table. Metabolic Characteristics of Obese IGT Youth Matched 2:1 to Obese IGT Adults for BMI, Sex, and Race.

Variables	Youth (n=34)	Adults (n=17)	P
Percent body fat (%)	43.9 ± 0.9	44.8 ± 1.8	NS
Fasting insulin (μU/mL)	45.0 ± 4.9	20.0 ± 1.5	<0.0001
Hepatic IS (mg/kgFFM/min·μU/mL)$^{-1}$	8.2 ± 1.2	17.1 ± 1.6	<0.0001
Peripheral IS (mg/kgFFM/min per μU/mL)	4.1 ± 0.4	7.0 ± 0.6	0.002
Total cholesterol (mg/dL)	166.3 ± 6.9	201.4 ± 9.7	0.009
HDL (mg/dL)	38.5 ± 1.0	49.9 ± 4.7	0.035
LDL (mg/dL)	100.3 ± 6.2	129.6 ± 8.1	0.007

Supported By: American Diabetes Association (7-08-JF-27 to S.L.); Eunice Kennedy Shriver National Institute of Child Health and Human Development (K24-HD1357, R01-HD27503); National Center for Advancing Translational Sciences (UL1-TR000005); National Institute of Diabetes and Digestive and Kidney Diseases (P30-DK462); National Center for Research Resources (5M01-RR00056, RR024153)

184-LB

A Unique Urine Metabolomic Signature for Type 2 Diabetes in Youth

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Type 2 diabetes (T2D) is increasing more rapidly in adolescents than in any other age group. Moreover, pancreatic β cell failure and complications such as hypertension, nephropathy and retinopathy appear faster in youth than in adults. Increased circulating branched chain amino acids (BCAAs) are associated with T2D and insulin resistance. However, it is not clear whether increased plasma BCAA concentrations result from increased synthesis, or impaired degradation or excretion. Here, we employed a targeted metabolomics approach to identify urine metabolites associated with T2D in youth, presenting potential urine biomarkers for clinical prediction and further insight into disease pathogenesis.

Methods: We measured 145 urine metabolites by LC-MS/MS in 3 cohorts: obese youth with T2D (n=30), obese youth without T2D (n=30), and age- and gender-matched healthy normal-weight control subjects (n=30). We also examined kidney cortex of db/db and control db/m mice.

Results: Following FDR correction, 36 of the 145 measured metabolites were found to differ between the 3 cohorts. These metabolites represented intermediates in 3 major pathways: BCAA metabolism, fatty acid metabolism and the TCA cycle. In T2D youth, BCAAs were increased in plasma but decreased in urine, suggesting impaired BCAA catabolism. To further investigate, we examined kidney tissue from db/db mice and found decreased gene expression of key enzymes related to BCAA catabolism. Western blot studies confirmed that reduced renal expression of branched-chain ketoacid dehydrogenase in db/db mice compared with controls.

Conclusions: Prior studies have reported increased plasma BCAA metabolites in youth and adults with T2D. Our data suggests impaired mitochondrial BCAA catabolism in classical insulin target tissues such as liver, muscle and adipose, and supports a role for dysregulated BCAA metabolism by the kidney. This dysregulated BCAA metabolism may affect insulin resistance and the development of kidney disease with T2D.

Supported By: American Diabetes Association (1-14-IN-27 to J.J.K.); University of California, San Diego; National Institutes of Health (UL1TR001442); Rady Children's Hospital

185-LB

Associations of Nutrient Deficiencies with Insulin Resistance and Inflammation in Lean and Obese Youths

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Background: Obese individuals are at risk for iron deficiency due to both insufficient dietary iron intake and trapping of iron through an interleukin-6 (IL-6) dependent pathway. Vitamin D deficiency further contributes to the proinflammatory state. Many studies suggest that iron excess is associated with insulin resistance, using surrogate measures of insulin resistance (e.g., HOMA-IR) and measures of iron that may be confounded by inflammation (e.g., ferritin).

Objective: To evaluate the associations of iron and vitamin D with inflammation and insulin resistance by the insulin modified frequently sampled intravenous glucose tolerance test (FSIGT).

Design/Methods: 19 obese (BMI z-score >2.0) and 28 lean (BMI z-score -2.0-1.0) subjects were recruited (mean age 14 years, range 9-17 years) in a cross-sectional study. Fasting serum was analyzed for iron status [soluble transferrin receptor (sTfR)], IL-6, and 25-hydroxy vitamin D (25[OH]D). Insulin sensitivity (Si) was determined by FSIGT. Iron deficiency was defined as sTfR level >8.3 mg/L. Vitamin D deficiency was defined as 25(OH) D level <20 ng/mL. Linear regression was used to measure the associations of 25(OH) D and sTfR with IL-6 and Si.

Results: 10% of obese subjects were iron-deficient (0% of lean). 37% of obese subjects were vitamin D deficient (vs. 10% of lean). sTfR was negatively associated with Si ($p<0.01$) and positively associated with IL-6 ($p<0.0001$). 25(OH) D trended toward a positive association with Si ($p=0.08$) and was negatively associated with IL-6 ($p<0.01$). There was no interaction between sTfR and 25(OH) D on either Si or IL-6.

Conclusions: Iron deficiency was identified among obese, but not lean youths. Higher vitamin D levels and better iron status are associated with increased insulin sensitivity and decreased inflammation in our small cohort. Micronutrient modulation may have a future role in dietary interventions for the prevention of insulin resistance.

PEDIATRICS—TYPE 1 DIABETES

186-LB

Geographic Access to Endocrinologists for Florida's Publicly Insured Children with Diabetes

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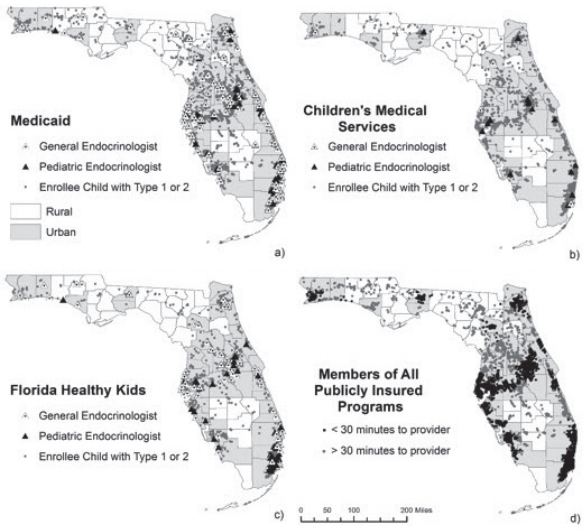
Socioeconomic status and race/ethnicity are associated with disparate health outcomes in type 1 and type 2 diabetes for pediatric populations, yet access to endocrinologists has not been adequately studied as a contributing risk factor. We examined driving times to in-network endocrinologists that publicly insured children with diabetes in Florida face. Enrollment, eligibility, and claims/encounter data were used to identify children with diabetes in Florida's Medicaid and Children's Health Insurance programs (n=7,233; type 1 diabetes 54%, type 2 diabetes 46%; mean age 12.2 [±4.62]). Members were geocoded to in-network endocrinologists using Navteq 2015 street data and ESRI Premium location software. Average drive times were aggregated by county, rural/urban member location, and race/ethnicity. Average driving times to pediatric endocrinologists were ≤30 minutes for children in urban areas but ≥70 minutes for children in rural areas. A county-level comparison of in-network providers to all available providers revealed rural counties have limited care options. White children faced the longest driving times; only 56% were ≤30 minutes from a pediatric endocrinologist. These data reify the importance of outreach strategies addressing geographic access and demonstrate that spatial barriers, alone, do not fully elucidate racial/ethnic disparities in pediatric diabetes.

Figure.



187-LB

Reduced Hypoglycemia with Continuous Glucose Monitoring in Newly Diagnosed Youth with Type 1 Diabetes

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Youth newly diagnosed with T1D were enrolled and randomized 2:1 to non-adjunctive (non-adj) use of Dexcom G5 CGM or standard care (no CGM). The objective of this pilot RCT was to demonstrate efficacy of initiating non-adj CGM early in the disease process. This trial started prior to non-adj CGM indication in December 2016.

Data presented are from the first 23 participants (age 2.9-16.2 years) enrolled within 30 days of diagnosis. Sixteen intervention participants were trained on the Dexcom G5 system at 2 sessions: session 1 was standard training, session 2 (2 weeks later) was non-adj training. CGM data were captured for intervention participants using G5 adjunctively for 2 weeks and non-adj thereafter. Seven control participants wore blinded G4 for one week at enrollment and ~6 weeks later.

Sample characteristics and glucose values are presented in the Table. Mean sensor glucose and percent time in target (sensor glucose 70-150 mg/dL) did not vary significantly between groups at any time point. Percent time in hypoglycemia (<60) was significantly different; controls experienced 3-4 times more hypoglycemia than the intervention group at both times (p<.02).

Preliminary results show that CGM can be feasibly introduced early in the course of T1D. The group using CGM had a lower incidence of hypoglycemia, and there was no significant change when non-adjunctive use was introduced.

Table.

	GROUP	
Variable/Characteristic	**Intervention (n=16)**	**Control (n=7)**
Age	10.7±2.9 yrs (range 4.7-15.2)	11.2±4.2 yrs (range 2.9-16.2)
Female (%)	50%	29%
A1c at diagnosis (%)	9.8±1.7	10.2±2.9
T1D duration at enrollment	22±6 days	18±8 days
Enrollment—first week of CGM data (intervention G5 adjunctive; control G4 blinded), **intervention group did not complete any blinded CGM wear		
Percent time using sensor (of week)	99%	84%
Mean Sensor Glucose (±SD)	146±32	141±46
Percent time in target (70-150 mg/dL)	62%	60%
Percent time in hypoglycemia (<70)	3%	8%
Percent time in hypoglycemia (<60)	1%	3%
Percent time in hyperglycemia (>250)	7%	9%
First week of non-adjunctive use for intervention		
Percent time with sensor values	89%	n/a
Mean Sensor Glucose (±SD)	149±39	
Percent time in target (70-150 mg/dL)	62%	
Percent time in hypoglycemia (<70)	2%	
Percent time in hypoglycemia (<60)	<1%	
Percent time in hyperglycemia (>250)	8%	
6 weeks post-baseline (intervention G5 non-adjunctive, n=12; control G4 blinded, n=5)		
Percent time with sensor values	88%	86%
Mean Sensor Glucose (±SD)	153±29	135±32
Percent time in target (70-150 mg/dL)	55%	60%
Percent time in hypoglycemia (<70)	2%	7%
Percent time in hypoglycemia (<60)	<1%	4%
Percent time in hyperglycemia (>250)	7%	5%

Supported By: Dexcom, Inc.

188-LB

HERV-W-Env, the Envelope Protein of Human Endogenous Retrovirus Type W, Is Involved in Type 1 Diabetes Pathogenesis

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Human endogenous retroviruses (HERVs), known to represent 8% of the human genome, have been associated with several autoimmune diseases. In particular, the HERV-W family has been involved in the pathogenesis of Multiple Sclerosis (MS). Precisely, the envelope protein of HERV-W (HERV-W-Env) displays proinflammatory and autoimmune properties that had initially been demonstrated in an MS perspective and subsequently turned out to be relevant for type 1 diabetes (T1D).

Indeed, we previously observed that HERV-W-Env protein is expressed in the sera of 60% of T1D patients, and that its mRNA is upregulated in PBMC of 57% of T1D patients. HERV-W-Env is also expressed in 75% of human T1D pancreas, by acinar cells, and in vitro experiments prove that it inhibits insulin secretion by human Langerhans islets.

In this new report, we present an extensive immuno-histological analysis of human pancreas from T1D patients, revealing a significant correlation between HERV-W-Env expression within the pancreas and macrophages infiltrates ($P < 0.01$). Importantly this infiltration of CD68 positive cells was found in the exocrine pancreas, in accordance with recent studies supporting the importance of pancreatic exocrine abnormalities in T1D pathogenesis. We then developed and characterized a transgenic mouse model in which HERV-W-Env is constitutively expressed under the control of CAG promoter. In this model, transgenic mice also displayed immune cells infiltrates in their exocrine pancreas ($P < 0.01$), a feature associated with significant hyperglycemia and lower levels of insulin.

Taken together, our results support the involvement of HERV-W-Env protein in the recruitment of immune cells within the pancreas of human T1D patients and transgenic mice. The combination of the pancreatic proinflammatory effects of HERV-W-Env and its direct inhibitory effects on insulin secretion unveils HERV-W-Env as a new pathogenic target in T1D, thus providing novel therapeutic perspectives.

189-LB

High Prevalence of Microalbuminuria in Children with Dual Diagnosis of Type 1 Diabetes and Celiac Disease

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Background: Celiac disease (CD) is a risk factor for development of retinopathy and nephropathy in adults with type 1 diabetes (T1D). Limited data in children exist.

Aims/Objective: Compare cardiovascular risk factors and diabetes complications in children with both T1D and CD compared to children with T1D alone.

Methods: Retrospective chart review of 90 children and adolescents with T1D and biopsy confirmed CD (from 2011-2015) was matched to controls with T1D alone for age, sex, race and duration of diabetes. BMI percentile, systolic/diastolic blood pressure percentiles, lipids (cholesterol, LDL, HDL, triglycerides), hemoglobin A1c and microalbuminuria (first morning urine specimen

For author disclosure information, see page LB107.

with albumin/creatinine ratio >30) were compared by Wilcoxon signed-rank tests and McNemar's tests for paired data between the two groups.

Results: 54% were male; 94% of patients were non-Hispanic white. Mean age of diagnosis of T1D was 7.5 ± 4.2 years; mean age of CD diagnosis was 12.8 ± 4.2 years. 59% (53/90) of children developed CD within the first 5 years of T1D diagnosis. Blood pressure and lipid profiles were not statistically different in those with CD+T1D compared to those with T1D alone. Median BMI percentile was lower in the CD+T1D group at diagnosis of CD (71.5 vs. 80.4; ns). Median HbA1c was 7.5% (IQR: 6.7-8.6) in those with CD+T1D vs. 7.7% (6.7-8.1) in those with T1D (ns). Microalbuminuria was found in 11% (10/90) of the CD+T1D group vs. 1/90 in T1D alone (p=0.01). 9 of the 10 CD+T1D patients with microalbuminuria were on ACE inhibitors.

Conclusion: Higher prevalence of microalbuminuria was found in children with T1D and CD despite no differences in cardiovascular risk factors when compared to matched controls with T1D alone. Further studies are needed to determine the factors contributing to the development of microalbuminuria in children with T1D and CD.

190-LB

Soluble α-Klotho Is Associated with Diabetes Duration and Glycemic Control in Youth with T1D

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Soluble α-klotho (klotho), a protein involved in bone mineral homeostasis, has recently been shown to be inversely associated with albuminuria in adults with T1D, suggesting a potential role as an early marker of kidney disease. In adults with T2D, it has been shown to be lower in those with higher HbA1c, suggesting a relationship with metabolic control. No study, to our knowledge, has evaluated the relationship between klotho and degree of albuminuria as well as glycemic control in youth with T1D.

As part of an ongoing study, 80 consecutive youth with T1D were evaluated (94% Caucasian, 50% male, mean age 15.9±2.9 years, duration of T1D 6.9±3.8 years, 2-year average HbA1c 8.3±1.4%, systolic BP (SBP) percentile 54±24 percentile, diastolic BP (DBP) percentile 69±17 percentile). Albuminuria was assessed by albumin/creatinine ratio (ACR) (median [IQ range] 9.45 [5.5-20.2] mg/g). Serum α-klotho level was determined by IBL (Immuno-Biological Labs, Japan, ELISA method) (median [IQ range] 1783.6 [1153.7-2053.3] pg/mL). eGFR was calculated per the Cystatin-C based Zappitelli method (mean ± SD 99.9±20.8 ml/kg/1.73m2).

Klotho did not correlate with ACR (r=0.04, p=0.69). There was no difference in klotho levels by quartiles of ACR (1197±315, 1380±651, 1292±637, 1293±584 pg/ml, lowest to highest quartile respectively, p= 0.48) or between those with normal (n=68) vs. abnormal (n=12) ACR (1270±540 vs. 1387±648 pg/ml, p= 0.81). There was no significant correlation between klotho and eGFR (r=-0.186, p=0.11), SBP percentile (r=0.0036, p=0.97) and DBP percentile (r=-0.079, p=0.51). However, klotho correlated significantly with HbA1c (r=-0.32, p=0.008) and diabetes duration (r=-0.314, p=0.009) even after adjusting for age.

This is the first study to show that serum α-klotho is associated with glycemic control and diabetes duration in a pediatric population with T1D. Serum α-klotho may be a potential early risk biomarker for diabetes complications in youth with T1D; longitudinal follow-up of this cohort is needed to confirm these observations.

Supported By: National Institutes of Health; Cochrane-Weber Endowed Fund in Diabetes Research; Fraternal Order of Eagles Diabetes Fund

191-LB

Norwegian Adolescents with Type 1 Diabetes on Intensive Insulin Treatment Score Low on Diabetes-Related Emotional Distress—Short Version of the Problem Areas in Diabetes Questionnaire Can Be Applied in Clinical Care

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The aim of this large nationwide study through the Norwegian Childhood Diabetes Registry (NCDR) was to evaluate patient reported diabetes-related emotional distress using the Problem Areas in Diabetes (PAID) scale. Subjective psychological well-being was measured using the World Health Organisation 5-Well-being Index (WHO-5). Self-report data were merged with biomedical variables from the NCDR.

The five item PAID scale (PAID-5) was validated against the 20 item PAID scale (PAID-20) and the WHO-5. A total of 763 adolescents between 11 and 20 years of age, 45% of the total eligible population, responded to the study, 50% girls, mean age 15.5 (SD 2.1) years, mean HbA_{1c} 8.6 (SD1.3) (70.5 mmol/mol, (SD 9.3)), 57% used insulin pumps. The Norwegian adolescent population mean score on PAID- 20 (range 0-100) was 16.9 (SD17.1). Increased PAID-20 scores were significantly associated with being a girl, increased age, incidents of ketoacidosis and increased HbA_{1c}. No significant associations were found for other biomedical variables. WHO-5 (range 0-100) scores were in general high with a mean of 69.9 (SD18.5). 63 patients (8.3%) had elevated PAID-20 (≥40), mean score on WHO-5 in this group of adolescents was 50 (SD20).

Correlation of 0.9 (p<0.001) was found between PAID-20 and PAID-5 scores and convergent validity was confirmed by correlation of 0.5 between WHO-5 and PAID-20 as well as PAID-5. ROC analyses between PAID-20 with cut-off point of ≥40 and the PAID-5 showed both high sensitivity (0.96) and specificity (0.91). We are the first group to report from a large population based study of adolescents a high correlation between scores on PAID-20 and the shorter PAID-5 with lower scores on psychological well-being (WHO-5). We suggest PAID-5 as a useful short screening tool among adolescents with type 1 diabetes in order to reveal those with elevated diabetes-related emotional distress.

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192-LB

Gut Virome Dynamics during Pregnancy in Mothers with Type 1 Diabetes

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The environmental factors that contribute to the initiation of islet autoimmunity (IA) and acceleration to type 1 diabetes (T1D) have yet to be conclusively established, but extensive epidemiological and molecular evidence support viruses as prime environmental triggers. However, there is a paucity of data examining the impact of exposure to viral infections in utero on the development of IA and precipitation to T1D. Moreover, very little is known about the population of viruses ("virome") in women during pregnancy, let alone in pregnant mothers with T1D. To elucidate dynamics of the gut virome during pregnancy, we examined 124 longitudinal fecal specimens collected from 35 women with T1D (n=70 specimens) and 25 without T1D (n=54 specimens) during multiple trimesters of pregnancy. Samples were tested using virome capture sequencing (VirCapSeq-VERT), which characterizes all vertebrate viruses known to infect humans. In most women, irrespective of T1D status, the gut virome changed significantly between trimesters within the same individual, in both species diversity and viral load. There was a trend to greater virus positivity in mothers with vs. without T1D (64% vs. 50%, p=0.1422), while the frequency of Picobirnavirus (p=0.0039) and Tobamovirus (plant virus; p=0.0433) was significantly higher in mothers with T1D. Bioinformatic analysis using the edgeR package identified 16 species of viruses differentially abundant between mothers with and without T1D (log fold-change >4; p<0.01). VirCapSeq-VERT and differential abundance results were validated by quantitative real-time PCR for five different viruses, confirming that mothers with T1D exhibit a unique gut virome profile during pregnancy. Whether this influences risk of IA/T1D in their offspring will be examined by longitudinal follow-up of the unique ENDIA cohort.

Supported By: Australian National Health and Medical Research Council; JDRF; The Leona M. and Harry B. Helmsley Charitable Trust

193-LB

Virome-Capture Sequencing of the Gut and Plasma Virome in Children with Islet Autoimmunity

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The role of enteroviruses (EVs) as prime environmental triggers of type 1 diabetes (T1D) remains controversial. A plethora of epidemiological and experimental data provide compelling support for the hypothesized etiological contribution of EVs to the development of islet autoimmunity (IA) and T1D, but two major weaknesses limit its widespread acceptance: the significant heterogeneity in experimental design and the selective focus on EVs in most studies. These may potentiate significant publication bias and overestima-

tion of the strength of association between EVs and T1D, compared to that of lesser examined viruses. To comprehensively re-evaluate the association between IA and all viruses without bias, we characterized the entire population of vertebrate-infectious viruses in the gut and/or plasma of 45 children with IA and age/gender matched controls. Virome capture sequencing (VirCapSeq-VERT) of 64 fecal and 118 plasma samples detected 28 different genera of viruses from over 50 million metagenomic reads. Overall, 89/182 (49%) of samples were positive for at least one eukaryotic virus. Detection sensitivity of VirCapSeq-VERT vs. qPCR was confirmed for the most commonly detected viruses, including EV and rotavirus. The frequency of viruses, inclusive of EVs, did not differ significantly between IA cases and control children. However, overall EV abundance was significantly higher in both stool and plasma of IA cases. More specifically, coxsackievirus A2 (CVA2), CVB3 and ECHOvirus 30 were present at significantly greater levels in case stool (log fold-change >12; p<0.01) while CVA16, CVB3 and CVB5 were more abundant in case plasma (log fold-change >2.5; p<0.01). These findings support an etiological role of EVs in IA/T1D and further the notion that viral load is a critical factor in EV-induced T1D pathogenesis. The superior sensitivity of VirCapSeq-VERT compared with conventional NGS highlights its vast potential to explore the association between viruses and IA/T1D.

Supported By: Diabetes Australia Research Trust; Australian National Health and Medical Research Council; Diabetes Australia

194-LB

Text-Message Intervention for Teens with Type 1 Diabetes (T1D) Preserves A1c: Results of an RCT

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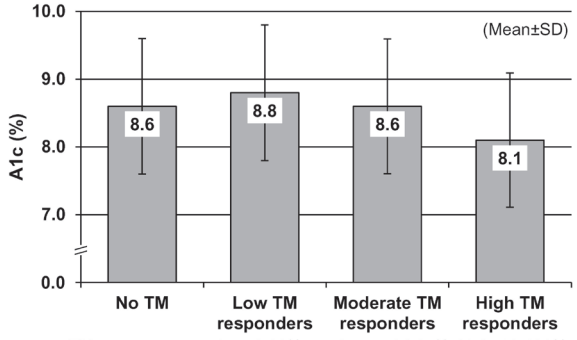
Healthcare transition for young persons with T1D remains challenging; success in adult care (visit frequency and A1c) post-transfer is best predicted by self-management during adolescence. We aimed to support self-care during transition and assessed the impact on A1c of 2 interventions, text messaging (TM) and problem-solving (PS), in a 2x2 factorial design.

In a 12-month, 2-site RCT, 301 teens (50% male, 22% minority) were randomized to TM, PS, TM+PS, or neither. At baseline, teens were 15.0±1.3 y/o with T1D for 6.5±1.3 yr; mean A1c 8.5±1.1%, 63% pump-treated; groups did not differ by baseline characteristics. All participants were seen quarterly. TM group received 2-way texts with daily reminders to check and reply with BG levels at self-selected times, starting with 1 text/day and gradually increasing to a max of 4 texts/day. The PS group received 5 modules focused on self-care emphasizing increased BG monitoring and insulin bolus dosing as well as self-advocacy and transfer preparation. Over 1 year, A1c increased overall to 8.7±1.2% (p<.008). In a multivariate mixed model, frequency of response to TM significantly predicted A1c (p<.003, Figure), while PS did not. A1c benefit in the TM+PS was similar to that in the TM group.

With heightened mobile use by teens, 2-way TM appears to preserve and may improve glycemic control in teens in T1D. Continued texting through transition may offer a means to support self-care post-transfer.

Figure.



Supported By: National Institutes of Health (R01DK095273, P30DK036836); JDRF (2-SRA-2014-253-M-B)

195-LB

Coxsackievirus B4-E2 Strain Isolated from a Patient with Type 1 Diabetes (T1D) Transactivates Human Endogenous Retrovirus Type W: Organ and Virus-Specific Activation-Like Herpesviridae in Multiple Sclerosis (MS)?

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Human endogenous retroviruses (HERVs) represent 8% of the human genome and have been associated with several autoimmune diseases. Most of HERV are repressed genetic elements, unless they are transactivated under pathological conditions. In particular, HERV-W, which has been involved in the pathogenesis of MS, can be transactivated by environmental viruses such as EBV, HHV6 or HSV-1. HERV-W sequences may encode the HERV-W-Env protein that causes immunoinflammatory effects, promotes autoimmunity and has direct cytotoxic effect on non-immune TLR4 positive cells.

We have previously observed that (i) HERV-W-Env protein is expressed in the sera of 60% of T1D patients (n=30) and in 75% of pancreas sections from nPOD cohort (n=20), (ii) its mRNA is upregulated in PBMC from T1D patients and (iii) it inhibits insulin secretion by human primary β cells.

Coxsackievirus B (CV-B) are enteroviruses that have been associated with T1D etiology. Here, we present data supporting the concept that HERV-W-Env could represent a missing link between environmental factors and T1D. Indeed, when the CV-B4E2 strain, previously isolated from a T1D pancreas, has been used for in vitro infection of human cells (Hep2), the transcription of HERV-W-Env mRNA has been significantly upregulated compared to non-infected cells ($p < 0.001$ at MOI=10-2; $p < 0.05$ at MOI=10-5). Interestingly, this effect seems to be strain specific as it was not observed with the CV-B4 strain, which was not isolated from T1D.

Taken together, our results indicate that HERV-W-Env mRNA could be transactivated by enteroviruses such as CV-B4E2. These results may explain a possible link between enteroviral infection and T1D, through the transactivation of HERV-W-Env, an endogenous retroviral protein with pro-diabetogenic features.

196-LB

Duodenal Atresia, Intestinal Malrotation, Annular Pancreas, Gastric and Pancreatic Heterotopia, and Insulin Dependent Diabetes Caused by a Novel Compound Heterozygous Mutation in RFX6

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RFX6, is essential for endoderm development and pancreatic islet function. Pathogenic variants in RFX6 cause Mitchell-Riley syndrome, a disorder of permanent neonatal diabetes and congenital gastrointestinal defects. We describe a novel compound heterozygous mutation in RFX6 causing severe gastrointestinal defects, growth failure and childhood onset diabetes. A premature female infant presented with annular pancreas, duodenal atresia and intestinal malrotation, repaired via laparotomy. At age 8, she had growth failure, normocytic anemia, and hyperglycemia, without polyuria or polydipsia. Islet cell antibody and MODY genetic testing were negative. She was diagnosed with type 1b diabetes and required low doses of insulin. At age 10, she developed epigastric pain. EGD revealed normal gastric mucosa. Stool samples were hemoccult positive, prompting further investigation. Capsule endoscopy revealed extensive polypoid lesions in the proximal duodenum. CT enterography and Meckel's scan demonstrated heterotopic gastric tissue in these polyps. A 50 cm resection of the proximal duodenum revealed 11 polyps staining positive for gastrin, ghrelin, pepsinogenC, MUC5AC, MUC2, insulin, PDX1 and amylase confirmed gastric, intestinal and pancreatic tissue in these polyps. Her anemia, abdominal pain, weight gain, linear growth acceleration and pubertal progression improved. Genetic analyses revealed a compound heterozygous mutation in RFX6. We describe a case of Mitchell-Riley syndrome due to a novel compound heterozygous mutation in RFX6. Our patient had annular pancreas, duodenal atresia, malrotation, childhood onset diabetes with gastric and pancreatic heterotopia which has been described in two other cases. This case highlights the importance of genetic testing for rare causes of diabetes in patients that present with diabetes and congenital gastrointestinal anomalies.

For author disclosure information, see page LB107.

197-LB

Patient Web Portal (PWP) Activation and Usage in Pediatric Diabetes Clinic

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PWPs improve patient communication with health care providers and health management involvement, but adoption is slow and use is variable among the medically underserved. In adults with diabetes, PWPs are associated with better glycemic control, but benefits in children are unclear. At our facility, patients >14 years old may use an account, and caregivers may have proxy accounts for patients of any age. Accounts are activated when the patient or proxy goes online and uses the code provided by our clinic. Our PWP allows appointment scheduling, refill requests, and school plan requests. In summer 2016 a student intern worked in clinic 3 days per week to guide patients through PWP activation and instruct them in PWP usage.

We used logistic regression in 2141 patients with ≥2 encounters in our clinic over the 12 months to evaluate predictors of PWP activation (age, gender, race/ethnicity, primary language, insurance, duration of diabetes, and hemoglobin A1c). In 1375 patients who attended clinic during the 2016 summer, we examined the effect of an in-person assistant on PWP activation rates and PWP usage over a seven month period.

Non-Hispanic white category (p=.001), English language (p<.001), private insurance (p<.001), and shorter diabetes duration (p=.006) were significantly associated with increased PWP activation. Clinic attendance on the intern's days increased odds of activation by 59% (p<.001), resulting in 56% activation rate for patients seen in summer 2016. 24% of all patients used the PWP, 7.4% for refills, 8.5% for scheduling, and 16.8% for school health plans.

Factors associated with risk of poorer outcomes were also associated with lower PWP activation, but it is unclear whether at risk patients would be more likely to engage in communication with the clinic if they had an active PWP. An in-person assistant improved activation rates, and nearly half of patients with an active account used it to communicate with the clinic.

PREGNANCY—BASIC SCIENCE/TRANSLATIONAL

198-LB

Oxidative Stress Linked to Lower Mitochondrial Fat Oxidation in Human Mesenchymal Stem Cells from High Adiposity Infants Born to Mothers with Obesity: The Healthy Start BabyBUMP Project

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Maternal obesity increases offspring risk for metabolic disease later in life, though the molecular mechanisms are unclear. We hypothesized that mesenchymal stem cells (MSCs) from umbilical cord tissue of infants born to mothers with obesity would demonstrate lower mitochondrial (MT) fat oxidation (FAO) and greater oxidative stress (OS) when differentiated to myocytes in vitro. MSCs were from term infants (39.8±0.2 wk) born to mothers with obesity, but no diabetes (Ob MSC, n=14; BMI: 34.6±1.0 kg/m^2) or to normal weight mothers (NW MSC, n=15; BMI: 21.1±0.3 kg/m^2). Glutathione redox (GSH: GSSG) assessed OS in undifferentiated (d0) and 21 day myogenic differentiating (d21) MSCs. Complete ($^{14}CO_2$) and incomplete (^{14}C-ASM) oxidation of radiolabeled fatty acids was measured at d21. Though all Ob MSCs had lower Total FAO vs. NW MSCs (^{14}C-ASM + $^{14}CO_2$; -30%, P<0.05), we observed a clear divergence within Ob MSCs for ^{14}C-ASM/$^{14}CO_2$ ratio, which represents MT efficiency for FAO and is linked to insulin resistance (NW: 35±4; ObLo: 19±2, n=5; ObHi: 51±2, n=9; P<0.0005). Elevated ^{14}C-ASM/$^{14}CO_2$ in Ob MSC, representing less MT efficiency, tracked with lower $^{14}CO_2$, and higher infant fat mass (24-48h postnatal; NW: 0.27±0.3, ObLo: 0.27±0.05, ObHi: 0.40±0.04 kg; P<0.05) and umbilical cord blood (CB) insulin (NW: 5.8±0.8, ObLo: 4.7±0.9, ObHi: 12.0±1.6 pM; P<0.05). GSH: GSSG was not different at d0, though Ob MSCs with high ^{14}C-ASM/$^{14}CO_2$ developed OS by d21 (GSH: GSSG: NW: 9.8±0.4, ObLo: 9.5±0.9, ObHi: 8.2±0.5; NW vs. ObHi, P<0.05; low GSH: GSSG=high OS). GSH: GSSG tends to correlate with $^{14}CO_2$ (r=0.350, P=0.08) and inversely correlates with CB insulin (r=-0.514, P=0.03). These data show that infants born to mothers with obesity, who also exhibit greater adiposity and CB insulin at birth, have MSCs with intrinsically reduced MT FAO and greater OS, suggesting programmed risk for metabolic dysfunction in this subset of children.

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199-LB

Effect of Maternal Diabetes Mellitus on Fetal Serum Exosomal microRNA Expression

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Exposure to diabetes in utero has long-term effects on the infant including predisposition to type 2 diabetes mellitus (DM) and obesity. Exosomes are small membrane vesicles secreted by cells that transfer microRNAs (miRNA) to recipient cells enabling gene-based communication. We hypothesize that exposure to maternal DM effects exosomal miRNA in the fetal circulation. Umbilical cord serum was collected from healthy, term offspring of women with type 2 or gestational DM (DM group) and normoglycemic controls undergoing elective C-section. Exosomes were isolated from which total RNA was extracted. C. elegans miRNA mimic was added during RNA isolation as spike-in control. Reverse transcription was performed on equal volumes of total RNA and quantitative PCR was performed. Expression of 7 miRNAs (miR-126, 130b, 148a, let 7a, 132, 29a and 222) was compared between groups using Mann Whitney U Test and p<0.05 was considered significant. These 7 miRNA were selected as they are known to be regulated by dysglycemia. All 7 miRNAs were detectable in the exosomes, average Cq < 32. Expression of miRNA-let7a was significantly higher in the DM group (p=0.044). miRNA-130b and miRNA-126 expression approached statistical significance. No difference in expression was observed in the other miRNAs. See Table 1. This study identifies increased abundance of specific miRNAs in fetuses exposed to the maternal diabetic milieu.

Table 1. Fold Change Expression of miRNA between DM vs. Control Groups.

	miR-126	miR-130b	miR-148a	miR-let7a	miR-132	miR-29a	miR-222
DM	1.56	1.41	0.94	1.28	1.29	2.21	1.83
P value	0.082	0.094	0.348	0.044	0.332	0.120	0.202

Supported By: Endocrine Fellows Foundation; National Institutes of Health; Harold Hamm Diabetes Center; CMRI Metabolic Research Program

200-LB

Feto-Placental Macrophages Maintain Antiinflammatory M2 Polarization Despite Presence of Gestational Diabetes Mellitus

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Background: Hofbauer cells (HBCs) are macrophages of the feto-placental unit. They possess an antiinflammatory M2 phenotype, however, recent studies claimed that infections and also diabetes during pregnancy cause a switch to a proinflammatory M1 state. Our study challenges this claim, showing that HBCs maintain antiinflammatory properties in spite of gestational diabetes mellitus (GDM) and associated low-grade inflammation.

Methods: HBCs were isolated from placentas of healthy and GDM women. Surface markers associated with M1 or M2 phenotype were measured by FACS. Immune histochemistry in placental tissue sections was used to confirm the phenotype within tissue. Supernatant from control and GDM-HBCs was used in a Multiplex ELISA-on-beads approach to measure secretion of cytokines, chemokines and growth factors. Macrophage-endothelial cross-talk was investigated by exposing human placental endothelial cells (pAECs) to conditioned medium from control and GDM-HBCs; endothelial activation was determined by adhesion molecule expression.

Results: FACS and immune staining showed that M2 markers CD206 and CD209 are increased in GDM-HBCs (+42% p=0.03; +72% p<0.001, resp.). Increased CD86, a M1 marker, was found in GDM-HBCs (+33%, p=0.08). No differences were found in cytokine, chemokine and growth factor secretion; only IL-1β and IL-6 secretion from GDM-HBC was increased (both about +50%, n.s.). Exposure to GDM-HBC supernatant did not induce ICAM-1, VCAM-1, selectins, and VE-Cadherin in pAECs compared to control-HBC supernatant.

Conclusion: Our data show that HBCs maintain their antiinflammatory M2 phenotype even in pregnancies affected by GDM. This consistent phenotype might be important for propagation of maternal tolerance against the fetus and protection of the fetus from a low-grade inflammatory environment, similar to the evolutionary adaptation in mammals allowing implantation of embryos in the mother's womb in early pregnancy.

Supported By: Austrian Science Fund (DK-MOLIN W1421)

201-LB

WITHDRAWN

202-LB

Effect of Maternal Diabetes Mellitus on Placental $VEGF_{165b}$, a Novel Isoform of Vascular Endothelial Growth Factor

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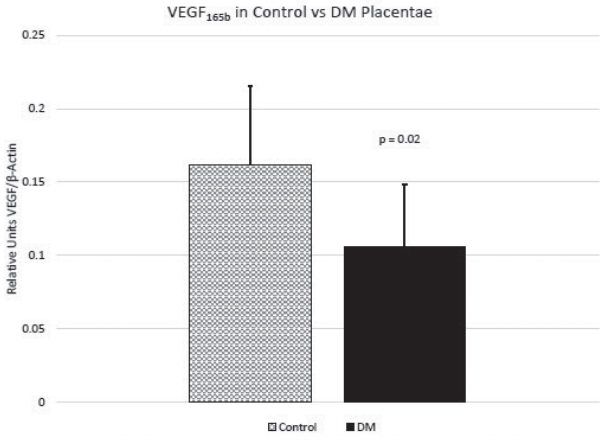
Fetal exposure to maternal DM yields both immediate and long-term effects on offspring. Preliminary data shows that vascular endothelial growth factor (VEGF) is increased in cord serum of diabetic pregnancies. Anti-angiogenic isoforms, such as $VEGF_{165b}$, have not been studied extensively in diabetic pregnancies. We hypothesized that the diabetic milieu leads to a decrease in cord and placental abundance of $VEGF_{165b}$, thereby altering regulation of angiogenesis in the fetoplacental unit. Cord serum and placentae were collected at delivery from otherwise healthy term offspring of women with T2DM or GDM and normoglycemic controls. $VEGF_{165b}$ was measured in cord serum by ELISA and in placentae by Western blot. Results were analyzed using Student's t-test, and $p<0.05$ was considered significant**.** $VEGF_{165b}$ was not detectable in cord serum. $VEGF_{165b}$ was found to be 34% higher in control placentae compared to DM ($p=0.02$). In utero exposure to DM increases VEGF in cord serum of diabetic pregnancies, but the ratio of angiogenic to anti-angiogenic factors may be even more important for vascular health. A relative decrease in $VEGF_{165b}$ in the fetoplacental unit may be associated with increased pathological vascular formation. We suspect that hyperglycemia and oxidative stress associated with DM contribute to these changes. Future studies will assess the abundance of total VEGF in DM and control pregnancies.

Figure.



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PREGNANCY—CLINICAL/EPIDEMIOLOGY

203-LB

Screening for Diabetes following Gestational Diabetes at St. Luke's Hospital in San Francisco, CA

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Introduction: The incidence of type 2 diabetes (T2DM) after gestational diabetes (GDM) increases markedly in the first 5 years after delivery. Women with GDM have a 7.43 higher risk of developing T2DM compared with those who had normal pregnancies. In 2015, only 31% of the patients that had GDM at a community hospital in San Francisco had a subsequent screening test for T2DM. We developed a quality improvement project to improve this rate utilizing different approaches.

Methods: Patients with GDM that delivered at a community hospital were included in this project. We distributed surveys to assess barriers to diabetes screening after delivery. Patients also received information on the risk of developing diabetes.

The intervention period started after delivery and it was divided in three trimesters. The first trimester patients received a reminder phone call about the screening test for T2DM. There was no intervention period in the second trimester, as this period was used as a baseline for comparisons. In the third trimester a congratulatory letter was sent to patients notifying them about a gift certificate upon completion and verification of the screening test for T2DM.

Results: A reminder phone call about the screening test for T2DM was the most effective intervention with 38% of patients completing the test vs. 26% in the control period, resulting in a 46% improvement. A letter with an incentive gift certificate did not seem to be as effective with only 29% of patients completing the post-delivery screening test for diabetes.

Conclusions: A reminder phone call to patients resulted in a 46% increase in the screening compliance rate compared to patients whom did not receive a reminder call in the control period. Additional cycles attempting different approaches are needed to further improve screening test for T2DM. Possible options include combining a phone call with a letter or email. The monetary reward did not seem to have an impact on post screening rates and is a non-sustainable intervention.

204-LB

BMI Change between Pregnancies and Neonatal Outcomes: Data from the Utah Population Database from 1989-2015

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Obesity in pregnancy is associated with adverse neonatal and maternal outcomes. Our study looked at the effect of inter-pregnancy weight change on outcomes. We investigated the impact of maternal inter-pregnancy body mass index (BMI) change between the beginning of the 1st (t1) and beginning of the 2nd (t2) pregnancy on neonatal outcomes.

We identified 265,219 women with singleton 1st and 2nd births between 1989 and 2015 from the Utah Population Database. Inter pregnancy BMI change was grouped as: <-1, [-1, 0), [0, +1), [1, 2), [2-4), ≥4 BMI units. The group with BMI change 0 to +1 unit was the reference. Analysis is presented on 1.) the whole population 2.) those with "normal" BMI (18.5-24.99 kg/m2) at t1. Neonatal outcomes included small for gestational age (SGA) and large for gestational age (LGA). Models were adjusted for age, race/ethnicity, education, smoking, diabetes, hypertension, assisted reproduction, prior SGA and LGA births.

Higher risk of LGA neonates was seen with rise in BMI units, and higher SGA risk as BMI units decreased. Women who lost more than 1 BMI units had a 17% reduction in LGA, 24% increase in SGA neonate. Women who gained > 4 BMI units had 34% increase in LGA, 18% reduction in SGA neonate. In women with normal BMI at t1, we saw an increased risk of LGA neonate of 15%, 36%, 54% for 1-2 units, 2-4 units and ≥4 BMI units increase respectively. Women with normal BMI at t1 also had an increased risk of SGA neonate of 28% and 14% with >1 BMI and 0 to 1 BMI units decrease respectively. All findings were highly statistically significant.

This is the first, large U.S. population study of the impact of inter-pregnancy BMI change on neonatal outcomes. We found significant impact of maternal inter-pregnancy BMI change on neonatal outcomes. This included women with normal t1 BMI. This is valuable healthcare information for all providers taking care of women of childbearing age. With this information, we plan to develop risk assessment tool to identify women at risk and develop counseling programs.

Supported By: University of Utah

205-LB

Higher Maternal 2-Hour Glucose Is Associated with Lower Placental DNA Methylation at PDE4B Locus

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Maternal hyperglycemia during pregnancy is associated with fetal growth and adverse outcomes over the short- and long-term in offspring. Placental adaptation to maternal hyperglycemia has been suggested as part of the pathophysiology explaining these associations, but the exact mechanism remains unknown. We tested associations between maternal glucose and DNA methylation across the genome in 448 fetal placenta samples collected at delivery from participants in our prospective birth cohort, Gen3G. Pregnant women were recruited at 1st trimester, and followed until delivery; all women performed a standard 2-hour 75g oral glucose tolerance test at 24-28 weeks. We measured genome-wide DNA methylation in placenta using the novel Illumina EPIC array covering >850,000 CpG sites. We applied stan-

For author disclosure information, see page LB107.

dard quality control procedures, and adjusted for technical batch effects. We analyzed 791,131 individual CpGs after excluding low quality and SNP associated probes. We performed association analyses using robust regression on M-values and controlled the false discovery rate at 5% (q <0.05). We found that higher maternal 2-hour glucose levels were strongly associated with lower methylation levels at 5 CpG sites located in the PDE4B locus (strongest association at cg13349623; β= -0.204; P=2.29x10^{-9}). Identified CpG sites are located within a regulatory region of PDE4B overlapping DNAse1 hypersensitivity cluster and histone H3K27Ac mark. PDE4B hydrolyzes the second messenger cAMP, which is a key regulator of many physiological processes. PDE4B has been implicated in inflammatory pathways, and suggested to participate in placental pathophysiology of preterm birth in animal models. This is the first study to report the epigenetic role of PDE4B in placental adaptation to maternal glycemia.

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206-LB

Maternal and Neonatal Outcomes and 1,5-anhydroglucitol in Pregnancies Complicated by Diabetes

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1, 5-anhydroglucitol (1,5-AG) is a measure of postprandial hyperglycemia (PH), from the previous 1-2 weeks. Low levels in pregnancy are associated with poor glucose control and macrosomia. We hypothesized that 1.) low 1, 5-AG is associated with enlarged 3rd trimester ultrasound abdominal circumference (AC) [a macrosomia surrogate] and related complications: cesarean delivery (CD) and neonatal hypoglycemia (NH); and 2.) lower 1, 5-AG levels would be seen in women with preeclampsia given association between hyperglycemia, vascular damage and preeclampsia.

A retrospective study of 403 diabetic pregnancies. Data were categorized and analyzed by type of diabetes. 1, 5-AG and A1C averaged over gestation. Table 1.

GDM women had the highest 1, 5-AG and lowest A1C, followed by T2DM and T1DM, suggesting less glucose exposure in GDM. Multivariate analysis, adjusting for maternal BMI, ethnicity and gestational age, showed an inverse relationship between 1, 5-AG and AC, p<0.001. Most T1DM women delivered by CD, followed by T2DM and GDM. Maternal 1, 5-AG was lower in the NH group, those with CD and preeclampsia.

Low 1, 5-AG is an indicator of macrosomia and its complications. Its association with CD and preeclampsia could have significant public health implications to reduce morbidity and healthcare cost. Given the shorter time interval compared to A1C makes it an optimal management tool in pregnancy.

Table 1. Results. 1, 5-AG and A1C Comparisons Between Groups [Mean (SD)]

Variables	Categories	Total (N=403)	Gestational diabetes (N=81)	Type 1 diabetes (N=150)	Type 2 diabetes (N=172)	P-value
Age (years)		31.39 (6.00)	32.48 (5.41)	28.90 (6.11)	33.04 (5.45)	<0.001
BMI (kg/m2)		31.71 (8.17)	34.14 (8.87)	27.07 (5.52)	34.58 (7.96)	<0.001
1, 5-AG (mcg/mL)		5.52 (4.03)	7.72 (4.19)	3.50 (2.59)	6.23 (4.21)	<0.001
A1C (%)		6.25 (1.01)	5.50 (0.54)	6.58 (1.06)	6.32 (0.94)	<0.001
AC* (cm)		30.99 (4.61)	31.53 (5.14)	31.12 (4.89)	30.64 (4.10)	0.37
C-section	No	145 (36.0%)	44 (54.3%)	41 (27.3%)	60 (34.9%)	0.001
	Yes	258 (64.0%)	37 (45.7%)	109 (72.7%)	112 (65.1%)	
Pre-eclampsia	No	340 (84.4%)	75 (92.6%)	117 (78.0%)	148 (86.0%)	0.01
	Yes	56 (13.9%)	5 (6.2%)	29 (19.3%)	22 (12.8%)	
	Missing	7 (1.7%)	1 (1.2%)	4 (2.7%)	2 (1.2%)	

1, 5-AG in mothers of neonates with and without hypoglycemia

Hypoglycemia		
No (279)	Yes (N=77)	P-value
5.7 (3.9)	4.4 (3.9)	0.006

1, 5-AG in women undergoing C-section

C-section		
No (145)	Yes (N=258)	P-value
6.7(4.2)	4.8 (3.8)	<0.001

1, 5-AG in women with and without preeclampsia

Preeclampsia		
No (340)	Yes (N=56)	P-value
5.8 (4.1)	3.9 (3.4)	0.001

A1C in women with neonates with and without hypoglycemia

Hypoglycemia		
No (279)	Yes (N=77)	P-value
6.2 (1.0)	6.7 (1.1)	<0.001

A1C in women undergoing C-section

C-section		
No (145)	Yes (N=258)	P-value
5.9 (0.8)	6.4 (1.1)	<0.001

A1C in women with and without preeclampsia

Preeclampsia		
No (340)	Yes (N=56)	P-value
6.2 (1.0)	6.8 (0.9)	<0.001

* Abdominal circumference by ultrasound during the 3rd trimester.

207-LB

Gestational Diabetes and Long-Term Renal Function: A Prospective Study of over 10 Years Follow-Up

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Chronic hyperglycemia is a risk factor for renal impairment. It is not clear whether gestational diabetes (GDM), independent of subsequent type 2 diabetes (T2D), is a risk factor for renal impairment after the index pregnancy. In the Diabetes and Women's Health Study, we examined the independent and joint associations of GDM and subsequent T2D on long-term renal function among 616 women with GDM-complicated and 620 without GDM-complicated pregnancies in the Danish National Birth Cohort. At 10+ years follow-up after the index pregnancy, serum creatinine (mg/dl), and urinary albumin (mg/l) and creatinine (mg/dl) levels were measured, from which estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2) and albumin-to-creatinine ratio (ACR; mg/g) were derived. T2D was diagnosed according to the ADA criteria based on HbA1c or oral glucose tolerance test results at follow-up (n=120); additional 75 women reported physician diagnosed T2DM. Women with prior GDM had significantly higher ACR (7.9 vs. 4.1 mg/g, P=0.03), and a higher prevalence of elevated ACR (ACR ≥ 20 mg/g; 4.8 vs. 2.3%, P=0.02) compared to women without GDM. Yet, these differences were not significant after adjusting for pre-pregnancy body mass index and other confounders. Women with prior GDM and subsequent T2D (n=186) had an increased risk of elevated ACR [aOR (95% CI=2.53 (1.01, 6.33)] compared to women with neither, even after adjusting for major confounders. GDM without subsequent T2D was not related to ACR levels. Compared to women without GDM or T2D, women with prior GDM with [β coefficient (95% CI) =8.2 (5.9, 10.4)] and without [β coefficient (95% CI) =3.0 (1.4, 4.6)] subsequent T2D had significantly higher eGFR after adjusting for major risk factors. Our findings suggest that women with GDM pregnancy are more likely to show signs of glomerular hyperfiltration at 10+years postpartum, indicating early stages of renal damage. However, only those with subsequent T2D showed further renal damage as indicated by elevated ACR.

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208-LB

Maternal Metabolism of Glucose and Lipids in Lactating and Non-lactating Women at 6-Weeks Postpartum

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Objective: To determine the effects of ongoing lactation on maternal metabolism of glucose and lipids at 6 weeks postpartum.

Methods: Twenty one (15 lactating and 6 non-lactating) women were studied at 6 weeks postpartum in the fasting state and during a two-step clamp. Stable isotopes were infused to quantitate endogenous glucose production (EGP), de novo lipogenesis (DNL) and rate of appearance of free fatty acids (RaFFA). Body composition was measured via DXA, intrahepatic triglycerides (IHTG) via magnetic resonance spectroscopy, and postpartum hormones via immunoassay.

Results: Lactating and non-lactating women were of similar age, body composition and IHTG. HMW adiponectin (53 ± 33 ng/mL/kg in lactating vs. 49 ± 17 ng/mL/kg in non-lactating women, P=0.76) and DNL (7.7 ± 4.6% in lactating vs. 7.5 ± 5.0% in non-lactating women, P=0.83) were not different between the groups. Fasting insulin was equally low in both groups (4.3 ± 5.0 in lactating vs. 6.1 ± 3.9 in non-lactating women, P=0.42). Lactating women had a 22% increase in fasting EGP (P=0.03) and reached their maximal response to insulin (M/I) during step 1 of the clamp rather than during step 2 of the clamp compared to non-lactating women. In lactating women only, plasma prolactin was positively associated with EGP (r=0.52, P=0.03) and glucose infusion rate during step 1 of the clamp (r=0.61, P=0.004), and negatively associated with IHTG (r= -0.57, P=0.03). For all women combined, HMW adiponectin was inversely associated with RaFFA (r= -0.52, P=0.048).

Conclusions: Insulin concentrations are low at 6 weeks postpartum regardless of lactation status. Low insulin and high prolactin concentrations during lactation appear to stimulate a higher basal EGP to support milk production while protecting the liver from excess fatty acids. Lastly, the higher whole-body glucose disposal observed during lactation cannot be attributed exclusively to insulin action in the presence of low adiponectin concentrations.

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209-LB

Newborn Body Habitus and Maternal Factors in GDM

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Maternal GDM is associated with risk of macrosomia and large for gestational age. Both macrosomia and neonatal body composition have been associated with measures of maternal metabolic health.

The purpose of this study was to examine if maternal metabolism affects neonatal weight and neonatal fat mass in women with treated GDM.

Methods: 43 women with GDM and their infants were included. Enrollment was at 30 weeks. Fasting maternal bloods were taken at 36 weeks gestation and cord blood at delivery. Infant anthropometry was assessed with air displacement plethysmography. Relationships between infant birthweight, infant % fat mass, and maternal variables were evaluated.

Results: Most women were treated with diet and lifestyle therapy alone (n=34 (79%)). Mean HbA1c was 31 mmol/mol (SD 3.9) and BMI 27.5 kg/m^2 (SD 6.34). Average neonatal birthweight was 3547.7g (SD 553.5), body fat % (boys 9.99 (SD1.55), girls (12.16 (SD5.60)). In all infants, there was a moderate correlation between infant weight and body fat % (rho 0.33, P=0.04). Nine of 43 infants had birthweight > 4000g, and 9 of 43 had body fat > 15%. However, only 5/9 infants with macrosomia also had body fat >15%. Birth weight was correlated with maternal cholesterol (rho=-0.39, P=0.01) and maternal age (rho=-0.39, P=0.009). Associations were examined by infant sex. In girls, birth weight correlated with cord LDL (rho=0.65, P=0.03), and body fat % was correlated with enrollment BMI (rho=0.49, P=0.03), maternal cholesterol (rho=-0.47, P=0.05) and cord LDL (rho=0.66, P=0.04). In boys, birth weight was correlated with maternal age (rho=-0.52, P=0.01), maternal cholesterol (rho=-0.52, P=0.02), and body fat % was not correlated with any maternal measure.

Conclusions: In these women with treated GDM, despite a broad range of birth weights and infant body fat %, there were few correlations with maternal metabolic factors from late gestation, and these were infant sex-specific. These results suggest that controlling GDM attenuates the relationship between maternal metabolism and infant growth.

Supported By: Australian Diabetes Society (to H.L.B.); Royal Brisbane and Women's Hospital Foundation

210-LB

Diagnosis and Management of Gestational Diabetes (GDM) Improves Maternal Weight Management during Pregnancy

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Despite entering pregnancy at higher body mass indices (BMI) and gaining more weight in the first trimester, women diagnosed with GDM gain less total gestational weight than women without GDM. We hypothesized that diagnosis and management of GDM prompts women to improve weight management during pregnancy. We used data from the "Health of Mothers" (HOMe) study, a prospective cohort study examining weight changes during and after pregnancy in women with and without GDM, to compare mean rate of gestational weight gain before and after GDM screening as well as mean rate of postpartum weight loss (up to the postpartum visit). Rate comparisons were conducted using weighted t-tests and inverse probability weighting to account for differences in age and pre-pregnancy BMI, 2 key risk factors for GDM. We included participants for whom age, pre-pregnancy BMI, and GDM status data were available (n=88; 39 with GDM, 49 without GDM). Pre-pregnancy BMI was significantly higher for women with GDM than for women without GDM (31.34 +/- 8.75 kg/m2 vs. 27.82 +/- 7.00 kg/m2, respectively, p=0.039); the groups were otherwise similar in terms of age, parity, race, income, insurance status, and education level. The groups did not differ significantly in their mean rate of gestational weight gain before GDM screening (0.41 +/- 0.26 kg/wk vs. 0.45 +/- 0.35 kg/wk, respectively, p=0.989) or in their mean rate of postpartum weight loss (-1.37 +/- 0.58 kg/wk vs. -1.28 +/- 0.46 kg/wk, respectively, p=0.506). However, women with GDM demonstrated a significantly lower mean rate of gestational weight gain following GDM screening than women without GDM (0.30 +/- 0.28 kg/wk vs. 0.53 +/- 0.28 kg/wk, respectively, p=0.004). These findings indicate women temporarily improve weight management during pregnancy in response to the diagnosis and management of GDM. Interventions designed to sustain improvements in maternal weight management after delivery may be useful in preventing T2DM after a diagnosis of GDM.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (P30DK092986)

EPIDEMIOLOGY—AGING

211-LB

Na/K-ATPase Mimetic pNaKtide Peptide Attenuates Aging in Old C57Bl6 Mice

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Aging is characterized by inevitable but progressive decline of physiological integrity, and is evident by a number of physiological changes including loss of cell division, oxidative stress, DNA damage, and senescence-associated gene overexpression. As we identified that the Na/K-ATPase can amplify oxidant signaling, we speculated that a peptide designed to inhibit this pathway, pNaKtide, might decrease senescence and also maintain physiological integrity. To test this hypothesis, C57Bl6 mice were divided into 6 groups as follows: (1) young control, (2) young control+pNaKtide, (3) old control (19 months) (4) old+pNaKtide, (5) old +Western diet (WD), and (6) old+WD+pNaKtide. The pNaKtide was administered every week (IP) for 2 months. Progression to senescence was evaluated in liver and kidney of mice by studying morphology changes and RT-PCR. Hepatic and renal tissue of old mice showed significantly elevated levels of p21, apolipoprotein J, Collagenase 1, fibronectin, pATM, p51 and pCHK2 as compared to young control. Old mice fed a WD had more deterioration of the above genes, along with elevated GTT and HOMA-IR levels. Morphological symptoms such as DNA damage, activation of senescence associated β-galactosidase, hepatic and renal fibrosis and inflammation were also significantly increased in old mice and old mice fed WD. On the contrary, old mice and old mice fed WD and treated with pNaKtide showed similar morphology and gene expression profile comparable to control group. Taken together, our study demonstrates for the first time that Na/K-ATPase mimetic pNaKtide significantly alleviated the genetic and phenotypic attributes of aging. pNaKtide is a novel drug for treating cellular damage responses that may contribute to manifestations of aging.

Supported By: National Institutes of Health

For author disclosure information, see page LB107.

EPIDEMIOLOGY—CARDIOVASCULAR DISEASE

212-LB

Intensive Blood Pressure Control Reduces Cardiovascular Events in Patients with Prediabetes

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The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated significant reductions in cardiovascular disease (CVD) events with intensive systolic blood pressure (SBP) treatment (<120 mm Hg) compared to standard treatment (<140 mm Hg) among people at high CVD risk but without diabetes. In a similar design/intervention in diabetes, the Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial did not demonstrate a significant reduction in CVD events with intensive SBP treatment. The effect of intensive SBP control in high CVD risk patients with prediabetes is unknown. We performed a sub-group analysis of SPRINT to determine if the effect of intensive vs. standard SBP treatment on the primary outcome (composite of non-fatal acute coronary syndrome, stroke, heart failure, or CVD death) and all-cause mortality was different among participants with prediabetes (baseline fasting blood glucose [FBG] ≥100 mg/dL, n=3898) vs. those with normal FBG (<100 mg/dL, n=5425). After a median follow-up of 3.3 years, the hazard ratio (HR) for the primary outcome was 0.83 (95% CI 0.66,1.03) and 0.69 (95% CI 0.53,0.89, p interaction 0.30) and for all-cause mortality was 0.71 (0.54,0.94) and 0.77 (0.55,1.06, p interaction 0.74) among those with baseline FBG <100 and ≥100 mg/dL, respectively. In SPRINT, the beneficial effects of intensive SBP control were similar among those with baseline FBG <100 and ≥100 mg/dL.

Table. Incidence rates and hazard ratios for the primary and secondary outcomes among participants with baseline fasting blood glucose above or below 100 mg/dl

	Baseline fasting blood glucose						
	< 100 mg/dl			≥ 100 mg/dl			
Outcome	Intensive Treatment (n=2,721) N (% /yr)	Standard Treatment (n=2,704) N (%/yr)	Hazard Ratio (95% CI)	Intensive Treatment (n=1,941) N (%/yr)	Standard Treatment (n=1,957) N (%/yr)	Hazard Ratio (95% CI)	P Value for Interaction
Primary outcome	142 (1.7)	174 (2.1)	0.83 (0.66 - 1.03)	101 (1.6)	144 (2.3)	0.69 (0.53 - 0.89)	0.30
Secondary outcomes							
Myocardial infarction	57 (0.7)	72 (0.8)	0.80 (0.57 - 1.14)	40 (0.6)	44 (0.7)	0.95 (0.61 - 1.45)	0.56
Acute coronary syndrome	23 (0.3)	17 (0.2)	1.32 (0.7 - 2.47)	17 (0.3)	23 (0.4)	0.76 (0.4 - 1.44)	0.23
Stroke	36 (0.4)	32 (0.4)	1.19 (0.73 - 1.91)	26 (0.4)	38 (0.6)	0.72 (0.44 - 1.2)	0.16
Heart failure	37 (0.4)	52 (0.6)	0.72 (0.47 - 1.1)	25 (0.4)	48 (0.8)	0.47 (0.29 - 0.76)	0.19
Death from cardiovascular causes	21 (0.2)	37 (0.4)	0.62 (0.36 - 1.06)	16 (0.3)	27 (0.4)	0.56 (0.3 - 1.04)	0.81
Death from any cause	89 (1.0)	125 (1.4)	0.71 (0.54 - 0.94)	65 (1)	84 (1.3)	0.77 (0.55 - 1.06)	0.74
Primary outcome or death from any cause death	197 (2.3)	240 (2.9)	0.82 (0.68 - 0.99)	134 (2.2)	182 (3)	0.73 (0.58 - 0.91)	0.42

Supported By: National Institutes of Health

213-LB

Describing the Cardio-Renal-Metabolic Patient within the Diabetes Collaborative Registry

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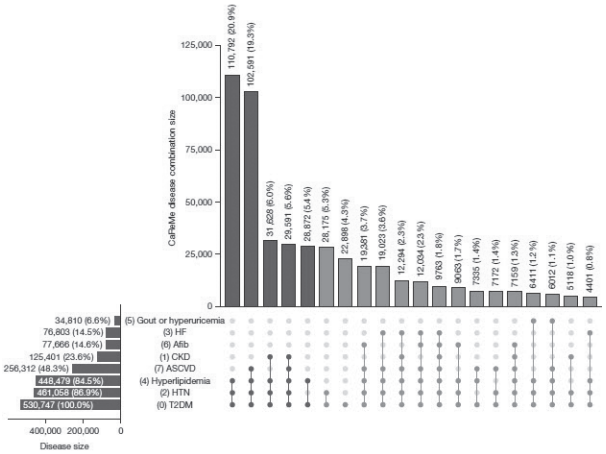
Several cardio-renal-metabolic (CaReMe) conditions, such as hypertension (HTN), hyperlipidemia, chronic kidney disease (CKD), atherosclerotic vascular disease (ASCVD), and heart failure are independently associated with worse prognosis in patients with T2D. The prevalence of these comorbidities, and their combinations, have not been well described in a contemporary T2D cohort. This cross-sectional study utilized the Diabetes Collaborative Registry to identify patients aged ≥18 years with T2D between January 1, 2013 and June 30, 2016. Concomitant CaReMe conditions included HTN, hyperlipidemia, CKD (Stages 3, 4, 5 and ESRD), ASCVD, atrial fibrillation, heart failure and gout. The prevalence of CaReMe conditions and their combinations were described. Of the 530,747 T2D patients included, only 4.3% had T2D without any other CaReMe comorbidities. HTN, hyperlipidemia, ASCVD and CKD were the most prevalent individual diseases at 87%, 85%, 48% and 24% respectively. Majority (59%) of patients had ≥3 other CaReMe comorbidities (Figure 1). T2D without concomitant CaReMe conditions is uncommon. The majority of T2D patients have ≥3 other CaReMe comorbidities, with HTN, hyperlipidemia, ASCVD and CKD being most common. These findings highlight the clinical need for novel T2D treatment strategies that address both glycemia and coexisting disease states in this high risk patient group.

Figure 1.



214-LB

Comparison of Lipid-Lowering Treatment in Patients with Diabetes and/or Cardiovascular Disease

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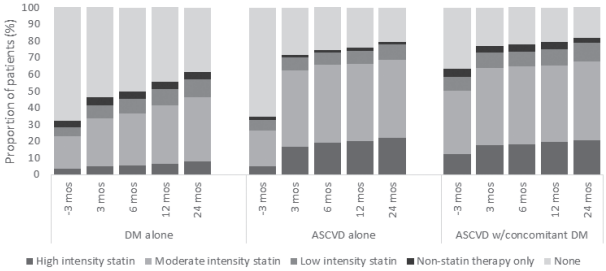
Many patients with DM or cardiovascular disease (CVD) do not receive adequate lipid lowering therapy (LLT) per ADA treatment guidelines. We characterized LLT treatment in Olmsted County, MN residents from 2005-2012 with DM alone (n=4503), ASCVD alone (n=2745), and CVD with concomitant DM (n=782). Patients were followed for up to 2 years from their index DM or CVD diagnosis, using a 5-yr look-back period to assess concomitant DM in the CVD+DM population (mean age at index 57, 70, and 71 yrs; 52%, 57%, and 56% male, respectively). At 3 months post-event, moderate-to-high intensity statins (MHIS) were prescribed to 34% of patients with DM alone; this increased to 46% by 2 yrs. 59% were not prescribed any statin therapy (Figure 1). In contrast, 62% of patients with CVD but not DM were prescribed MHIS within 3 months post-event; however, 30% were on no statin therapy, with minimal change over 2 years (Figure 1). In patients with CVD with concomitant DM, 64% were prescribed MHIS by 3 months (18% high and 47% moderate intensity), and 27% were not prescribed any statin; change was minimal over 2 years (Figure 1). These data show that despite the known added CV risk of DM, prescription patterns are markedly similar between CVD patients with and without concomitant DM and suggest that additional educational efforts may be needed to improve adherence to guideline-based lipid treatment in high-risk patients with DM and in patients with DM and known CVD.

Figure 1. Lipid-Lowering Therapy (LLT) Prescriptions in Patients with Diabetes (DM), ASCVD alone, or ASCVD with Prior DM, 3 Months Before and Up to 24 Months after Diagnosis, 2005-2012.



Supported By: Amgen Inc.; National Institute on Aging (R01AG034676)

215-LB

A Metabolic Signature of Increased CVD Risk Points to Novel Targets to Reduce CVD Complications

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Cardiovascular disease (CVD) is responsible for much of the increased morbidity and mortality of type 2 diabetes (T2D). A better understanding of the etiologic links between CVD and T2D is needed to develop new diagnostic and therapeutic tools to tackle this problem. To this end, we per-

formed global metabolomic profiling by means of the Metabolon platform on baseline plasma samples from a nested case-control set derived from a prospective T2D cohort. Included were 128 cases who experienced a fatal or non-fatal CVD event during follow-up and 324 controls who did not. Cases and controls were group-matched by sex (28.9 vs. 34.9% women), baseline eGFR (72.5 ± 21.6 vs. 74.4 ± 20.1 ml/min/1.73 m^2), and length of plasma storage (11.0 ± 2 vs. 10.6 ± 2 years). The mean age and duration of diabetes were 58.1 ± 5.5 and 15.1 ± 8.2 vs. 58.2 ± 5.7 and 14.6 ± 7.9 year, respectively. A total of 669 metabolites were measurable in >80% of subjects. In a logistic model adjusted for multiple testing and controlled for the matching variables, 62 of these metabolites were associated with subsequent CVD events (qFDR <0.05); 28 of these, including the most significant one (orotidine, qFDR=$8x10^{-5}$), belonged to a highly correlated group of modified (acetylated, C-glycosylated, sulfated) metabolites that have been recently shown to predict kidney function loss. Other significant biochemical groups included acylcarnitines and long-chain phospholipids. Results were not significantly affected by adjustment for BMI, c-HDL, ACR, HbA1c, and concomitant medications. Importantly, the association with modified metabolites was only marginally affected by adjustment for the eGFR slope during follow-up, indicating that the effect of these metabolites on CVD risk was mostly independent from their association with increased risk of GFR loss. These results point to previously unidentified metabolic pathways that could be targeted to prevent CVD in T2D. Studies are in progress to validate these findings in other settings.

Supported By: National Institutes of Health

EPIDEMIOLOGY—CLINICAL—DIAGNOSIS AND SCREENING

216-LB

Reproducibility of Prediabetes Classification upon Repeat Testing: The Vitamin D and Type 2 Diabetes (D2d) Study

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Practitioners frequently encounter patients who appear to have prediabetes based on abnormal fasting plasma glucose (FPG) and/or HbA1c levels, but the reproducibility of classification is unknown. Data from the D2d Study (an NIH trial assessing vitamin D supplementation for diabetes prevention in people at risk) were used to address this gap in knowledge. 1271 people with prediabetes based on FPG 100-125 mg/dL and HbA1c 5.7-6.4% measured by the central laboratory at Screening Visit 1 had retesting with FPG, HbA1c, and a plasma glucose at 2 hours (2hPG) during a 75g OGTT at Screening Visit 2 (median [IQR] 21 [14-29] days later); 99% of those with both FPG and HbA1c in the prediabetes range at visit 1 met at least one ADA criterion for prediabetes or diabetes on repeat testing; 84% were in prediabetes range (13% with one, 42% with two, and 29% with three criteria), and 14% were in diabetes range. Among those with prediabetes on retesting, 77% (823/1073) continued to have both FPG and HbA1c in the prediabetes range; among those with levels in the diabetes range, 62% (112/180) met only the 2hPG criterion (≥200 mg/dL).

Conclusion: Nearly all people meeting both FPG and HbA1c criteria for prediabetes on initial testing will meet at least one criterion for prediabetes or diabetes on follow-up testing. Adding an OGTT for follow-up evaluation increases the sensitivity for recognizing previously undiagnosed diabetes.

Table.

Retesting Result	No.	%
All three tests normal	18	1.4
ADA criteria in prediabetes range	**1073**	**84.4**
Only HbA1c prediabetes	121	9.5
Only FPG prediabetes	43	3.4
Only 2hPG prediabetes	2	0.2
HbA1c and FPG prediabetes	455	35.8
HbA1c and 2hPG prediabetes	59	4.6
FPG and 2hPG prediabetes	25	2.0
All three tests prediabetes	368	29.0
ADA criteria in diabetes range	**180**	**14.2**
Only HbA1c diabetes	14	1.1
Only FPG diabetes	22	1.7
Only 2hPG diabetes	112	8.8
HbA1c and FPG diabetes	1	0.1
HbA1c and 2hPG diabetes	3	0.2
FPG and 2hPG diabetes	24	1.9
All three tests diabetes	4	0.3
Totals	**1271**	**100.0**

Supported By: American Diabetes Association (1-14-D2D-01 to A.G.P.); National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health

217-LB

Differences in HbA1c "Glycation" across the Spectrum of Glucose Tolerance

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Glucose-independent differences in HbA1c levels are recognized in patients with T2DM, but whether "glycation" varies earlier in the natural history is unknown. We used screening study data to determine how differences in "glycation" are affected by glucose tolerance status. We pooled 3106 generally healthy subjects not known to have diabetes in the Screening for Impaired Glucose Tolerance study (n=1571) and the VA Screening for Diabetes study (n=1535); they were 34% female and 65% black, and had mean age 52 yr, BMI 30 kg/m^2, and HbA1c 5.6%. By ADA 75g OGTT criteria, 1723 (55%) had normal glucose metabolism (NGM, FPG <100 and 2hPG <140), 1162 had prediabetes (PreDM, 37%), and 221 (7%) had T2DM. Using each subject's mean from the OGTT FPG and 2hPG, and the 1hPG after 50g glucose on a separate day, to mimic pre and postmeal levels during the day, linear regression was used to derive [HbA1c=0.008* GLUC + 4.697]; the HbA1c glycation index (HGI) for each subject was expressed as [observed-predicted HbA1c]; and subjects in glucose tolerance groups were divided into tertiles of HGI. In NGM, median HbA1c in low, moderate, and high HGI tertiles was 5.1, 5.4, and 5.9% (p<0.001), and median glucose 104, 100 and 101 mg/dl (p<0.001); in PreDM, median HbA1c in HGI tertiles was 5.2, 5.7, and 6.1% (p<0.001), with median glucose 130, 123 and 122 mg/dl (p<0.001); in T2DM, median HbA1c in HGI tertiles was 5.6, 6.1, and 6.8% (p<0.001), with median glucose 179, 173 and 183 mg/dl (p=0.050). While differences in glucose within NGM, PreDM and T2DM groups were not clinically significant, HbA1c differences between HGI tertiles widened as glucose tolerance worsened (p<0.001). Moreover, black race was strongly associated with higher HGI (p<0.001).

Conclusion: Since HbA1c glycation differences exist even in NGM, and can move people with similar glucose levels into different diagnostic categories, and since black race is associated with higher glycation, use of HbA1c to identify PreDM and T2DM may require concomitant glucose testing for definitive diagnosis.

218-LB

The Hemoglobin Glycation Index (HGI) Influences Glycemic Classification: The Vitamin D and Type 2 Diabetes (D2d) Study

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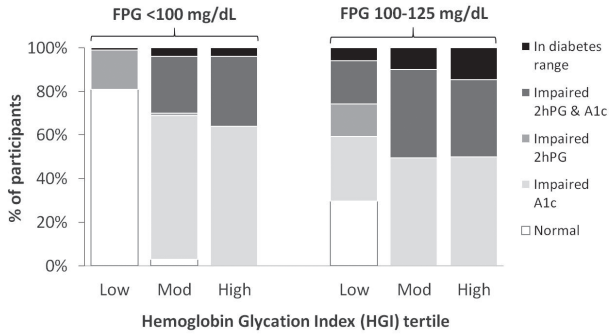
While interpersonal variation in HbA1c independent of glucose levels captured by HGI is recognized, HGI's potential impact on glycemic classification has not been studied. We used D2d study data to assess the influence of HGI on glycemic classification, as determined by an abnormal HbA1c and/or 2-hour glucose (2hPG) in a 75-g OGTT. The regression equation (Predicted HbA1c=0.009 x fasting plasma glucose [FPG] + 4.919) was estimated in 6516 participants with FPG <126 mg/dL at Screening Visit 1. HGI was determined as the difference between observed and predicted HbA1c in a subset of 3960 who had FPG, 2hPG and HbA1c at Screening Visit 2. This subset was divided into low, moderate, and high HGI tertiles. The proportion of African Americans increased across tertiles (18% vs. 28% vs. 54%, for low, moderate, and high HGI respectively; p <0.01). Among participants with FPG <100 mg/dL (n=968), the prevalence of HbA1c and/or 2hPG in prediabetes and diabetes range was 18% and 1% respectively in the low HGI tertile, and 96% and 4% in the high HGI tertile (all p <0.01). Among those with FPG 100-125 mg/dL (n=2821), the prevalence of HbA1c and/or 2hPG in prediabetes and diabetes range was 64% and 6% respectively in the low HGI tertile and 84% and 16% in the high HGI tertile (all p <0.01). In people with similar FPG values, those with higher HGI are more likely to have HbA1c or 2hPG values in the prediabetes or diabetes range.

Figure.



Supported By: American Diabetes Association (1-14-D2D-01 to A.G.P.); National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health

219-LB

Night Shift Work, MTNR1B Common Genetic Variant, and Type 2 Diabetes: Findings from the UK Biobank

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Introduction: Night shift work (NSW) has been associated with an increased risk of type 2 diabetes (T2D), possibly as a result of chronic misalignment between biological and social rhythms. MTNR1B T2D risk variant rs10830963 also has strong adverse effects on insulin secretion/sensitivity. We investigated whether NSW exacerbates the association between MTNR1B and T2D.

Methods: The UK Biobank is a prospective study in the UK. Work schedule was self-reported and T2D status was determined via self-report and ICD10 codes. Analysis included workers of European descent with genetic data and information on current [n=82,314; day workers (ref; n=68,050), shift work without NSW (n=6,976), sometimes NSW (n=4,094), usual NSW (n=1,100), and always NSW (n=2,084)] or lifetime (n=18,256) work schedules. The association between MTNR1B, shift work and T2D (n=2,596) was examined using logistic regression, adjusted for age, sex, and ancestry. Interaction was tested using MTNR1B × shift work cross-product term.

Results: Each additional risk G allele (allele frequency =28%) was associated with 13% higher odds of T2D [OR(95% CI) =1.13 (1.06-1.2)]. Any shift work was associated with higher odds of T2D [shift work without NSW: 1.24 (1.08-1.42); sometimes NSW: 1.21 (1.02-1.44); usual NSW: 1.72 (1.30-2.28); and always NSW: 1.33 (1.06-1.67)]. Higher intensity of NSW (each additional average NSW per month) was also associated with 4% higher odds of T2D [1.04 (1.0-1.08)]. While current shift work did not exacerbate the association between MTNR1B and T2D [1.00 (0.94-1.08)], the effect of MTNR1B on odds of T2D was greatest in the highest intensity of NSW [>8 NSW/month; 2.36 (1.12-5.0)].

Conclusion: NSW intensity may exacerbate the relationship between MTNR1B variant and T2D in the UK Biobank. The Shift work, Heredity, Insulin resistance, and Food Timing (SHIFT) Study (NCT02997319) introduces high resolution assessment of work, diet and sleep and their effect on metabolism to further elucidate this interaction.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

220-LB

Acceptability of a Home-Use Oral Glucose Tolerance Test (OGTT) for Screening Children and Adolescents with Cystic Fibrosis for Cystic Fibrosis Related Diabetes (CFRD)

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CFRD is the most common secondary complication of CF, affecting nearly 20% of adolescents and 40-50% of adults. Undiagnosed CFRD is associated with significant decline in lung function and nutritional status, with an increase in mortality. Screening for CFRD is important in minimising the nutritional and pulmonary consequences of diabetes. The current gold standard screening tool, the OGTT, is resource intensive and inconvenient for patients, leading to poor uptake. To overcome these issues a disposable self-administered electronic OGTT test kit containing everything required to perform the OGTT at home has been evaluated. The aim of the study was to establish if the home-use OGTT kit is usable and acceptable as an alternative to the conventional in-clinic test, with the objective of increasing the annual uptake of screening for CFRD in children with CF. Out of 58 eligible children, 39 were invited to participate in the study, with 34 consenting and 29 completing the study; 28 successful OGTT procedures were completed at home at the first attempt. One child required a second test kit which was completed successfully. Two children did not complete the OGTT procedure due to lack of tolerance of the supplied glucose drink. Feedback questionnaires were provided with the OGTT kits and 17 of these were returned. Respondents reported the following; the kit worked correctly, was easy to use and instructions were easy to follow (100%); preference for at-home OGTT over in-clinic OGTT (82% prefer at-home, 6% prefer in-clinic, 100% of the 12 who had previously undertaken an in-clinic OGTT prefer at-home), 9 OGTT procedures were performed by the child, with supervision.

We conclude that the home-use OGTT kit is easy to use, acceptable to patients and preferred to the in-clinic alternative. The convenience and accessibility of at-home OGTT could have a major positive impact on the frequency and uptake of screening for CFRD.

EPIDEMIOLOGY—DIABETES COMPLICATIONS

221-LB

Birth Weight and Risk of Type 2 Diabetes Mellitus, Cardiovascular Disease, and Hypertension in Adults: A Meta-analysis of 14,334,930 Participants from 135 Studies

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Background: Birth weight has been associated with several chronic diseases in adults. However, shape and gender specificity of the association have not been well explored. Therefore, we aimed to systematically examine the associations between birth weight and aforementioned diseases in adults and assess gender-specific risks.

Methods: We systematically searched PubMed, EMBASE and Web of Science for studies published between 1980 and 2017. Estimates were pooled with random-effects model, allowing for the possibility that true associations differed between populations.

Findings: We identified 49 studies with 4,053,304 participants assessing the association between birth weight and T2DM, 33 studies with 5,946,477 participants for CVD and 53 studies with 4,335,149 participants for HT. 1kg increase in birth weight was associated with a 22% (95% CI: 13 to 30) reduction in risk of T2DM, a 16.5% (95% CI: 14 to 19) reduction in risk of CVD, and a 23% (95% CI: 12 to 32) reduction in risk of HT. Gender-specific binary analyses showed that only females had increased risk of T2DM and CVD at the upper tail of the birth weight distribution. Categorical analyses of six birth weight groups and dose-response analyses showed U-shaped associations of birth weight with T2DM and CVD, but linear inverse association with HT. Participants with birth weight lower than 2.5kg have the highest risks of T2DM (50%), CVD (32%), and HT (41%), and those with birth weight higher than 4.5kg had a 19% (95% CI: 4 to 36) higher risk of T2DM and a 22% (95% CI: 8 to 37) higher risk of CVD compared to the reference birth weight group

(4.0 to 4.5kg). The lowest risks for T2DM, CVD and HT were observed at 4.0kg BW, 3.75kg, and higher than 4.0kg, respectively.

Interpretation: These findings indicate that birth weight is associated with risk of T2DM and CVD in a U-shaped manner that is stronger among female, though inversely associated with risk of HT.

222-LB

Diabetes Ketoacidosis Is the Most Common Etiology of 30-Day Readmission after an Episode of Diabetic Ketoacidosis: A Nationwide Analysis Using the National Readmission Database

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Background: Diabetic ketoacidosis (DKA) is a serious complication of diabetes. Early hospital readmissions (within 30 days of discharge) for DKA is a high-priority healthcare quality measure and a target for cost reduction.

The aim of this study is to measure the percentage of readmissions within 30 days in patients with DKA and evaluate causes and risk factors.

Methods: This is a retrospective cohort study using the 2014 National Readmission Database of adult patients readmitted after an episode of diabetic ketoacidosis. ICD9 codes were used to identify diabetic ketoacidosis and the etiologies for readmission based on their primary diagnosis. Logistic regression was used to assess for statistical significance and a p-value less than 0.05 was considered significant.

Results: We included a total of 42,208 patients that were admitted for ketoacidosis during January and November of 2014. Almost 15% of patients (6,252) were readmitted within 30-days. Two thirds of the readmissions were due to diabetes manifestations, being the most common cause for readmission a repeated episode of ketoacidosis (49.8%). Other nondiabetic causes included sepsis/septic shock (6.3%), acute kidney injury (2.7%) and acute congestive heart failure (2.1%). We found that patients older than 75 years, female gender, a length of stay more than 3 days, and comorbidities such as congestive heart failure, hypertension, end stage renal disease and chronic lung disease were risk factors for a readmission within 30 days of discharge. Intensive care unit (ICU) admissions or hospital teaching status were not factors that significantly influenced on readmission.

Conclusion: Almost 50% of patients readmitted within 30 days after an episode of ketoacidosis are readmitted with a diagnosis of ketoacidosis. Diabetics discharged after a ketoacidosis episode need a close follow-up to prevent another admission due to ketoacidosis.

223-LB

Lifestyle Intervention Lowers Mortality in Chinese Adults with Impaired Glucose Tolerance: Thirty-Year Follow-Up of Da Qing Diabetes Prevention Study

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Evidence of the effect of diabetes prevention on mortality is sparse. We investigated the effect of lifestyle intervention on mortality over a 30-year period among participants with impaired glucose tolerance (IGT) in the Da Qing Diabetes Prevention Study (DQDPS). The DQDPS was a cluster randomised trial, conducted in Da Qing, China from 1986 to 1992, in which 576 adults with IGT were randomised by clinic to a control group or one of three lifestyle intervention groups (diet or exercise or both). 438 were in the intervention groups and 138 in the control group. At the end of the trial, follow-up to assess all-cause mortality was continued. By the end of 2016, 30 years after randomization, mortality data were available for 542 (94.1%) of the original participants, 407 (92.9%) in the intervention and 135 (97.8%) in the control groups. 184 deaths (45.2%) had occurred in the intervention and 75 [55.6%] in the control groups (p=0.018). All-cause mortality rates in the intervention groups were 18.16 (95% CI 15.53-20.78) vs. 23.69 (95% 18.33-29.05)/1000 person-years in the control group (p=0.036). After adjustment for clinic cluster, the risk of death was 26% lower in the intervention than in the control group (hazard ratio 0.74 (95% CI 0.56-0.98; p=0.037) with a greater reduction of the hazard ratio in women, 0.57 (95% CI 0.35-0.95; p=0.03), than men 0.86 (95% CI 0.61-1.20; p=0.34). The 6-year lifestyle intervention program among Chinese adults with IGT continues to show a significant reduction in all-cause mortality over 30 years, especially in women, indicating the long-term clinical benefits of lifestyle intervention in this high-risk population. These results add to the growing body of evidence to adopt lifestyle interventions as public health measures in China and worldwide.

Supported By: Centers for Disease Control and Prevention

224-LB

Geographical Disparity in Prevalence of Diabetes-Related Major Cardiovascular Conditions among Medicare Beneficiaries with Diabetes, U.S. States, 2013

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Cardiovascular conditions are major complications of diabetes. State-specific information on the prevalence of those complications is not readily available. Centers for Disease Control and Prevention and RTI International created a web-based diabetes state burden toolkit to report state-specific diabetes-related data, including the prevalence of cardiovascular conditions among Medicare beneficiaries aged 65+ years with diabetes based on the 2013 Master Beneficiary Summary File from the Centers for Medicare and Medicaid Services. Here we reported state-specific age-adjusted prevalence rates for 3 major cardiovascular conditions (coronary heart disease [CHD], congestive heart failure [CHF], and peripheral vascular disease [PVD]) among beneficiaries aged 65+ years with diabetes. We plotted state distribution maps by their quartile values. The overall age-adjusted prevalence of CHD, CHF, and PVD were 46.8%, 26.2%, and 20.7%, respectively, but prevalence greatly varied across states. Prevalence of CHD ranged from 35.0% in Hawaii to 55.2% in Florida; CHF ranged from 17.1% in Hawaii to 30.3% in Michigan; PVD ranged from 9.7% in Idaho to 28.9% in Pennsylvania. Louisiana, Michigan, New Jersey, New York, Ohio, and Texas were in the top quartile for each of these 3 conditions. While diabetes is more common in southern states, the prevalence of diabetes-related cardiovascular conditions is higher not only in southern states like Texas and Louisiana but also in some mid-west and northeastern states. Although geographic patterns varied by condition, the prevalence was generally lower among western states. Our results on geographical disparities in the prevalence of diabetes-related cardiovascular conditions may guide policy decisions and help allocate health care resources to target areas in need.

225-LB

Associations of Dairy-Derived Serum Fatty Acids with Insulin Sensitivity and Beta-Cell Function in an Indigenous Canadian Community: The Sandy Lake Health and Diabetes Project (SLHDP)

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Recent evidence has documented inverse associations of fatty acids derived from dairy consumption with type 2 diabetes (T2DM) risk. However, few data are available from Indigenous populations, where both T2DM and food insecurity are prevalent. We aimed to investigate the associations of pentadecanoic acid (15:0), heptadecanoic acid (17:0), trans-palmitoleic acid (16:1-9t) and trans-vaccenic acid (18:1-11t) with insulin sensitivity (IS) and beta-cell function (BCF) in an Indigenous Canadian community. We conducted a cross-sectional analysis using data from the SLHDP (2003-05). 316 participants (> 12 y) without T2DM were assessed for anthropometric and lifestyle factors, fasting glucose, insulin, and a 75-g OGTT. Serum 15:0, 17:0, 16:1-9t, and 18:1-11t were quantified using gas chromatography. IS was calculated using the Matsuda index (ISOGTT) and the inverse of homeostasis model assessment of insulin resistance (1/HOMA-IR). BCF was calculated using the insulinogenic index (IGI) divided by HOMA-IR (IGI/IR) and the insulin secretion-sensitivity index-2 (ISSI-2). Linear regression models were adjusted for sex, age, and waist circumference. We tested for interaction by IGT and high triglycerides (Tg). There were no significant associations of any of the fatty acids with IS or BCF after covariate adjustment. However, in participants with IGT, 15:0 was associated with IGI/IR and ISSI-2 (β= 1.77, 95% CI=0.62, 2.92; β=0.76 (0.35, 1.16) respectively), 17:0 was associated with ISSI-2 (β=0.66 (0.09, 1.23)) and 16:1-9t was associated with ISOGTT (β=0.34 (0.01, 0.66)) (all $p<0.05$). Similarly, in those with high Tg, 17:0 was associated with IGI/IR and ISSI-2 (β=1.18 (0.27, 2.09); β=0.57 (0.14, 0.99), both $p<0.05$). These findings highlight potential benefits of dairy intake in subjects at higher risk for T2DM and may inform strategies for improving diet quality in Indigenous Canadian populations.

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226-LB

Long-Term Changes in Retinal Vascular Measures and Cognitive Impairment In Type 1 Diabetes

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Cognitive impairment (CI) in type 1 diabetes is common and disabling, but biomarkers of early detection are not yet available. Retinal vascular measures are promising biomarkers of CI in elderly and type 2 diabetes, but have not been well studied in type 1 diabetes. We examined longitudinal changes in retinal vascular measures in relationship with CI in a cohort of middle-aged adults with childhood onset type 1 diabetes from the ongoing observational Pittsburgh Epidemiology of Diabetes Complications Study (n=122; 53% male; mean years of age, duration, and education at time of cognitive exam: 49.4, 41.0, 14.9, respectively). All participants had retinal images taken ≥3 times from 1986 to 2014 and underwent an extensive cognitive exam in 2010-2015. Central retinal arteriolar and venular caliber equivalents (CRAE, CRVE) were determined via computer-assisted methods from fundus photos of the right eye. CI was classified as "absent", "mild", or "clinically relevant" based on the number of cognitive test scores 1.5SD or worse than published norms (0, 1, 2+, respectively). Change over time in CRAE and CRVE was compared by CI status using median regression analysis adjusted for education and duration (or age). The contribution of hyperglycemia and complications to these associations was tested. Over the study's duration, CRAE narrowed by 14.0% and CRVE narrowed by 15.0% (median at entry and at last follow-up: 178.9 and 156.9 μM for CRAE; 265.9 and 226.0 μM for CRVE). Hyperglycemia and microvascular complications, but not blood pressure parameters, were related to larger CRAE narrowing. CRAE narrowing was significantly greater in those with clinically relevant CI as compared with the other two groups (t=-2.94; p=0.003). The association was independent of covariates, but hyperglycemia reduced this association (t=0.17; p=0.87). Associations with CRVE were not significant. Faster retinal arteriolar narrowing over time may be an early biomarker of CI in middle aged adults with long duration type 1 diabetes.

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227-LB

Depression in Adults with Type 1 Diabetes: The Role of Cerebral Small Vessel Disease

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For reasons not fully understood, depression is more common in people with type 1 diabetes than in the general population. Aging studies show that depression is strongly related to cerebral small vessel disease (i.e., white matter hyperintensities, WMH) and that WMH predict poor response to antidepressants (AD). We previously reported a higher than expected burden of WMH in middle-aged adults with childhood-onset type 1 diabetes; we now hypothesize that WMH are related to depression in this same cohort. We examined the cross-sectional association between WMH (% of total brain volume) and clinically relevant depressive symptoms (DEP, per Beck Depression Inventory >=10) among 80 participants from the Pittsburgh Epidemiology of Diabetes Complications Study (50% male; mean age 50 yrs; mean duration 42 yrs in 2010-13). AD use, severity and duration of hyperglycemia (HbA1c months), blood pressure, lipids, smoking, cardiovascular disease, and diabetes-related microvascular complications were assessed. The prevalence of DEP was 23% (18/80); 42% of DEP reported AD use vs.15% of non-DEP. Logistic regression models, controlling for education and AD use, revealed a 7-fold higher odds of DEP per unit increase in WMH (OR=7.1; 95% CI 1.5-34.9; p=0.02). Controlling for AD use, DEP had significantly worse HbA1c months, lower education, and higher prevalence of polyneuropathy than non-DEP (all p<0.05). Neither HbA1c months nor polyneuropathy modified the association of WMH with DEP. The robust association between WMH and DEP suggests a vascular origin for DEP in this cohort. Although hyperglycemia did not explain this association cross-sectionally, it may have precipitated development of WMH far in advance of our study. Future type 1 diabetes studies should examine these associations longitudinally, including the effects of WMH on AD response. Addressing DEP in this patient population may improve diabetes management and reduce negative health outcomes, including dementia, disability, and early mortality.

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228-LB

Dysmorphic Erythrocytes Were More Valuable than Microscopic Hematuria in Diagnosis of Nondiabetic Renal Disease in Type 2 Diabetics

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Objective: The study sought to make certain the value of dysmorphic erythrocytes in differential diagnosis of diabetic nephropathy (DN) and nondiabetic renal disease (NDRD) in type 2 diabetics.

Methods: We examined 525 patients with type 2 diabetes who underwent kidney biopsies between 1997 and 2015. All patients with persistent overt proteinuria were include. The exclusion criteria were a pathological diagnosis of DN combined with NDRD. Thus, 471 patients were finally enrolled. Microscopic hematuria was defined as > 3 or > 10 red blood cells per high-power field. Glomerular hematuria was diagnosed as dysmorphic erythrocytes > 80%. Clinical findings and predictive value of different standard's hematuria were compared between patients with DN and those without.

Results: There were 182 patients in DN group, 289 patients in NDRD group. There was a statistically significant difference between the DN group and the NDRD group (Table 1). In the three kinds of hematuria, glomerular hematuria had the higher value of specificity (82%), maximum positive predictive value (80%) and AUC (0.66). Nephrotic syndrome was an independent risk factor for hematuria (OR=0.2,P<0.01).

Conclusion: Dysmorphic erythrocytes were more valuable than microscopic hematuria for predicting NDRD in type 2 diabetics. Nephrotic syndrome was an independent risk factor for hematuria.

Table 1. Clinical and Laboratory Indexes of Patients.

	DN group (n=182)	NDRD group (n=289)	*P*-value
Sex (male, %)	126 (69.2%)	195 (67.5%)	0.76
Age (years)	49.36±9.84	49.94±11.66	0.56
Diabetes duration (months)	137.11±81.24	49.11±54.16	<0.01
HbA1c (%)	6.96±1.49	6.70±1.20	0.05
Scr (μmol/L)	149.97±92.50	113.36±82.48	<0.01
eGFR (mL/min/1.73 m^2)	56.96±27.07	77.88±30.73	<0.01
24-h urinary total protein (g)	4.47±3.36	3.62±4.42	0.03

229-LB

Relationship of Uric Acid Clearance and Serum Uric Acid Levels with All-Cause Mortality in Type 2 Diabetes

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Introduction: Recent studies have suggested relationship between elevated serum uric acid levels and an increased risk of all-cause mortality in patients with type 2 diabetes. However, other studies have reported conflicting results. Furthermore, is unclear if higher levels of serum uric acid are due to increased production or decreased clearance of uric acid as a result of renal impairment in diabetes.

Aim: The aim of this study was to investigate the relationship between baseline serum uric acid levels and uric acid clearance with all-cause mortality in type 2 diabetes.

Methods: Serum samples and timed urine collection were collected in 2000-2001 from 360 patients with type 2 diabetes attending a diabetes clinic. Routine clinical and biochemical data was collected at baseline. We measured uric acid concentrations in stored serum and urine samples and calculated uric acid clearance from 24 hour urine collections. After a 15 year follow-up of this cohort, mortality data was attained from the Australian Institute of Health and Welfare Death Registry.

Results: During the follow-up period 102 patients died. In a multivariate logistic regression analysis, that included baseline serum uric acid levels, uric acid clearance, chronic kidney disease (CKD) stage, age, HbA1c, systolic blood pressure, diabetes duration, sex, renin-angiotensin system inhibitor use, diuretic use and history of macrovascular disease, only serum uric acid levels (p=0.032) and diuretic use (p=0.006) emerged as independent predictors of all-cause mortality.

Conclusion: Serum uric acid levels were significantly associated with all-cause mortality after adjusting for other baseline variables including CKD stage and uric acid clearance in patients with type 2 diabetes. Further studies are necessary to determine if increased serum uric acid production, as opposed to reduction in uric acid clearance, is an important independent predictor of cardiovascular death, as opposed to all cause mortality, in diabetes.

EPIDEMIOLOGY—NUTRITION

230-LB

Food Pantry Clients Living with Diabetes Report High Demand for Diabetes-Appropriate Food

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The presence of food insecurity makes diabetes mellitus (DM) management more challenging due to an often limited access to diabetes appropriate food. We analyzed data from the Hunger in America 2014 national survey to examine the types of food that individuals with a household history of DM seeking assistance at food pantries most want and are unable to obtain compared to those without a household history of DM. 52,612 food pantry clients responded on behalf of their household (35% household history DM; 27% uninsured; 83% < 130% federal poverty line). Households with a DM member were more likely to want and be unable to obtain fruits and vegetables (61% vs. 56%, $p < 0.01$), protein (51% vs. 48%, $p < 0.01$), and dairy (46% vs. 44%, $p < 0.01$); there was no difference in grains (p=0.82). Households with DM members were also more likely to buy the cheapest food available even if it may not have been the healthiest option (83% vs. 81%, $p < 0.01$). These associations persisted in regression analyses controlling for age, race, education, household income, and insurance status. Similar trends were found when comparing households with and without a history of hypertension.

We conclude that households with DM members receiving assistance from food pantries have a high demand for healthy food items, with a higher odds of wanting and not receiving diabetes appropriate food compared to households without DM members.

Table.

	Household w/ DM member	Household w/out DM member	p-value
Participants	17,472 (35%)	32,279 (65%)	
Uninsured[a]	21.8%	30.5%	< 0.001
% Federal Annual Poverty Line			0.7
0-130%	83.1%	82.8%	
130-185%	12.3%	12.5%	
> 186%	4.6%	4.7%	
Food Preferences			
Wanted/Unable to Obtain Fruits/ Vegetables	61.4%	56.2%	< 0.001
Wanted/Unable to Obtain Protein	51.4%	48.3%	< 0.001
Wanted/Unable to Obtain Grains	14.0%	14.1%	0.8
Wanted/Unable to Obtain Dairy	45.7%	43.7%	< 0.001
Wanted/Unable to Obtain Non-Food Items	20.7%	21.9%	0.002
Coping Strategies			
Choose Cheapest/Less Healthy Food	83.2%	81.1%	< 0.001

[a] Primary respondent/anyone in household.

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231-LB

Time Trend of Dietary and Lifestyle Factors and Their Impact on Diabetes Burden in China

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Background: Type 2 diabetes (T2D) in China has been increasing rapidly in short period.

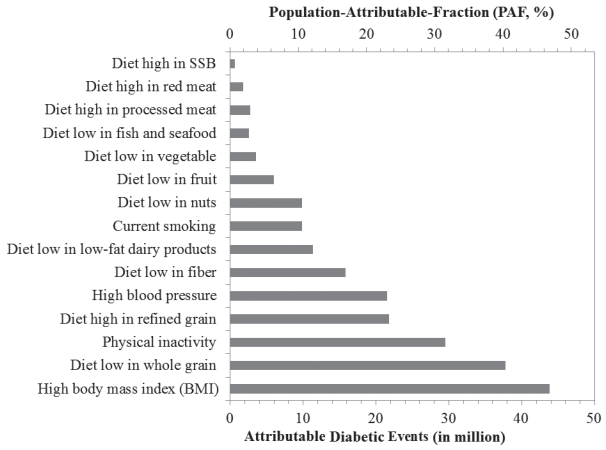
Objective: To examine the secular trends in risk factors, estimate their impact on T2D burden from 1991 to 2011, and project trends in next 20 years.

Methods: China Health and Nutrition Survey. T2D events attributable to all non-optimal levels of each risk factor was estimated by Comparative Risk Assessment method.

Results: A high body mass index (BMI) was estimated to be responsible for 43.8 million T2D events in 2011. A low intake of whole grains and high intake of refined grain were responsible for 37.8 million and 21.8 million T2D events, respectively. Increasing physical inactivity and blood pressure was estimated to be responsible for an increase of 13.1 and 4.8 million T2D cases from 1991 to 2011, respectively. Although intakes of fiber, low-fat dairy products, nuts, fruit, vegetables and fish and seafood increased over time, average intake was below optimal levels and estimated to be responsible for 15.8, 11.3, 9.9, 6.0, 3.6 and 2.6 million T2D events, respectively in 2011.

Conclusion: In China, a high BMI and low intake of whole grains but high intake of refined grains is the most important individual risk factors related to the national T2D burden; decreasing physical activity and increasing blood pressure also significantly contributed to the increase in T2D burden. Overall dietary quality improved modestly but remained suboptimal.

Figure 1. Diabetes Events Attributable to 15 Individual Risk Factors in 2011.



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232-LB

Dietary Patterns Characterized by Higher Plant Food Intakes Are Associated with a Decreased Metabolic Risk

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Background: Over the last decades there has been a steady increase of the Metabolic Syndrome (MetS), a condition that is associated in the development of diabetes and a number of debilitating chronic diseases. The identification of factors that may help in the prevention of the MetS is thus of primary importance.

Objective: The purpose of the study was to investigate the associations of diverse dietary patterns with the MetS and its component factors.

Methods: Cross-sectional analysis of 1278 subjects (mean age 63 years) with a complete set of clinical and dietary data. Dietary pattern were based on a validated food-frequency questionnaire. Subjects were classified as non-vegetarian, semi vegetarian, pesco vegetarian, lacto-ovo vegetarian and strict vegetarian. ANCOVA was used to determine associations between dietary pattern and metabolic risk factors while controlling for possible confounding factors such as sex, age, ethnicity, physical activity and other relevant factors. Non-vegetarians were defined as the group of reference.

Results: After adjustments the analysis of the MetS risk factors showed that the odds ratio of having a waist circumference that was over the risk threshold was halved for pesco vegetarians (OR=0.49, CI=0.32-0.73) and semi vegetarians (OR=0.49, CI=0.36-0.67) and reduced by two thirds for strict vegetarians (OR=0.32, CI=0.19-0.55). The OR for high blood pressure was reduced by half for lacto-ovo vegetarians (OR=0.53, CI=0.39-0.72) and the OR of high glucose levels was significantly reduced in lacto-ovo vegetarians (OR=0.64, CI=0.45-0.92) and strict vegetarians (OR=0.42, CI=0.22-0.78). After adjustments strict vegetarian had the lowest risk for MetS (OR=0.33, CI=0.17-0.61) followed by lacto-ovo vegetarians (adjusted OR=0.65, CI=0.47-0.90).

Conclusions: Dietary patterns characterized by lower intakes of animal products are associated with a lower metabolic risk profile and may thus contribute to a reduced metabolic risk.

233-LB

Dietary Intake and Physical Activity Predictors of Gestational Diabetes: A Systematic Review

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The prevalence of gestational diabetes mellitus (GDM) is rising across the globe, along with GDM-related complications and higher risk of obesity and

For author disclosure information, see page LB107.

type 2 diabetes in offspring. There is an urgent need to establish key modifiable risk factors which reduce the onset of GDM.

We systematically reviewed current literature for observational studies that reported dietary intake or physical activity (PA) levels and risk of GDM, using PubMed, Medline, CINAHL, Science Direct and EMBASE databases. Our search produced 1167 hits, and 40 studies met selection criteria including singleton pregnancy, study which reported diet or PA data during pre-pregnancy or early pregnancy period and GDM as an outcome measure. Studies were assessed for quality based on a modified Quality Criteria Checklist from American Dietetic Association. Of the 40 studies, which collectively captured data on 125 798 pregnant women, 29 obtained a positive quality rating and 11 were neutral. As the search captured a wide variety of dietary elements, we categorized them into 1 of 7 groups including: Caffeine, Carbohydrates, Fast Food, Fat, Protein, Calcium and Overall Dietary Patterns.

Diets rich in fruits and vegetables such as Mediterranean Diet (MedDiet), Dietary Approaches to Stop Hypertension (DASH) diet or Alternate Healthy Eating Index diet (AHEI) were associated with reduced incidence of GDM in 7 out of 9 studies. In contrast, frequent consumption of potato, meat/processed meats, and proteins derived from animal based sources increased the risk of GDM. PA was found to be protective against onset of GDM in 14 of 17 studies, and the degree of protection increased with greater levels of PA. It was assessed that the diet and GDM studies were more likely to adjust for a range of confounding variables, compared to PA studies. Diet and PA are undoubtedly associated with GDM, and are important to be considered in health promotion and clinical interventions to reduce risk of GDM. The systematic review was registered at PROSPERO as CRD42016027795.

EPIDEMIOLOGY—OTHER

234-LB

Persistent Organic Pollutants and Risk of Type 2 Diabetes: A Prospective Investigation in Nurses' Health Study II

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Background: Prospective evidence regarding background persistent organic pollutants (POPs) exposure and type 2 diabetes (T2D) risk remains limited and inconclusive.

Objectives: We investigated the association between plasma POP concentrations and incident T2D in the Nurses' Health Study II.

Methods: Three organochlorine pesticides and 20 polychlorinated biphenyls (PCBs) were measured in 793 T2D case-control pairs confirmed by supplementary questionnaire.

Results: In multiviarate-adjusted model, hexachlorobenzene (HCB), β-hexachlorocyclohexane (β-HCH), p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), PCB toxicity equivalence factor score (PCB-TEF) odds ratios (ORs, 95% confidence intervals [CIs]) were associated hight T2D, and odds ratios (ORs, 95% confidence intervals [CIs]) comparing extreme POP tertiles were between 1.56(1.14, 2.13) and 3.64(2.59, 5.13). Further adjusting for previous weight change (from cohort enrollment to blood draw) and concurrent body mass index (BMI) attenuated these associations, but those for PCB-TEF remained significant (OR [95% CI]= 1.74[1.12, 2.70]; P_{trend}=0.008). Older age, smaller previous weight gain, and shorter lactation durations were each independently associated with higher concentrations of all POPs, whereas concurrent BMI was positively associated with most POPs except highly-chlorinated PCBs. When analysis was stratified by weight change before blood draw, ORs (95% CIs) of T2D comparing extreme (high vs. low) POP groups ranged from 1.92(0.99, 3.72; P_{trend}=0.02 for HCB) to 2.67(1.34, 5.30; P_{trend} <0.001 for β-HCH) in the lowest weight gain group, and were 0.90(0.50, 1.62; P_{trend}=0.64 for PCB-TEF) to 1.45(0.79, 2.65; P_{trend}=0.20 for β-HCH) in the highest weigh gain group (all $P_{interaction}$ <0.05).

Conclusions: Our findings highlight the strong impact of lifestyle factors, especially previous weight gain, on circulating POP concentrations and their associations with subsequent T2D risk.

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235-LB

Differential Influence of Sleep Duration on Glucose Levels According to Work Timing: Results from the Korean National Health and Nutrition Examination Survey 2010-2015

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Blood glucose levels according to sleep duration by traditional regular work timing and shift work have not been clarified. The current analysis is an attempt to evaluate the undisclosed relationship among sleep duration, shift work, and glucose levels. We analyzed the data of 9123 subjects from the KNHANES 2010-2015. We classified sleep duration into three groups: <6, 6-8, and >8h/day. In traditional regular time workers group, mean fasting blood glucose (FBG) levels showed a U-shaped according to sleep duration (95.1 vs. 93.8 vs. 95 mg/dL, P=0.027), whereas in shift workers group, FBG levels were significantly decreased across sleep duration (93.3 vs. 92.3 vs. 88.5 mg/dL, P=0.001). In traditional regular time workers group, short sleep duration was associated with higher FBG (B, 95%(CI): 1.33 [0.26 to 2.4]), whereas after adjusting for age, sex, socioeconomic status, lifestyle factors, and daily total calorie intake, long sleep duration significantly increased risk of higher FBG level (2.01 [0.35 to 3.68]). On the other hand, the reverse was true in the shift worker group. Long sleep duration was associated with lower FBG by both unadjusted and after adjustment (-3.79 [-5.97 to -1.62], -2.19 [-4.35 to -0.03]). Our results suggest that the impact of sleep duration on glucose levels differs according to whether or not they are shift worker.

Table. Linear Regression Analysis for Fasting Blood Glucose According to Sleep Duration by Shift Work.

Variable	Univariable		Multivariable*	
	B (95% CI)	p-value	B (95% CI)	p-value
traditional regular time work				
Sleep duration (hours)				
< 6	1.33 (0.26, 2.4)	0.015	0.61 (-0.42, 1.64)	0.245
6 - 8	1.00 (Reference)		1.00 (Reference)	
> 8	1.16 (-0.58, 2.89)	0.192	2.01 (0.35, 3.68)	0.018
Shift work				
Sleep duration (hours)				
< 6	1.01 (-0.83, 2.86)	0.281	-0.1 (-1.91, 1.7)	0.911
6 - 8	1.00 (Reference)		1.00 (Reference)	
> 8	-3.79 (-5.97, -1.62)	<0.001	-2.19 (-4.35, -0.03)	0.047

236-LB

Diabetes and Breast Cancer: Smoke, but No Fire?

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Many factors have been proposed linking aspects of diabetes and antidiabetes therapies to breast cancer. An association would be of public health significance although high-risk groups could be targeted for screening. We examined any direct or indirect link wherever adequate data existed. A series of systematic reviews with meta-analysis were conducted following PRISMA guidelines. Studies published in English and with a prospective design were included. Summary relative risks (SRR) were computed using random-effect models and standard methods were used to assess heterogeneity and publication bias. Women with diabetes had an increased risk of breast cancer which was restricted to post-menopausal ages and type 2 diabetes (SRR=1.16, 95% CI (1.04, 1.29)). A high Body Mass Index (BMI) increased the risk of breast cancer in women at post-menopausal ages: a 5 unit increase in BMI was associated with a 20% reduction in risk of ER^+PR^+ breast cancer. BMI appears to act as a classical confounder in the association between diabetes and breast cancer risk. As regards treatments, there was modest evidence that Metformin alters the risk of breast cancer and no evidence, from randomised trials or prospective studies, that use of insulin glargine increases the risk of breast cancer not even for prolonged use over five years based on 5 studies (SRR=1.15, 95% CI (0.74, 1.79)) nor in seven years of follow-up in the ORIGIN randomised trial (HR=1.01, 95% CI (0.60, 1.71)). Increasing physical activity significantly decreased breast cancer risk in women of all ages. Our meta-analyses demonstrated a very small potential increase in breast cancer risk associated with increased nutritional glycaemic index/load but no evidence of association with fasting glucose, circulating IGF-1 concentrations, serum insulin, C-peptide and adiponectin levels. There have been a large number of false starts and alerts raised potentially linking diabetes with breast cancer risk. However, the current evidence strongly suggests that there is no strong common factor other than BMI.

237-LB

Joint Effects of Serum Vitamin D3 and Periodontitis on Insulin Resistance, Prediabetes, and Type 2 Diabetes

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Background: A bidirectional relationship exists between periodontitis and diabetes. Evidence also suggests that periodontists is associated with other glycemic abnormalities. Vitamin D3 supplementation is shown have anti-inflammatory benefits, and be inversely associated with glycemic measures. Therefore, the aim of this study investigates the joint effects of serum vita-

min D3 [25(OH) D3], and periodontitis on HOMA-IR, prediabetes, and type 2 diabetes (T2DM).

Methods: Using data from 2009-2010 National Health and Nutritional Examination Survey, the sample was restricted to adults over 30 years of age, who were eligible for the oral health examination, with serum [25(OH) D3] levels, fasting glucose and insulin measures. The full analytic sample, including those with T2DM was (n=1631), and a restricted sample of participants without T2DM (n=1369). Using surveylogistic multivariable regression analysis we examined the following joint effects: 1.) vitamin D insufficiency [25(OH) D3 <50 nmol/L] and moderate to severe periodontitis (VD+PD+); 2.) vitamin D insufficiency [25(OH) D3 <50 nmol/L] and mild to no periodontitis (VD+PD-); 3.) vitamin D sufficiency [25(OH) D3 >50 nmol/L] and periodontitis (VD-PD+); and compared these groups to the doubly unexposed reference group (VD-PD-).

Results: The joint effect of vitamin D3 insufficiency without periodontitis (VD+PD-) was significantly associated with HOMA-IR, OR=1.60 (95% CI 1.20, 2.13) but not associated with prediabetes or T2DM. Conversely, vitamin D3 sufficiency with periodontitis (VD-PD+) was not associated with HOMA-IR, prediabetes, or T2DM. The joint effects of both exposures together (VD+PD+) was significantly associated with HOMA-IR and T2DM, OR=1.63 (95% CI 1.06, 2.51), and OR=2.53 (95% CI 1.37, 4.67), respectively.

Conclusion: In this cross-sectional, nationally representative sample, the joint effects of vitamin D3 and periodontitis appear to differ for HOMA-IR, prediabetes and T2DM.

238-LB

Serum Vascular Adhesion Protein-1 Is Associated with Obesity and Plasma Adiponectin, and Predicts the Incidence of Diabetes

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Vascular adhesion protein-1 (VAP-1) participates in the pathogenesis of diabetic complications. Physiologically, VAP-1 in tissue enhances glucose uptake. Studies in skeletal muscles and liver tissues suggest a role of soluble VAP-1 in glucose homeostasis. Since there is no evidence in human, we investigated the relationship of serum VAP-1 (sVAP-1), obesity, adipocytokines and incident diabetes in this cohort study. From 2006 to 2012, 600 subjects without diabetes from Taiwan Lifestyle Study were included and followed regularly. Diabetes was diagnosed by an oral glucose tolerance test, hemoglobin A1c, and the use of antidiabetic agents. Abdominal fat areas were measured by abdominal computed tomography and sVAP-1 was analyzed by ELISA. sVAP-1 was associated negatively with body mass index (BMI, r=-0.1449, p=0.003), waist circumference (r=-0.1425, p=0.004), abdominal visceral (r=-0.1457, p=0.003) and subcutaneous (r=-0.1025, p=0.035) fat areas, and serum C-reactive protein (r=-0.2035, p<0.0001), and positively with plasma adiponectin (r=0.2086, p<0.0001), adjusted for age and gender. After 4.7±2.6 years, 73 subjects (12.2%) developed incident diabetes. Subjects with sVAP-1 in the highest tertile showed the lowest incidence of diabetes. Every 1 standard deviation increase in sVAP-1 was associated with a 34% decrease in the incidence of diabetes (HR=0.66, 95% CI=0.5-0.88, p<0.01), adjusted for age, gender, BMI, family history of diabetes, hemoglobin A1c, HOMA2-%B and HOMA2-IR.

In conclusion, sVAP-1 is associated with obesity and plasma adiponectin, and can predict the incidence of diabetes in human. Our findings provide first evidence in human for the role of soluble VAP-1 in glucose homeostasis.

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239-LB

Racial Differences in Spatial Patterns for Poor Glycemic Control in the Southeastern United States

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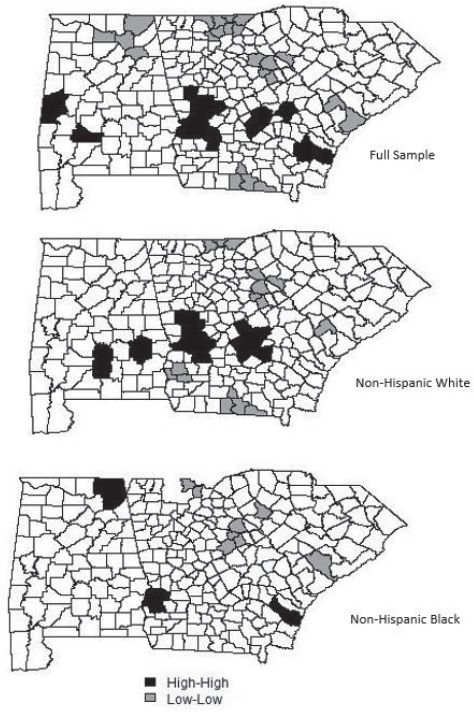
Background: Evidence consistently shows racial minorities have worse outcomes, but little has focused on understanding spatial patterns or differences that may be explained by regional variation.

Methods: Data on 64,022 non-Hispanic black (NHB) and non-Hispanic white (NHW) Veterans with diabetes living in Georgia, Alabama, and South Carolina in 2014 was used. HbA1c was categorized as controlled (<8%) and uncontrolled (>=8%). Logistic regression was used to understand the additional explanatory capability of spatial random effects. Data aggregated at the county level was used to identify hotspots in the distribution of uncontrolled HbA1c, tested using local Moran's I test.

Results: In unadjusted analyses, NHB had 37% higher odds of uncontrolled HbA1c (95% CI 1.32, 1.41). After adjusting for demographics and comorbidities the odds ratio decreased to 1.09, but remained significant (95% CI 1.05, 1.13). The odds ratio further decreased after incorporating spatial effects (OR: 1.07, 95% CI 1.03, 1.11), but remained significant. Hotspots of high HbA1c could be detected, and differed across race groups.

Conclusions: Spatial patterns in glycemic control differ between NHB and NHW Veterans with type 2 diabetes. Spatial effects helped explain more of the disparity in uncontrolled HbA1c than adjusting only for demographics and comorbidities, but significant differences remain.

Figure.



Local Indicators of Spatial Association (LISA) map indicating hotspots of uncontrolled diabetes (dark colored counties) and controlled diabetes (gray colored counties) among Veterans in the southeastern United States in 2014.

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240-LB

Relationship between Diagnosis of Kidney Disease and Measures of Access to Care and Quality of Care in Adults with Diabetes: A 10-Year Survey Analysis

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Background: Kidney disease is the most expensive complication of diabetes. This study was done to examine the relationship between the diagnosis of kidney disease and measures of access to care and quality of care (QoC) in adults with diabetes.

Methods: We analyzed 17,702 (weighted sample of 17,857,175) adults with diabetes in the United States using data from 2002-2011 Medical Expenditure Panel Survey (MEPS). Access to care variables included: usual source of care, overall medical access to care and prescription access while QoC variables included: ≥2 hemoglobin A1c tests, feet exam by a doctor, dilated eye exam, blood pressure check, and medical visit in past year. Chi-square tests were used to investigate unadjusted relationships, followed by logistic regression adjusted for relevant sociodemographic factors and comorbidities. Analyses accounted for sampling weights, clustering and stratification design of MEPS to estimate nationally representative results.

Results: In unadjusted analyses for access to care variables, differences between those with diabetes and kidney disease differed from those with diabetes only in their likelihood of having a usual care provider (p=0.02) and access to prescription medication (p=0.04). However, after adjustment no statistically significant differences remained. All adjusted analyses for QoC measures were significant (at p<0.01 level), with those diagnosed with kidney disease more likely to have two A1c tests in the past year (OR=1.76),

feet checked by doctor (OR=1.54), received dilated eye exam (OR=1.32), have blood pressure checked (OR=2.49), and medical visit in past year (OR=2.45).

Conclusions: Access to care is relatively high and the QoC indicators in patients with diabetes and a diagnosis of kidney disease are being met. However, there is room for improvement in access to care in this patient population to avoid the expensive complication of end stage renal disease.

EPIDEMIOLOGY—TYPE 1 DIABETES

241-LB

Results of the Multicentric Study RENACED on Type 1 Diabetes Mexican Patients

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Introduction: Information regarding treatment, follow-up and outcomes of type 1 diabetes (T1D) Mexican patients is limited. An online system, RENACED, was created to have a longitudinal T1D registry with real-life data in Mexico.

Methods: Descriptive and bivariate analysis of 743 T1D patients registered on RENACED in 16 Mexican States (28 different medical units), until 2/22/2017.

Results: Forty percent of patients were men, with median age 21 years and median age at diagnosis 11 years old. Median diabetes duration from diagnosis was 10.5 years. Median HbA1c at diagnosis and in the last visit were 11.8% and 8.6%, respectively. Twelve percent have family history of T1D and 55% of T2D. SMBG is performed in 92%, 36% perform it ≥4 times/day. Regarding treatment, 26% are on CSII, 64% on MDI with insulin analogues, 8% on MDI with human insulin, 1.2% on premixed insulin, 1% on basal insulin only. Patients that perform SMBG ≥4 times/day, had lower HbA1c levels (8.2; CI95% 7.9-8.4) than those that monitor less (8.6; CI 95% 8.4-8.9) ($p<0.05$). Also, lower HbA1c levels ($p<0.05$) were observed in patients that used CGM (7.8; CI 95% 7.5-8.1 vs. 8.7; CI 95% 8.5-8.9), CSII (7.9; CI 95% 7.6-8.1 vs. 8.8; CI 95% 8.6-9.1), or Metformin (8.0; CI 95% 7.4-8.6 vs. 8.7; CI 95% 8.5-8.9). An HbA1c level <7% was found in 19% of patients. The presence of mild/moderate hypoglycemia is 71% and of severe hypoglycemia is 19%. Presence of retinopathy, neuropathy and nephropathy was found in 15%, 13% and 12.5%, respectively.

Conclusions: According to the literature, the percentage of patients with HbA1c at goal is lower than desired, even though many are on state-of-the-art treatment. Performing SMBG ≥4 times/day, CGM use, CSII and Metformin are associated with better glycemic control. This is the first online system for T1D registry in Mexico. A larger number of cases will lead to better national representation.

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242-LB

Maternal Obesity and the Risk of Childhood-Onset Type 1 Diabetes

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Background: A few studies have suggested that maternal pre-pregnancy obesity or excessive gestational weight gain predicts higher risk of childhood type 1 diabetes, but results are not consistent and the mechanisms are unknown. No previous study has explored the corresponding association with paternal anthropometry to evaluate whether maternal obesity could reflect shared unmeasured background characteristics.

Methods: We evaluated the associations of parental anthropometric measurements with the offspring's risk of type 1 diabetes among 132,331 children participating in the Norwegian Mother and Child Cohort Study (MoBa) and the Danish National Birth Cohort (DNBC). The associations with type 1 diabetes, as defined by national childhood diabetes registers (n=499 cases), were evaluated using Cox proportional hazards regression. Parental anthropometric measurements were self-reported.

Results: 81,630 children participated from MoBa (mean age at end of follow-up, 11.0 years) and 50,701 from DNBC (mean age at end of follow-up, 15.5 years). The incidence rate of type 1 diabetes was 32.7 cases per 100,000 person-years in MoBa and 28.5 cases per 100,000 person-years in DNBC. Both maternal pre-pregnancy obesity, HR 1.41 (95% CI: 1.06, 1.89), and paternal obesity, HR 1.51 (95% CI: 1.11, 2.04), was associated with childhood type 1 diabetes. In contrast, there was no strong evidence of an association between maternal gestational weight gain and childhood type 1 diabetes.

Conclusion: While maternal obesity predicted higher risk of childhood type 1 diabetes, the causal nature of this observation is questioned by a similar observation for paternal obesity, which might reflect unobserved confounding by shared parental lifestyle characteristics.

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243-LB

Where Are the Missing Children? Development and Implications of Improved Type 1 Diabetes Prevalence Estimates in Less-Resourced Countries

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Aim: Current estimates of type 1 diabetes (T1D) prevalence in less-resourced countries produced by the International Diabetes Federation (IDF) have various limitations. These include an assumption of zero mortality, a developed-country age-of-onset distribution with a fixed prevalence/incidence ratio, age range restricted to <15 years (y), and no temporal incidence changes. We developed a model to address these limitations.

Methods: A discrete time Markov illness-death model with age and calendar-year-dependent transition probabilities was developed in R 3.3.1. A novel feature of the model is the inclusion of a two-fold impact of diabetes on mortality: a probability of death at onset (from misdiagnosis, or during initial ketoacidosis episode), as well as a sustained excess mortality.

Results: The model was validated against 17 y of incidence/prevalence/mortality data from Uzbekistan, with correlation of r=0.93 and marked improvement compared to estimates based on IDF Atlas assumptions; and also against 15 y of similar data from New South Wales, Australia (difference with model 1.3%).

Prevalence was modelled for various countries under varying assumptions. Data indicates that in a country such as Nigeria, the proportion of children aged 0-<15 y who die at onset and/or within 6 months of developing T1D may be 90% or more. In sub-Saharan Africa, a very conservative estimate is that there are over 2,000 deaths annually <15 y alone.

Conclusion: This model improves prediction of incidence or prevalence or mortality in young people with T1D under varying measurements/estimations of two of these parameters. Results demonstrate the need for public health and clinical interventions in many countries to prevent deaths from misdiagnosis and improve ongoing management. A further implication is that numbers will quickly rise when care improves, requiring expansion of clinical services and increased requirements of insulin and other supplies.

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244-LB

Impact of Excessive Gestational Weight Gain and Prepregnancy BMI on Prevalence of Large-for-Gestational-Age Infants in Two Cohorts of Women with T1DM

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Background: Despite improvements in treatment modalities, prevalence of large-for-gestational age (LGA) remains high among mothers with TIDM. Higher birthweight is associated with increased risk of obesity and TIIDM among offspring. We aimed to establish the change in LGA prevalence and associations between gestational weight gain (GWG) and LGA outcomes among mothers with TIDM between periods 1978-1995 and 2002-2008.

Research Design and Methods: Analysis of mothers with TIDM enrolled in Diabetes in Pregnancy Program Project Grant (PPG), a cohort from 1978-1995 (n=333) and those enrolled in Consortium on Safe Labor (CSL), a multi-center cross-sectional study from 2002-2008 (n=358). LGA was defined as birthweight >90th percentile adjusted for gestational age, sex and race. GWG was defined according to 2009 Institute of Medicine (IOM) guidelines. Logis-

tic regression and generalized estimating equations were used to estimate odds ratios.

Results: LGA prevalence showed no significant improvement over a 30-year period (PPG: 36.5% vs. CSL: 38.7%). Normal weight women within IOM guidelines showed a reduction (PPG: 39.8% vs. CSL: 32.1%), p<0.05. More women entered pregnancy as overweight from PPG (16.8%) to CSL (27.0%), p<0.001. Increase in women who exceeded IOM guidelines from PPG (42.3%) to CSL (56.3%), p<0.001. In CSL, normal weight women exceeding IOM guidelines [OR 2.14 95% CI (1.17, 3.91), p=0.013] and overweight women exceeding IOM guidelines [aOR 2.25, 95% CI (1.18, 4.28), p=0.013] were at higher risk of LGA compared to normal weight women within IOM guidelines.

Conclusions: Despite advancements in treatments for TIDM, increases in BMI and GWG may be hindering expected improvements in LGA. Normal weight women who remained within IOM guidelines saw a reduction in LGA prevalence, confirming the importance of adherence to IOM guidelines for GWG to reduce LGA rates, particularly for women with TIDM who enter pregnancy as overweight.

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GENETICS—TYPE 1 DIABETES

245-LB

Nanoscale Proteomics Profiling of Laser Capture Microdissected Human Islets Revealed Novel Proteome Changes of the Islet Cells at the Pre-T1D Stage

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Clinical T1D is preceded by an asymptomatic phase where ongoing autoimmune destruction of the insulin-producing beta cells occurs. However, little is known regarding the exact molecular changes occurring in vivo within pancreatic islets and surrounding cells during the pre-T1D phase. Herein, we applied a recently developed enabling technology, termed Simplified Nanoproteomics Platform (SNaPP), for interrogating the proteomes of human islets and acinar tissues isolated by laser capture microdissection (LCM) from nondiabetic and prediabetic autoantibody positive (AAb+) subjects obtained from the Network for Pancreatic Organ donors with Diabetes (nPOD) cohort.

Human islets and acinar tissues from age/sex matched paired nondiabetic and prediabetic AAb+ subjects (n=6) were isolated by LCM. ~100 islet slices, corresponding to about two islet equivalents (IEQs), isolated from 10 µm tissue slices from each subject were analyzed by the SNaPP system. The SNaPP system utilizes online trypsin digestion and sample cleanup for reproducible LC-MS/MS analysis of nanogram protein quantities, thus enabling effective proteome profiling of LCM samples. The analyses resulted in the identification and quantification of ~3200 islet proteins. Bioinformatics analyses revealed that nearly half of the significant altered proteins were related to extracellular exosomes or secretion. Moreover, a number of interesting biological processes including ER to Gorgi vesicle-mediated transport, viral process, and NIK/NF-KappaB signaling are implicated in the prediabetic islet dysfunction.

In summary, the SNaPP system enables relatively deep quantitative proteome profiling of LCM-islets from pre-T1D subjects. The observed altered protein expression levels should provide a rich resource for identifying novel molecules relevant to autoimmune destruction and adaptive response of human islet cells underlying the pre-T1D phase.

Supported By: National Institutes of Health/Human Islet Research Network (UC4DK104167)

GENETICS—TYPE 2 DIABETES

246-LB

The Role of Inflammation in Type 2 Diabetes and Obesity and Their Complications

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There is a well-established association between markers of inflammation, type 2 diabetes (T2D), obesity, coronary artery disease (CAD) and other complications of diabetes. It remains unclear whether chronic inflammation makes a causal contribution to the development of T2D and obesity, or is merely a consequence. If the latter, it is possible that chronic inflammation secondary to T2D and obesity plays a role in complications. There is a strong genetic predisposition underlying these traits that can be used to investigate the role of inflammation. Genome-wide association statistics were assembled for 33 traits including (a) inflammatory diseases and markers (e.g., CRP); (b) T2D, obesity/BMI and related traits; and (c) CAD and other diabetic complications. LD score regression was used to estimate genetic correlations between the inflammatory traits and the other phenotypes. We detected a positive genetic correlation (p<0.05) between CRP levels and a range of metabolic traits including T2D, obesity, CAD and peripheral vascular disease (PVD) and a negative correlation with diabetic kidney disease in subjects with T1D. We constructed genetic risk scores (GRS) for each of the inflammatory traits from independently associated variants ($p<5x10^{-8}$ or FDR p<0.05). The GRS for increased CRP was associated with increased risk of T2D but reduced risk of CAD ($p<3.1x10^{-4}$). The associations of CRP score with both traits was driven by variants pleiotropic for lipid and CRP levels. Amongst inflammatory disease traits, only the GRS for rheumatoid arthritis showed any association with diabetes complications (decreased risk of chronic kidney disease (CKD) in subjects with T2D [OR, 0.90 [0.85-0.94], $p=1.4x10^{-5}$]). There was limited evidence of a shared genetic background between inflammatory traits on the one hand, and T2D/obesity and the complications thereof on the other. This argues against a direct contribution of inflammatory processes to the development of T2D, obesity and their complications.

Supported By: Novo Nordisk Foundation

247-LB

Role of the Tribbles 3 Promoter and SP1 in Glucose-Induced Gene Expression and Glucose Toxicity in Diabetes

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Background: While glucose-induced insulin resistance requires the hexosamine biosynthetic pathway (HBP), we have shown that the pseudokinase TRIB3 is induced by glucose in skeletal muscle requiring HBP and causes glucose toxicity. Yet, the mechanism by which glucose regulates TRIB3 gene expression remains unknown.

Hypothesis: Specific cis or trans elements in the TRIB3 promoter region modulate the induction of TRIB3 gene expression by glucose via HBP.

Results: A 2.44 Kb DNA fragment of the TRIB3 promoter (-1700 to +737) was subcloned and transiently transfected into L6 muscle cells. TRIB3 promoter activity increased progressively up to 15-fold (P<0.01) with advancing glucose treatment (0, 5, and 25 mM) for 24h. To identify the responsible regulatory elements, transfections were performed using sequentially truncated promoter constructs. When a 5' sequence containing SP1, E-box, and USF sites was deleted to generate an intermediate length construct (-980 to +737), glucose responsive promoter activity was lost. However, based on a shorter construct (-400 to +737) including 2 SP1 sites, glucose again augmented promoter activity 10-fold (P<0.01). Thus, factors between -980 and -400 could silence glucose-induced promoter activity in the shortest construct; but, the suppressive effects were not evident when cells were transfected with the full length construct.

Conclusion: 1.) The induction of TRIB3 by glucose is due its ability to stimulate TRIB3 promoter activity in a dose-dependent manner; 2.) Regulation of the TRIB3 promoter is complex in that there are interacting regions that both mediate and suppress glucose responsiveness; (3) SP1 sites appear to be critical in the regulatory action of glucose on the TRIB3 promoter which is of interest since the activity of SP1 is known to be modulated by O-linked glycosylation involving the HBP. While further studies are underway, TRIB3 and TRIB3 promoter regulation are attractive targets for prevention of glucose toxicity in diabetes.

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248-LB

Fingerprint Asymmetry as an Early Indicator of T2DM Risk

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Early screening tools, coupled with an effective intervention, could help many people avoid T2DM. Models for determining risk for T2DM that include phenotypic characteristics can be quite successful, but are based on characteristics (BMI, waist circumference) that are often manifested after the development of metabolic abnormalities. Models that incorporate genetic variants can provide insights into risk prior to the development of associated health problems. However, the costs involved for the models that involve genetic testing can be prohibitive. Fingerprints form during gestation, and are potentially influenced by the same environmental factors that influence the expression of genes involved in T2DM. We tested the hypothesis that fluctuating asymmetry in fingerprints can be used as an early predictor of

T2DM by assessing asymmetry scores for each finger pair using a wavelet-based analysis. In a previous study in Southeastern Ohio (100% white/Caucasian; 165 prints), asymmetry scores for finger pairs IV and V significantly predicted T2DM controlling for gender and age. In the current study, we used the same methodology to determine if fingerprint asymmetry would predict T2DM across a more ethnically diverse population from Northern California (41% white/Caucasian, 26.5% African American, 14.5% Asian American, 18% Hispanic; 48 prints). In the multivariate model that best fit our data (Likelihood Ratio Chi-square=37.0, df=9, P=0.0001), asymmetry in finger pairs IV (P=0.014) and V (P=0.001) were significant, as well as age (P=0.028). The model also included interactions between finger pairs IV and V (0.002), ethnicity and age (0.0001), and age and asymmetry for finger pair V (0.002). These results add support to the hypothesis that a model based on asymmetry in fingerprints has the potential to be a powerful, early predictor of propensity to develop T2DM. In addition, fingerprint asymmetry has the potential to complement genetic studies to improve our understanding of gene x environment interactions involved in T2DM.

249-LB

Meta-analysis in a Large Hispanic/Latino Sample Identifies Known and Novel Loci for Type 2 Diabetes and Lipid Traits

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We present the results of the largest genome-wide meta-analyses of type 2 diabetes and lipid traits conducted in a Hispanic/Latino population, comprising 14,150 T2D cases and 22,648 controls, and ~22,500 samples with blood lipid measurements. Genome-wide genotype data was imputed to 1000 Genomes Project phase 1 or 3 for all contributing cohorts, followed by association analysis with adjustment for age, sex, and principal components as needed to control for population substructure and both with and without body mass index adjustment. Meta-analysis was performed, weighting effect size estimates by inverse standard error, and genome-wide significant results were classified according to their prior report status. Sixteen genome-wide significant loci were identified for T2D, including 10 novel loci. Three T2D-novel loci map to genes that have been previously implicated in obesity and related traits, including NUDT3, KIRREL, and SERPINA3. The most significant novel loci included rs140138659 ($p=2.44x10^{-20}$), intronic to ARHGEF28 and rs72784941 ($p=3.92x10^{-9}$), intergenic between C16orf52 and VWA3A. Three loci were novel for lipid traits. For total cholesterol, rs3747207 ($p=1.35x10^{-8}$) is intronic to PNPLA3, a triacylglycerol lipase associated with alcohol-related cirrhosis and hepatic lipid content in obesity. For triglycerides, rs12154627 ($p=8.67x10^{-11}$) is intergenic between KLF14, a gene linked to HDL cholesterol and waist-to-hip ratio, and MIR29A, a microRNA which has been previously associated with several cancers and type 2 diabetes. Also for triglycerides, rs2276305 ($p=9.79x10^{-9}$) is exonic to HTR3B. These findings demonstrate the utility of large-scale GWAS of metabolic traits in under-investigated and admixed samples for discovery and refinement of top signals, as well as the need for conditional and pleiotropic analyses to elucidate the complex biology underlying these signals.

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250-LB

WITHDRAWN

IMMUNOLOGY

251-LB

Autoimmunity and Beta-Cell Function among Youth with Diabetes in Haiti

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Autoimmune markers are a key component in the etiologic classification of youth onset diabetes, yet such information in Haitian people, including the frequency of islet autoantibodies (AAb), is largely unknown. Therefore, we evaluated 3 AAb (GADA, IA-2A, ZnT8A) and their relationship with clinical and biological phenotypes, in 91 subjects aged < 22 years with diabetes diagnosed within the previous 23 months (51.7% men; age at diagnosis 13.3 ± 4.2 years; diabetes duration 11.7 ± 8.3 months). At diagnosis, the triad of polyuria, polydypsia, polyphagia was present in 80.2%; 90.1% had weight loss; 7.7% had signs of malnutrition; and 19.8% displayed ketoacidosis. At evaluation, all were utilizing insulin, 38.5% were positive for ≥ 1 AAb, HbA_{1c} was 10.5 ± 2.9%, and fasting C-peptide (FCP) was 0.9 ± 1.1 ng/mL (normal range: 0.5-3.2 ng/mL). FCP was low, normal and high in: 40.0%, 57.1% and 2.9% of AAb^+ pts, respectively; and 49.1%, 45.5% and 5.5% of AAb^- pts, respectively. AAb positivity rates were: GADA 28.6%, ZnT8A 11.0%, and IA-2A 8.8%. Combined GADA + ZnT8A and GADA + IA-2A assays detected 1 or 2 AAb^+ in 35.2% and 31.9% of pts, respectively. All 7 pts with malnutrition history were AAb^- (p=0.03). Thyroperoxidase and thyroglobulin antibodies were positive in 1.1% and 2.2%, respectively. Within 3, 6 and 12 months of diagnosis, 53.8% (7/13), 52.0% (13/25) and 43.4% (23/53) had ≥ 1 AAb^+, respectively. ZnT8A was 4 times more frequent before than after age 12 years (24.0% vs. 6.1%, p=0.02). Preliminary genetic data showed no association of DRB1 for 36 pts compared to 19 controls (p=0.31). Our study suggests high proportion of atypical diabetes among Haitian youth with diabetes, and frequent persistence of β-cell function for some months after disease onset. GADA, ZnT8A, and IA-2A assays should be combined for detection of classic β-cell autoimmunity. Thyroid autoimmunity appears uncommon in the young diabetic population. These findings open up perspectives for improved youth diabetes care in Haiti through better disease diagnosis.

252-LB

Progression of Type 1 Diabetes from the Prediabetic Stage Is Controlled by Interferon-α Signaling

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Type I interferons (IFN), originally described as anti-viral cytokines, are pleiotropic factors that induce potent immunoregulatory programs thought to potentiate chronic inflammation and autoimmunity including type 1 diabetes (T1D). Using two well-characterized virus-induced mouse models of T1D (fast onset and slow onset Rip-LCMV), we sought to define the species of type I IFN and mechanisms involved causing T1D, as well as therapeutic approaches that target IFN-I signaling to prevent diabetes by preserving β-cell function. Blockade of IFN-α but not IFN-β using either an antibody or a selective S1PR1 agonist, CYM-5442, prevented T1D in the fast onset model. The mechanism was two-fold. First, blockade of IFN-α did not affect the differentiation or expansion of virus (autoimmune) specific CD8+ T cells, but nevertheless limited the migration of autoimmune T cells to the external boundaries around the islets and prevented their entry into the islets so they could not be positioned to engage and kill insulin-producing β cells. Selective ablation of the IFN-I receptor (Ifnar) in β-cells did not significantly disrupt disease progression, suggesting that IFN-α has a pathogenic role on cells outside the islets. CYM-5442, besides restricting antiself CD8+ T cells to the rim of the islets, enhanced the expression of negative immune regulator receptors on antiself T cells thereby limiting their killing ability. By such means, insulin production was preserved and glucose regulation was maintained. The multi-step interdiction of S1PR1 agonism on lymphocyte migration to pancreatic islets coupled with IFN-α suppression and upregulation of negative immune regulators including PD-1 suggests that similar therapy might be considered for humans during the prediabetic period when autoantibodies to GAD65 and insulin are present and blood glucose levels are normal. This is currently being examined in the slow onset Rip-LCMV T1D model that results in prediabetic period of months before onset of T1D.

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253-LB

Human Probiotic Bacteria and Gluten-Free Diet in Prevention of Type 1 Diabetes in NOD Mice

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Environmental factors play important if not major role in the rapidly increasing incidence of type 1 diabetes (T1D) in developed countries. Studies in spontaneous animal models of T1D documented that the quality of SPF housing conditions, and gut microflora (e.g., re-derivation of breeding nucleus) modify penetrance of the diabetes incidence. In this study we tested whether the effect of highly diabetes preventive, gluten-free Altromin diet is dependent on gut microlfory by monitoring its effect in germ-free NOD mice. Second, we have studies the effect of three human probiotic bacteria Lactobacillus casei, Lactobacillus plantarum, and E coli Nissle on the development of spontaneous diabetes incidence in the NOD mice both in the context of gut microflora in SPF conditions and in ex-germ-free mono-associated NOD mice. We also investigated how the 3 probiotic bacteria influenced regulatory immune mechanisms in the mucosal and control lymphatic organs in SPF NOD mice. A regimen with intragastric applications of 10^9 CFU per dose led to slightly delayed and decreased diabetes incidence in SPF NOD mice, being highest for the Lactobacillus casei species. Flocytometry immunomonitoring of cell subsets influenced by probiotic bacteria (Lactobacillus casei) documented that among various immune cells proportions of Foxp3 Tregs, NK cells as well as ILC1 and ILC3 cells were influenced by Lactobacillus casei within the mucosal (mesenteric and pancreatic LN) compartment. We suggest that dietary manipulations (gluten-free diet), probiotic bacteria and their mucosal immune mechanisms may represent a promising and inexpensive approach for a primary prevention of type 1 diabetes.

254-LB

$CD25^+CD127^{hi}$ Frequency Correlates with Length of Remission in T1D: Exploring Potential Mechanisms and Pathways

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T1D is an autoimmune disorder that leads to the destruction of pancreatic islets and insulin insufficiency. Initiation of treatment triggers partial remission in most patients, but length of remission (LoR) can vary from a couple of months to a year. Mechanisms that affect LoR are largely unknown, but are theorized to depend upon a combination of genetic and environmental risk factors. Our lab, using co-variate analysis has reported that frequency of $CD4^+CD25^+CD127^{hi}$ cells at diagnosis correlates with LoR when combined with either HbA1c, IDAA1c or C-peptide, with a high frequency correlating with longer LoR. These cells have a predominantly central memory phenotype, but express neither the Tr1 or Treg markers. The purpose of this study was to characterize the function and frequency of $CD25^+CD127^{hi}$ cells in healthy subjects to elucidate a potential mechanism for its association with LoR during recent onset T1D. We used healthy donor PBMCs to characterize $CD25^+CD127^{hi}$ cells compared to other memory cell subsets including $CD45RO^+$ cells, RO^+CD25^- cells and Tregs. We found that ~20% of all $CD45RO^+$ cells are $CD25^+CD127^{hi}$. Sorted $CD25^+CD127^{hi}$ cells have a high proliferative capacity upon stimulation and produce significantly higher levels of IL-2, IFN-γ, IL-4 and IL-17 than other memory cell subsets tested. $CD25^+CD127^{hi}$ cells thus are a mixed population of Th1, Th2 and Th17-type cells. Next, we checked the response of $CD25^+CD127^{hi}$ cells in unstimulated and stimulated PBMCs and found that they have a Th2 bias that increases as they express higher levels of the IL-2R, CD25. Thus, $CD25^{hi}CD127^{hi}$ cells have a higher frequency of Th2 pre-committed ($CXCR5^-$ $CXCR3^-$ $CCR4^+$) and committed ($IL4^+$ $GATA3^+$) cells than $CD25^+CD127^{hi}$ cells, which in turn have a greater Th2-type bias than $CD25^-CD127^{hi}$ cells. Overall these data suggest that the $CD25^+CD127^{hi}$ cells have the potential for promoting partial remission by driving the response toward a protective Th2-type and away from a pathogenic Th1 profile.

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255-LB

Prolonged Clinical Remission of Type 1 Diabetes Mellitus Treated with Sitagliptin and Vitamin D3 Could Be Related to Changes in $CD8^+$ Lymphocytes Count Expressing $CD26^+$

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Type 1 diabetes mellitus (T1DM) is a chronic disease characterized by a destruction of pancreatic beta cells by a damaging and complex autoimmune process with activated $CD8^+$ cytotoxic T lymphocytes (TL) often detected in analysis of pancreatic islets infiltrates. TL have a membrane-associated protein with DPP-4 activity-CD26-which has a marked influence on the development, migration, and production of cytokines by TL. Patients with T1DM often experience a partial remission of the disease (honeymoon phase), although a remission lasting more than 1 year is uncommon.DPP-4 inhibitors have been used to reestablish immunological tolerance and have successfully prevented and reversed T1DM in NOD mice. Vitamin D displays actions on the immune system, including effects on innate and acquired immunity. In this study, we compared, by flow cytometry (BD-FACSCalibur), the TL subsets ($CD3^+$,$CD4^+$,$CD8^+$,$CD4^+/CD26^+$ and $CD8^+/CD26^+$) among 10 T1DM (16-43 years, 7F/3M) treated only with insulin, 5 T1DM (20-47 years, 3F/2M) treated with insulin and sitagliptin 100 mg/day plus vitamin D3 5.000 IU/day and 2 new-onset T1DM (13 and 15 years,1F/1M)) pretreatment with sitagliptin and vitamin D3. Eight healthy donors (19-34 years, 6F/2M) and 9 women (15-39 years) with Hashimoto's thyroiditis were control group. We showed that patients with T1DM treated with sitagliptin and vitamin D3 had prolonged clinical remission (from 1 to 5 years). T1DM treated with sitagliptin and vitamin D3 showed reduced $CD8^+/CD26^+$ TL count when compared with T1DM treated only with insulin (p=0,022). Differences in HbA1c, fasting C-peptide levels, insulin dose diary and 25-OH vitamin D3 were also statistically significant (p<0,05). Two patients are still without insulin.

In conclusion, prolonged remission in T1DM is possible with sitagliptin plus vitamin D3 use and changes in the TL subsets could be related with this result.

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256-LB

Elevations in Proinflammatory Lipids during the Prediabetic Phase of T1D: Link to Ca^{2+}-Independent Phospholipase A2beta Activation

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Type 1 diabetes (T1D) is a consequence of autoimmune destruction of beta-cells, involving activation of cellular immunity leading to leukocyte infiltration of islets. An understudied area is the role lipid signals play in this process. We find that the Ca^{2+}-independent phospholipase A_2beta (iPLA_2beta) is induced under a diabetic milieu and the mitigation of iPLA_2beta attenuates beta-cell death. The iPLA_2beta, a member of the PLA_2 family, hydrolyzes the sn-2 substituent from glycerophospholipid substrates to yield a free fatty acid, which can be metabolized to bioactive lipids. Macrophages participate in autoimmune-mediated destruction of beta-cells and we reported that iPLA_2beta activation favors M1 proinflammatory phenotype, suggesting that iPLA_2beta-derived lipids (iDLs) contribute to inflammatory responses promoting beta-cell death. Here, we utilized peritoneal macrophages to assess the relevant lipid pools impacted by iPLA_2beta activation. Macrophages were treated with DMSO (vehicle), IFNg+LPS (to induce M1 polarization), or IL-4 (to induce M2 polarization). At 16h, the media and cell pellet were collected and processed for assessment of eicosanoid and sphingolipid classes of bioactive lipids via UPLC ESI-MS/MS. These analyses revealed that proinflammatory lipids in prediabetic NOD (nonobese diabetic, 4 wks of age) were higher both basally and following activation, relative to C57BL/6J mice. Interestingly, their abundances decreased in the 8 and 15 wk-NOD. Similar analyses revealed production of several proinflammatory and antiinflammatory lipids was decreased and increased, respectively, from macrophages and islets of NOD.iPLA_2beta$^{-/+}$, relative to age-matched NOD-WT. These findings suggest that iDLs generated by immune- and beta-cells contribute to the onset of T1D and raise the possibility that iPLA_2beta and/or iDLs are candidates that can be targeted to counter T1D development.

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257-LB

β-Cell Changes in Response to Checkpoint Inhibition

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Type 1 diabetes (T1DM) arises from destruction of insulin producing pancreatic β cells by infiltrating autoreactive cytotoxic T cells. Patients with cancers, who are treated with checkpoint inhibitors, may rapidly develop diabetes that resembles T1DM in the loss of β cells but is seen in older individuals and occurs more rapidly. While checkpoint inhibitor-induced diabetes has been reported with monoclonal antibodies targeting the PD-1/PD-L1 axis, it has not been reported with anti-CTLA-4. The rates of this complication are low and there is little understanding about why some individuals treated with these drugs develop diabetes and others do not and why it is not seen with anti-CTLA-4 mAb alone. We hypothesized that the response of β cells to immune stressors may be responsible for the selective

For author disclosure information, see page LB107.

loss of tolerance with PD-1/PD-L1 antagonists and this clinical observation. We cultured allogenic human islets with peripheral blood mononuclear cells (PBMCs) from healthy donors in the presence of checkpoint inhibitors (monoclonal antibodies to PD1 or CTLA4) or control immunoglobulin. In islet-PBMC cocultures treated with anti-PD-1, but not anti-CTLA-4 mAbs, we observed a significant increase in inflammatory cytokines including IL-2, IL-17, IL-13 and IFNγ, which was highly stimulated with addition of anti-PD-1 mAb. When pancreatic islets were treated with IFNγ alone, there was an increase in expression of PD-L1, but not CD80 or CD86, the CTLA-4 ligands, on β cells. We observed similar responses in β cells from NOD mice during progression of autoimmune diabetes. PD-L1, but not CD80 or CD86, were detected on β cells from NOD mice upon confrontation with islet infiltrates. Our preliminary studies of human β cells exposed to inflammatory mediators and NOD mice suggest that the PD-1/PD-L1 pathway plays a role in β cell tolerance and that PD-L1 expression in response to inflammatory stressors occurs possibly as a protective response.

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258-LB

Insulin Antibody IgG4/IgG1 Ratio as a Biomarker of Ongoing Islet Destruction in New-Onset Type 1 Diabetes (T1D)

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Background: Immunotherapy trials at T1D onset may preserve remaining ß-cells, lessen hypoglycemia and provide a favorable milieu for islet replacement, yet we lack accessible biomarkers of ongoing ß-cell immune destruction to monitor efficacy and manage immunotherapy.

Aims: Patients almost always develop anti-insulin antibodies (IA) after starting SQ insulin. We tested how IA isotype ratios evolve after T1D onset in relation to measured C-peptide, as marker of putative ß-cell destruction.

Methods: Monthly postprandial venous samples starting at onset (range 7-36 mo, median 22 mo post-onset) in 11 children developing IA after starting SQ insulin, were tested for IA IgG isotypes 1, 2, 3 and 4 by validated radiobinding assay. Single control samples (10 longstanding T1D and 7 T2D patients, all with IA on SQ insulin) were also tested for IA IgG1, IgG4 and standard islet autoantibodies. C-peptide was tested in all samples.

Results: At onset, IA was dominated by IgG1 (IgG4/IgG1 ratio >0.7 in only 1/11) and C-peptide was always detectable (range 0.9-3.7, median 1.7 ng/ml). Over time, C-peptide levels fell (to range 0.0-0.9, median 0.5), indicating few remaining ß-cells and declining insulitis. IA IgG4 increased (IL4-dependent Th2-type response) and an IgG4/IgG1 ratio >0.7 was detected in 10/11 subjects (p=0.0003). If the shift towards IgG4 marked diminishing insulitis, we hypothesized that longstanding T1D (>5 yr) on SQ insulin with undetectable C-peptide and autoantibody-negative T2D on SQ insulin should both have IA but no insulitis, so also more IgG4. Indeed, IA IgG4/IgG1 ratios were >0.7 in most patients (8/10, p=0.002 and 5/7, p=0.01, for longstanding T1D and T2D, respectively, vs. new onset T1D).

Conclusions: These preliminary data suggest that IA isotypes may be an accessible venous biomarker of active ß-cell destruction. Further validation will use immunotherapy trial samples to test if IA IgG4/IgG1 ratios predict AUC C-peptide changes in responders vs. nonresponders.

259-LB

Clinical Heterogeneity among Pediatric Patients with Autoimmune Type 1 Diabetes Stratified by Immunoglobulin Deficiency

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Autoimmune type 1 diabetes (AT1D) may coexist with other autoimmune conditions and immunodeficiency. The aims of a study were to define the frequency of immunoglobulin deficiency among pediatric patients with AT1D and to identify specific clinical features of patients with immunoglobulin serum deficit. 457 pediatric AT1D patients attending one clinic were studied. All of them were positive for at least one anti-islet antibody. Individuals under 4 years of age were four excluded and finally 411 patients (89.9%, aged 8.9+/-3.8 yrs) completed the study. Additional 50 patients with AT1D and IgA deficiency recruited from other 4 centers served as a replication cohort. Immunoglobulin class IgA, IgG, IgM, IgE and IgD serum levels were measured using nephelometry and ELISA kits. Subclasses of IgG (G1-G4) and IgA (A1-A2) were also studied. At least 1 class immunoglobulin deficiency was found in 91 (22.1%) individuals from the first cohort. The most frequent was IgA (IgADef) (8.7%), as well as IgG (6.2%), IgM (5.1%) and complex multiple immunoglobulin (2.1%) deficiencies. Interestingly, only IgADef was linked with some clinical features. Patients with AT1D and IgADef had higher frequency of autoimmune comorbidities (67.8% vs. 37.3%, p=0.002), (38.1% vs. 16.8%, p=0.001), as compared with other AT1D patients. Non-immune related disorders coexisted more frequently in IgADef group (20.9% vs. 7.1%, p=0.005), especially neurological features (9.3% vs. 2.7%, p=0.04). Moreover, in the IgADef group first degree relatives frequently had autoimmune diabetes (27.9% vs. 5.9%, p=0.0002). In the replication cohort comorbidities were present in 69% and positive family history of AT1D in 42%. Immunoglobulin deficits are relatively frequent among pediatric patients with AT1D and may be associated with autoimmune and non-immune related disorders, suggesting that this group has unique clinical characteristics with inherited background.

Supported By: Diabetes Poland

260-LB

Oxidative Posttranslational Modification of Type 1 Diabetes Autoantigens

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During the progression of type 1 diabetes (T1D), infiltrating leukocytes generate an inflammatory environment consisting of reactive oxygen species (ROS) and proinflammatory cytokines, leading to β-cell destruction and enhancement of the adaptive immune effector response of islet-specific CD4 and CD8 T cells. Ergo studies to further define the redox-dependent mechanisms involved in autoimmune dysregulation are warranted. Growing evidence suggests that ROS regulate autoimmunity by inducing oxidative post-translational modifications of T1D autoantigens, facilitate epitope spreading of newly exposed autoantigens, and function as signaling molecules to regulate T cell responses. However, the molecular mechanisms are not currently understood. We recently demonstrated the importance of immune cell-derived NADPH oxidase (NOX), an enzyme responsible for superoxide synthesis and the widely known "respiratory burst" in neutrophils and macrophages, to mature autoimmune responses in T1D. We tested the hypothesis that NOX-derived ROS synthesis induces oxidative post-translational modifications (PTM) of pancreatic β-cell autoantigens to enhance T cell activation. Non-Obese Diabetic (NOD) mice unable to generate superoxide (NOD.Ncf1^{m1J}) are highly resistant to T1D development. When cocultured with NOD.Rag.Ncf1^{m1J} islet cells, BDC-2.5 splenocytes generated significantly lower levels of nitrite ($p<0.05$) and IFN-γ ($p<0.05$) compared to splenocytes co-cultured with NOD.Rag islets. BDC-6.9 splenocytes also produced significantly less IFN-γ in the presence of NOD.Rag.Ncf1^{m1J} islets compared to NOD.Rag islets ($p<0.0001$). Furthermore, analysis of the T cell activation markers CD25, CD44 and CD69 showed that islets from NOD.Rag.Ncf1^{m1J} mice elicited a decrease in T cell activation. Taken together, our data provide evidence that oxidization of pancreatic β-cells augment T cell effector responses in T1D.

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261-LB

Identification of T-Cell Epitopes of Endogenous Retrovirus Gag Protein in Prediabetic NOD Mice

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Endogenous retrovirus (ERV) antigens are candidate autoantigens in several autoimmune diseases including type 1 diabetes (T1D). We previously demonstrated that an ERV, similar to murine leukemia retrovirus (muLV), is expressed in pancreatic islets in nonobese diabetic (NOD) mice, whose Env and Gag antigens are targets of autoantibodies and autoreactive T cells, respectively. Interestingly, cloning and DNA sequencing of the islet-expressing Gag gene revealed a group of highly homologous Gag gene variants. To test whether these different Gag variants contain peptides stimulating autoreactive T cells, we screened altered peptide ligands (APLs) that represent the variable sequences of the individual Gag variants expressed in the islets. Several APLs can activate T cells from prediabetic NOD mice, but not diabetes-resistant mice to release IFN-gamma, including one peptide that codes for a region controlling host susceptibility to muLV infection. Importantly, two APLs of this peptide varied in their capability to induce tolerance in neonatal NOD mice to prevent diabetes. The peptide dominantly expressed in the islets is more efficient than the one not expressed, suggesting that individual ERVs or Gag antigens may function differently in regulating autoimmunity in the islets. Class II MHC tetramers of this peptide identified T cells in periphery and pancreatic draining lymph nodes revealing that the number of tetramer-positive T cells increases as disease progress. These data support that failure of T cell tolerance to ERV Gag antigens may contribute to T1D.

Supported By: National Institutes of Health

TRANSPLANTATION

262-LB

WITHDRAWN

INSULIN ACTION—ADIPOCYTE BIOLOGY

263-LB

The Melanocortin 2 Receptor Accessory Protein (MRAP) Regulates Lipolysis in Adipose Tissue

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Numerous studies have shown that MRAP is essential for the activation of cAMP-PKA pathway in the adrenal cells when responding to ACTH, the sole ligand for G protein-coupled melanocortin 2 receptor (MC2R). In humans, the loss-of-function mutations in MRAP were reported to account for 20% of the familial glucocorticoid deficiency type 2 (FGD2) cases. Despite that MRAP was originally identified as a fat-specific gene in mice, the specific function of MRAP in adipose tissue has yet to be determined. Herein, we found that ACTH was able to activate PKA-mediated phosphorylation as well as lipolytic response in human subcutaneous fat explants, indicating the presence of functional MC2R-MRAP signaling complex in human adipocytes. In differentiated mouse 3T3-L1 adipocytes, knockdown of MRAP expression using specific siRNA significantly reduced ACTH-induced lipolysis, whereas adenovirus-mediated MRAP overexpression led to augmented lipolytic response to ACTH. To better understand the physiologic role of MRAP, we constructed a transgenic mouse model that overexpresses MRAP specifically in adipose tissue. In comparison to the wild type animals, the transgenic mice on a high-fat diet displayed a significant decrease in the gain of total body weight and overall fat mass, which was accompanied by improved insulin sensitivity as revealed by insulin and glucose tolerance tests. Moreover, the plasma free fatty acid levels exhibited a more drastic elevation in the transgenic mice when adipose lipolysis was stimulated via intraperitoneal injection with ACTH rather than CL-316243, a β3-adrenergic agonist. Furthermore, the real-time PCR data showed that expression of genes related to fatty acid oxidation was significantly higher in the white adipose tissue from the transgenic mice than that from the wide type mice. Collectively, our data strongly suggest that MRAP, as the essential accessary protein of MC2R, promotes the fat burning by enhancing adipose lipolysis and FA oxidation in response to ACTH.

264-LB

Ewing Sarcoma Gene (EWS) Dependent PGC-1α Protein Stability Regulates Mitochondrial Homeostasis

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The global epidemic in obesity and metabolic disease has stimulated an explosion of interest in adipose tissue and its function. White adipose tissue comprises the majority of adipose tissues in humans and is depot of unutilized fat in the form of triglycerides. In contrast, brown adipose tissue oxidizes fat to provide heat and is rich in mitochondria. In response to a cold environment or adrenergic stimulation to expend energy through by activate mitochondria. The transcriptional coactivator PGC-1α is a central regulator of mitochondria biogenesis, function and cellular energy metabolism in brown adipose tissue, but its transcriptional and posttranscriptional regulator was not well understood. Recently, we demonstrated that Ewing's Sarcoma gene, EWS, is required for determining embryonic brown adipocyte fate during development. Loss of EWS leads to a significant decrease in mitochondria abundance and activity, which is caused by a rapid degradation of PGC-1α. EWS inactivation leads to increased ubiquination and proteolysis of PGC-1α via proteasome pathway. Consistent with these findings, mitochondrial abundance and activity are significantly reduced in brown fat and skeletal muscles of Ews deficient mice. Complementation of EWS in Ews mutant cells restores PGC-1α protein level and mitochondrial abundance. We found that expression of E3 ubiquitin ligase, FBXW7 (F-box/WD40 domain protein 7), is increased in the absence of Ews and depletion of fbxw7 in Ews mutant restores expression and mitochondrial density. Furthermore, expression of mitochondrial biogenesis, respiration and fatty acid β-oxidation genes is significantly reduced in the liver of Ews mutant mice. These results strongly suggest that a novel role of EWS in mitochondrial and cellular energy homeostasis by controlling PGC-1α protein stability, and further implicate altered mitochondrial and energy metabolism in cancer harboring the EWS translocation.

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265-LB

Blnc1 Preserves Metabolic Homeostasis by Integrating Adipose Tissue Thermogenesis and Healthy Expansion

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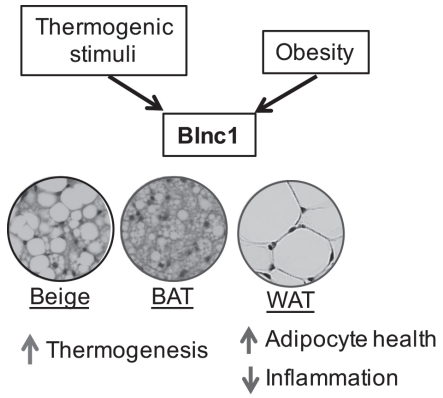
Long noncoding RNAs (lncRNAs) are emerging as powerful regulators of diverse biological processes. Whether lncRNAs contribute to physiological regulation of key aspects of adipocyte biology and metabolic homeostasis has not been established. Here we show that Brown fat lncRNA 1 (Blnc1) expression was elevated in adipose tissue from obese mice. Fat-specific transgenic expression of Blnc1 delayed high-fat diet-induced obesity through increased thermogenesis and energy expenditure. Surprisingly, Blnc1 transgenic mice exhibited a markedly improved metabolic profile despite similar weight gain in wild type and transgenic mice following prolonged high-fat feeding. Analyses of white adipose tissue revealed an unexpected function of Blnc1 in ameliorating adipose tissue inflammation and preserving adipocyte health during obesity. Blnc1 attenuates TNFα-induced proinflammatory signaling and cytokine/chemokine release by cultured adipocytes in a cell-autonomous manner. This study illustrates an unexpected role of lncRNA in maintaining adipose tissue integrity and systemic metabolic homeostasis.

Figure.



Supported By: American Diabetes Association (1-15-BS-118 to J.D.L.); National Institutes of Health

266-LB

FGF-21 Serves as a Liver-Adipose Tissue Axis Signaling to Protect against Adipose Tissue Fibrosis and Systemic Insulin Resistance in Obesity

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Fibroblast growth factor-21 (FGF-21) is the hormone secreted by the liver during fasting. Because clinical trials have reported promising results of the circulating protein FGF-21 in obese patients with type 2 diabetes with reduced body weight, this has sparked interest in identifying the mechanism of action of FGF-21. Our recent studies characterize that activation of TGFβ1 contributes to excess accumulation of collagen fibers surrounding fat cells in patients with obesity. To determine the endocrine effect of FGF-21 on visceral obesity, we used FGF-21 transgenic (FGF-21-TG) mice that overexpress human FGF-21 in the liver using the apoE promoter. We showed that FGF-21 TG mice were resistant to high fat, high sucrose diet-induced obesity, fat mass elevation, and systemic insulin resistance. Adipocyte hypertrophy in epididymal white adipose tissue (WAT) was reduced in FGF-21 TG mice. Strikingly, excessive collagen fibers surrounding adipocytes in epididymal fat depots, as assessed by Masson Trichrome and Sirius Red staining, were significantly reduced. The anti-fibrotic effect of FGF-21 was attributed to suppressed extracellular matrix (ECM) synthesis, as evidenced by decreases in mRNA expression and positive staining intensity of collagen type I, type III, type VI, fibronectin, and lysyl oxidase (LOX), a key collagen cross-linking enzyme. Expression and positive staining areas of MMP-9 and TIMP-1, key regulators of collagen turnover, were reduced. Importantly, the

number of α-SMA+ myofibroblast-like cells was decreased, suggesting that the circulating hepatokine FGF-21 resolves fat interstitial accumulation of ECM in obesity, a metabolically unfavorable fat microenvironment, by reduced ECM synthesis and degradation and repressed fibroblast activation. Therefore, we establish FGF-21 as the hepatokine that is part of a novel liver-adipose tissue signaling axis to combat adipose tissue fibrosis and dysfunction in obesity.

Supported By: American Diabetes Association (1-15-BS-216 to M.Z.); National Institutes of Health

267-LB

PTK2B Plays a Critical Role in Beige Adipocyte Differentiation

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Adipose tissue development is a tightly regulated process which requires the sequential and organized expression of numerous genes and proteins. Phosphorylation of key signal transduction cascades and transcription factors is one of the mechanisms that controls adipogenesis and adipocyte function. Despite recognition of the importance of kinases in adipocyte development and function, relatively little is known about the role of specific kinases in regulating thermogenic (brown or beige) adipocyte development and function. Here, we demonstrate that the non-receptor protein tyrosine kinase 2 beta (PTK2B) plays a critical role for murine beige adipocyte development and function. PTK2B protein expression is associated with beige adipocyte differentiation and CRISPR/Cas9 mediated knock-out of PT2KB in cultured, immortalized, inguinal stromal vascular fraction cells results in impaired beige adipocyte differentiation with significantly reduced thermogenic gene and protein expression, as well as altered mitochondrial respiration. Additionally, we provide evidence that PTK2B deletion impairs insulin-stimulated glucose uptake in beige adipocytes.

In conclusion, our data establish a unique role for PTK2B in thermogenic beige adipocytes and provide a novel target for interventions which increase energy expenditure to ameliorate obesity and diabetes.

268-LB

Unconventional Secretion of Adipocyte Fatty Acid Binding Protein

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Fatty acid binding protein 4 (FABP4) is a cytoplasmic lipid carrier functioning in adipocytes to facilitate lipolysis. Genetic or pharmacologic depletion of the protein provides protection from insulin resistance, asthma, atherosclerosis and inflammation. Whereas protection from metabolic dysfunction has been considered due to the intracellular functions of the protein, recent literature has shown that serum FABP4 levels are elevated in patients with metabolic syndrome. However, FABP4 is a leaderless protein and the mechanism of its release from adipocytes is unknown. Moreover, FABP4 secretion increased with cAMP and correlated positively with free fatty acid (FFA) efflux. The amount of FABP4 secretion is less than 1% of total FFA efflux implying that the protein does not mediate release of bulk lipid in response to lipolytic stimulation. To evaluate the mechanism of FABP4 secretion we have used the 3T3-L1 adipocyte cell culture model and examined the role of secretory autophagy. Surprisingly, FABP4 secretion was potentiated when lipophagy and lysosomal exocytosis were blocked using chemical inhibitors of lysosomal acid lipase and Bafilomycin A1 respectively. However, classical autophagic inhibitors such as 3MA (3-Methyladenine) or wortmannin attenuated FAPB4 secretion significantly and autophagic inducer N-Acetyl sphingosine greatly potentiated secretion, thereby suggesting the requirement for earlier autophagic components. Consistent with the requirement for secretory autophagy, genetic knockdowns of ATG13 or FIP200, genes involved in early events of phagophore formation attenuated secretion. Our studies suggest that FABP4 secretion from adipocytes is regulated by cAMP and is mediated through non-degradative secretory autophagy.

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269-LB

Functional Roles of PPARγ in Brown Adipocytes

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Brown adipose tissue (BAT) plays a critical role in metabolic homeostasis. BAT dysfunction has been shown to be associated with the development of obesity through imbalance between energy expenditure and energy intake. The nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) is considered to be the master regulator of adipogenesis. However, the role of PPARγ and Thiazolidinediones (TZDs) in the regulation of BAT metabolism remains unclear. TZDs, selective PPARγ activators, improve systemic insulin resistance in animals and humans. In the present study, we generated brown adipocyte-specific PPARγ deficient mice (BATγKO) to examine in vivo role of PPARγ and TZDs in the regulation of BAT metabolism. Brown adipocyte-specific PPARγ deletion promoted severe whitening of brown fat and morphological alteration of BAT mitochondria in electron microscopy examinations. Brown adipocyte-specific PPARγ deletion also reduced mRNA expression of BAT selective genes, including Dio2, Pgc1a and Ucp1, in BAT. BATγKO mice developed glucose intolerance and systemic insulin resistance on high fat diet without difference of body weight and adiposity. Although there was no difference of energy expenditure between littermate controls and BATγKO mice in calorimetry, norepinephrine-induced thermogenesis was impaired in BATγKO mice. Furthermore, we find that pioglitazone treatment improved diet-induced insulin resistance in littermate controls but not in BATγKO mice. These findings suggest that BAT PPARγ is required for the maintenance of brown adipocyte function and the systemic insulin sensitizing effects of TZDs.

270-LB

Constitutive Coactivator of PPARγ (CCPG) Knockdown Transdifferentiates C2C12 Myoblasts into Brown Adipocytes

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Background: Constitutive coactivator of Peroxisome proliferator activated receptor γ (CCPG) is characterized as a novel constitutive coactivator of PPARγ. Being enriched in metabolic tissues, CCPG interacts with PPARγ and promotes adipogenesis. However, the potential role of CCPG in other tissues, especially the CCPG-enriched skeletal muscle, remains unclear.

Methods and Results: We generated a shRNA-mediated stable CCPG knockdown (~70% decreased) C2C12 cell line along with a controlled scrambled shRNA C2C12 cell line. CCPG knockdown prevented the differentiation of C2C12 myoblasts into myotubes. Real timePCR showed decreased transcript levels of myogenic regulatory factor MyoD and myosin heavy chain in CCPG knockdown compared to control C2C12 myoblasts. Myosin immunostaining confirmed the reduction of myotube from the C2C12 knockdown cells after the differentiation induction. Phase contrast imaging showed markedly increased lipid droplets, which were further confirmed by oil red-O staining. In addition, cellular energetic analysis using the Seahorse XF24 Bioanalyzer showed increased basal and maximal oxidative metabolism in CCPG knockdown C2C12 cells. Radiolabelled metabolism assessment showed a consistent upregulation of glucose uptake and oxidation rates. Moreover, both transcript and protein expression of PPARγ coactivator 1α (PGC-1α) were upregulated, followed with increased mtDNA copy number in CCPG knockdown C2C12 cells. The upregulation of Uncoupling Protein 1(UCP1) mRNA and proteins revealed that CCPG knockdown C2C12 cells were transdifferentiated into brown adipocytes.

Conclusions: CCPG deficiency impairs C2C12 myoblast differentiation but instead facilitates the transdifferentiation into brown adipocytes via upregulation of PGC-1α. Since thermogenic brown adipocytes have emerged as new targets for the treatment of obesity, the present finding may provide insights into new therapeutic targets for obesity and type 2 diabetes.

271-LB

Proinflammatory Role of PPARγ S273 Phosphorylation in Insulin Resistance

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Over-nutrition promotes adipose tissue (AT) inflammation and lipolysis, ultimately leading to steatosis, insulin resistance, and type 2 diabetes. The thiazolidinediones (TZDs) are a potent class of antidiabetic drugs that improve insulin sensitivity, but whose use is limited due to increased risk of severe side effects. Recently, we have shown that TZDs alter PPARγ function by a novel biochemical mechanism: reversal of an inhibitory phosphorylation on PPARγ at S273. However, it is unknown whether this modification is causally related to insulin resistance. Here we demonstrate that mice with a non-phosphorylatable allele of PPARγ at S273 (S273A knock- in; A/A) are protected from insulin resistance without the TZD-associated side effects. Indeed, hyperinsulinemic-euglycemic clamp experiments revealed improved insulin sensitivity as evidenced by increased whole-body glucose uptake and enhanced insulin-mediated suppression of plasma NEFA. Consistent with a link between AT lipolysis and inflammation during obesity, A/A mice on a high-fat diet also exhibited decreased AT macrophage numbers and reduced markers of inflammation. Given that PPARγ has diverse roles in both adipocyte and non-adipocyte cells, including macrophages, we sought to determine cell autonomous effects of PPARγ S273 phosphorylation. While generation of bone marrow chimeras using wild type recipient mice with an

A/A immune system failed to improve AT inflammation, A/A recipient mice showed decreased inflammation irrespective of donor genotype. Moreover, A/A ex vivo differentiated adipocytes exhibited a blunted inflammatory response to a pro-inflammatory stimulus, suggesting a dominant role for the adipocyte in the reduction of inflammation. Together, these results highlight the diabetogenic role of PPARγ S273 phosphorylation suggestive of a strong antiinflammatory role of PPARγ modulation. Selective inhibition of PPARγ phosphorylation may provide a powerful therapeutic avenue for treatment of metabolic disease.

INSULIN ACTION—CELLULAR AND MOLECULAR METABOLISM

272-LB

Glucokinase Is Rate Controlling for Insulin-Stimulated Liver Glycogen Synthesis in Both Normal and Insulin-Resistant Rats

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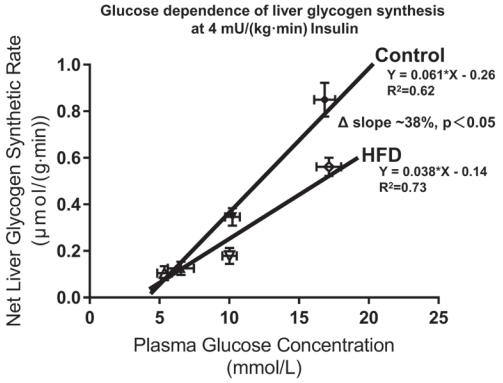
Insulin-stimulated hepatic glycogen synthesis is important for postprandial glucose homeostasis, and its disruption results in postprandial hyperglycemia. Multiple insulin-regulated enzymes participate in hepatic glycogen synthesis, and the rate-controlling step responsible for insulin control of glycogen synthetic flux under normal and insulin resistant conditions is unknown. To address this question we performed a series of pancreatic clamps with somatostatin and [U-^{13}C] glucose under several different plasma glucose and insulin concentrations in both control regular chow fed male SD rats and insulin resistant high fat diet fed (HFD) rats. Hepatic metabolites, and both direct and indirect glycogen synthetic fluxes, were assessed by LC-MS/MS. Neither hyperglycemia alone nor hyperinsulinemia alone promoted net hepatic glycogen synthesis in control or HFD rats. During hyperinsulinemia, hyperglycemia dose-dependently increased hepatic glycogen synthesis; HFD rats manifested a marked (-38.0%, $P<0.05$) reduction in hepatic glycogen synthetic rates vs. control. Metabolic control analysis yielded a control coefficient for glucokinase >1 in both groups.

Conclusion: Glucokinase is the rate controlling step for insulin-stimulated liver glycogen synthesis and it is a key therapeutic target in nonalcoholic fatty liver disease associated hepatic insulin resistance.

Figure.



273-LB

Characterization of Functional Sequence Motifs in Lipolytic Inhibitor G0/G1 Switch Gene 2

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G0/G1 switch gene-2 (G0S2) is a selective inhibitor of adipose triglyceride lipase (ATGL), the rate-limiting enzyme that catalyzes lipolysis of triacylglycerol (TG)-containing lipid droplets (LDs). G0S2, a 103-amin acid basic protein, contains a central hydrophobic domain (HD) important for binding and inhibiting ATGL. Sequence analysis revealed the G0S2 HD is flanked by a positively charged sequence (Pos-Seq) at the N-terminal end. Similar sequence arrangements were previously shown to be critical for targeting proteins to LDs. However, it remained to be determined whether LD localization and ATGL inhibition are mediated by different motifs within this sequence of G0S2. Here, by analyzing a series of internal deletion mutants, we identified residues 27-30 of G0S2 HD as critical for ATGL interaction and inhibition. While a G0S2 mutant lacking the entire HD failed to traffic to LDs, none of these small internal deletions disrupted LD localization. Moreover, simultaneous mutation of three positively charged residues (Arg-20, Lys-22 and Lys-25) in the Pos-Seq to neutrally charged Ala abolished ATGL-independent localization of G0S2 to LDs. Surprisingly, coexpression of this triple mutant (TA) of G0S2 with a mutant ATGL deficient in LD localization promoted translocation of both proteins to LDs. In an in vitro enzyme activity assay, the TA mutant displayed an ATGL inhibitory activity comparable to that of wild type G0S2. Previously we demonstrated the importance of G0S2 function in energy metabolism via its ability to enhance hepatic TG accumulation. Interestingly, when overexpressed in mouse primary hepatocytes, the G0S2 TA mutant was less efficient at allowing for TG accumulation compared to wild type protein. Collectively, these results highlight the importance of G0S2 structural domains in maintaining its LD localization, mediating ATGL inhibition and promoting intracellular TG deposition.

274-LB

Loss of Insulin Stimulated Cholesterol Synthesis in Astrocytes Causes Increased 7-Ketocholesterol and Circadian Rhythm Defects

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The brain requires insulin to regulate cholesterol synthesis. In insulin deficient diabetes there is a decrease in SREBP2 (sterol responsive element binding protein 2), the major transcription factor driving cholesterol synthesis, resulting in decreased brain cholesterol synthesis. In order to understand the consequences of decreased brain cholesterol synthesis we generated an SREBP2 knockout (KO) from astrocytes, the major cholesterol producing cells in the brain. The resulting mice showed microcephaly and impaired memory. Despite these changes, cholesterol content per mg of protein was not reduced, due to an increase in cholesterol synthesis by other cells in the brain. This resulted in alterations in the composition of cholesterol-derived steroids in the brain. Thus, steroid profiling from astrocyte SREBP2-KO mice and floxed controls demonstrated a 2.2-fold increase in 7-ketocholesterol in brain tissue with a smaller increase in serum. Interestingly, 7-ketocholesterol is also increased in the serum of patients with diabetes, where it acts as an inverse agonist of the nuclear receptor RORα, an important modulator of circadian rhythms. Indeed, the astrocyte-specific SREBP2 KO mice showed a lengthened circadian period when housed in constant darkness, consistent with inverse agonism of 7-ketocholesterol on RORα. This was also observed in vitro using the C6 rat glioma cell line stably expressing a luciferase-reporter driven by the BMAL1 promoter. When these cells were treated with 7-ketocholesterol they showed a similar lengthening of the circadian period. These data demonstrate how diabetes mediated changes in brain steroid composition could lead to altered circadian rhythms, further complicating metabolic control in diabetic patients.

Supported By: National Institutes of Health (K08DK097293-05)

INSULIN ACTION—GLUCOSE TRANSPORT AND INSULIN RESISTANCE IN VITRO

275-LB

WITHDRAWN

276-LB

Glial Growth Factor-2 Regulates Glucose Transport in Cardiac Myocytes via an Akt-Dependent Pathway

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Diabetes is a major risk factor for cardiovascular diseases, including heart failure. Increased glucose uptake has been reported to be cardio-protective, yet the pathways regulating glucose transport in the heart remain elusive. Neuregulin, a paracrine factor, promotes glucose transport in skeletal muscle via the ErbB receptors. We hypothesized that treatment with neuregulin-1β isoform, glial growth factor 2 (GGF2), will enhance glucose transport in the healthy and failing myocardium. Cardiac myocytes were isolated from healthy adult rats and age-matched rats with myocardial infarction (MI) (n=4-15/group). Glucose uptake was measured using a fluorescent D-glucose analog. The translocation of the glucose transporter (GLUT) 4 to the cell sur-

face, the rate-limiting step in glucose uptake, was measured using a photolabeled biotinylation assay. Similar to insulin, acute in vitro GGF2 treatment increased glucose uptake in healthy cardiac myocytes (by 40 and 49%, respectively, P=0.002). GGF2 also increased GLUT4 translocation in healthy myocytes by 138% (P<0.01), while ErbB 2/4 receptor blockade (by Afatinib) abolished these effects. In addition, GGF2 enhanced Akt phosphorylation (at both threonine and serine sites, by 75% and 139%, respectively, P=0.029 and P=0.01), which was blunted by ErbB 2/4 receptor blockade. GGF2 treatment increased the phosphorylation of AS160 (an Akt effector) by 72% (P<0.05), as well as the phosphorylation of PDK1 and PKC (by 206% and 100%, respectively, P<0.05). During MI, GLUT4 translocation was downregulated by 44% (P=0.004) and was partially rescued by both in vitro insulin and GGF2 treatment.

In conclusion, our data demonstrate that acute GGF2 treatment increased glucose transport in cardiac myocytes by activating the ErbB 2/4 receptors and key downstream effectors (i.e., PDK1, Akt, AS160 and PKC). These findings highlighted novel mechanisms of action of GGF2, which warrant further investigation in patients with diabetic cardiomyopathy.

Supported By: Acorda Therapeutics

INSULIN ACTION—SIGNAL TRANSDUCTION, INSULIN, AND OTHER HORMONES

277-LB

A Novel Pathway Essential for Canonical Leptin Signaling in Hypothalamic Neurons

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Obesity is a worldwide health problem, but we still do not understand the molecular mechanisms responsible for overeating. Leptin is made by adipose tissue and then acts in the hypothalamus to inhibit caloric intake. Importantly, obese people exhibit high circulating levels of leptin, yet the hypothalamus no longer responds to this hormone to suppress appetite. We previously reported a novel signaling pathway for insulin in liver and endothelium. This pathway, abbreviated "NSAPP" after its 5 major proteins, begins when insulin stimulates the NADPH oxidase-4 (NOX4) to generate $O_2^{\bullet -}$. After conversion of $O_2^{\bullet -}$ into H_2O_2 by superoxide dismutase-3 (SOD3), the pathway ends when aquaporins (AQPs) channel H_2O_2 to inactivate PTEN and protein tyrosine phosphatases. For the current study, we hypothesized that the NSAPP pathway is also required for leptin action in hypothalamic neurons.

Leptin-stimulated production of intracellular H_2O_2 in mouse hypothalamic cell lines GT1-7 and HypoA-POMC/GFP was monitored with a fluorogenic probe (CellROX). Knockdown was performed using shRNA lentiviruses.

We found that all proteins of the NSAPP pathway are present in rat hypothalamus. In murine hypothalamic cell lines, leptin induced a burst in intracellular CellROX staining that we definitively identified as H_2O_2 by its quenching by catalase. Inhibition of NOX4 with diphenyliodonium abolished the leptin-induced H_2O_2 burst and blocked leptin signaling to key tyrosine phosphorylation sites on JAK2 and STAT3. Strikingly, knockdown of SOD3 also blocked leptin signaling to JAK2 and STAT3.

Our results indicate that leptin activates the NSAPP pathway in hypothalamic neurons. Moreover, this novel pathway is essential for canonical leptin signaling to JAK2/STAT3, which regulate key neuropeptides that control appetite. Remarkably, insulin and leptin both require the NSAPP pathway, suggesting that a defect in this pathway could explain simultaneous resistance to the appetite-suppressing effects of both hormones.

278-LB

Autophagy Protects Cardiomyocytes against Palmitate-Induced Death

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Autophagy is an intracellular autodigestive process, by which a cell may maintain the integrity of its function and structure. This study sought to investigate the role of autophagy in protecting cardiomyocytes exposed to palmitate (Pal) to model lipotoxic cardiomyopathy.

Results: Incubation of H9c2 cells, an embryonic rat cardiomyocyte cell line, with 500 μM Pal, progressively and time-dependently increased autophagy as evidenced showed by increased LC3-II levels approximately to 3.5 fold at 6 h time point relative to vehicle-treated cells (P<0.05). The phosphorylation of mTOR at S2448 and its inhibitory phosphorylation of ULK1 at S777 were not altered in the presence of Pal. Additionally, the phosphorylation of AMPK at T172, an upstream activator of ULK1, was not changed by

Pal incubation. Pal incubation decreased Akt1 phosphorylation at S473 and T308, which was accompanied by increased Atg13 abundance in Akt1 immunoprecipitates from Pal-incubated H9c2 cells relative to vehicle-treated cardiomyocytes. Relative to scrambled siRNA-transfected cardiomyocytes, silencing Akt1 decreased basal levels of autophagy in the vehicle-treated cardiomyocytes (P<0.05) and markedly attenuated Pal-induced autophagy as evidenced by LC3-II levels (P<0.05). Pal incubation for 6 h did not induce cardiomyocyte death as measured by MTT. However, when either Akt1 or Atg5 was silenced to suppress autophagy initiation, Pal incubation progressively and time-dependently decreased cardiomyocyte survival approximately by ~40% at 6 h time point. Pal-induced cardiomyocyte death in the face of autophagy suppression was accompanied by an increase in apoptosis as evidenced by increased levels of cleaved Caspase 3 and cleaved PARP (P<0.05 relative to vehicle-treated cardiomyocytes).

Conclusion: Pal incubation dephosphorylates Akt1 and promotes its interaction with Atg13 to initiate autophagy, which promotes cardiomyocyte survival likely by inhibiting apoptosis.

INTEGRATED PHYSIOLOGY—CENTRAL NERVOUS SYSTEM REGULATION OF METABOLISM

279-LB

Histone Deacetylase-4 in Steroidogenic Factor-1 Neurons of the Ventromedial Nucleus of Hypothalamus Is Required for Normal Glucoregulation in Female Mice

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Studies suggest that histone modification is a key process to modulate chromatin condensation and subsequent gene repression and class IIa Histone deacetylases (HDACs) directly mediate the action of several key metabolic hormones including insulin, glucagon, and leptin. Glucose and energy homeostasis are largely governed by distinct types of hypothalamic neurons. However, whether and how individual member of class IIa HDACs in key hypothalamic neurons contribute to glucose metabolism and energy homeostasis is not understood. Here we found that female, but not male, mice lacking a class IIa HDAC, HDAC4, specifically from steroidogenic factor-1 (SF-1)-expressing neurons ($HDAC4^{SF1KO}$) of the ventromedial nucleus of hypothalamus displayed elevated blood glucose levels compared to their littermate controls ($HDAC4^{SF1KO}$; 104.4 ± 2.9 vs. control; 90.3 ± 3.2 mg/dl, P<0.01, t-test) under long-term high-fat challenge. Despite elevated glucose levels, however, $HDAC4^{SF1KO}$ mice showed comparable food intake, body weight, and glucose tolerance compared to their littermate controls. Consecutive monitoring of blood glucose levels at 4-hour interval over 24-hour period revealed that female, but not male, $HDAC4^{SF1KO}$ showed significantly high glucose level at the beginning of the dark cycle ($HDAC4^{SF1KO}$; 106 ± 9.4 vs. control; 93.6 ± 7.9 mg/dl) and maintained higher glucose levels throughout the day. In addition, co-immunoprecipitation in hypothalamic extracts demonstrates that HDAC4 directly binds to estrogen receptor alpha, a main mediator of estrogenic action on metabolic regulation.

Our results indicate that the gene repression in SF-1 neurons by HDAC4 may represent a novel mechanism for rhythmic regulation of glucose metabolism in female mice. Understanding the metabolic regulation by HDAC4 in this brain site should facilitate the identification of sexually dimorphic mechanisms relevant in the glucoregulation.

280-LB

Impaired Adaptive Thermogenesis in Mice Lacking Glycerol-3-Phosphate Acyltransferase-4

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Glycerol-3-Phosphate Acyltransferase 4 (GPAT4) catalyzes the first step of glycerolipid synthesis and is highly expressed in liver, white adipose (WAT) and brown adipose (BAT). Previously, mice with a constitutive knockout (KO) of GPAT4 were shown to maintain body temperature during acute cold exposure. In order to circumvent potential gene compensation associated with constitutive knockouts, we developed a line of Cre-ER/loxP inducible GPAT4KO mice. After tamoxifen-induced gene deletion, body temperature transmitters were implanted and mice housed at thermal neutral (27°C) for 14 days, followed by an acute cold (4°C) challenge. Surprisingly, GPAT4KO mice rapidly lost body temperature vs. tamoxifen-treated controls. After 60 min at 4°C, body temperature in KO animals had fallen by 7°C. To deter-

mine whether this impaired response was downstream of classical thermogenic pathways, we treated GPAT4KO mice with a β3-adrenergic agonist. Consistent with the impaired response to cold, β3-induced thermogenesis was significantly attenuated in GPAT4KO mice. Pronounced, tamoxifen-dependent reduction of GPAT4 expression was observed in liver and WAT, but not BAT. Histology of WAT and BAT from mice housed at 27°C revealed a dramatic reduction in lipid content associated with tamoxifen treatment. This tamoxifen-mediated lipid depletion has been previously reported, and we hypothesize that this reduction in lipid revealed the critical role of GPAT4 in fuel utilization for body temperature regulation. Our data support a model of acute adaptive thermogenesis in which much of the fuel required to maintain body temperature must pass through the glycerolipid synthesis pathway prior to its oxidation for thermogenesis.

281-LB

Expression of GLP-1 Receptors in Insulin-Containing Interneurons of the Cerebral Cortex

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Glucagon-like peptide-1 (GLP-1) receptors are expressed by pancreatic beta cells and promote insulin secretion. Our recent results showed that insulin is released by neurogliaform neurons in the cerebral cortex, but the expression of GLP-1 receptors on insulin producing neocortical neurons has not been tested. GLP-1 receptor agonists have neural effects and are therapeutically promising against mild cognitive impairment and Alzheimer's disease. We harvested the cytoplasm of electrophysiologically and anatomically identified neurogliaform interneurons during patch clamp recordings performed in slices of rat neocortex. Using microarrays, we compared the expression pattern of mRNAs in neurogliaform cells harvested in conditions corresponding to hypo- (0.5 mM) and hyperglycemia (10 mM) in the brain. Molecular pathway analysis revealed that these changes in extracellular glucose concentration had the most significant effect on the pathway known as "type 1 diabetes mellitus signaling." Validation of the expression of key genes of this pathway was successful by single cell rtPCR. In addition, single cell digital PCR revealed GLP-1 receptor expression in neurogliaform cells and showed that copy numbers of mRNAs of the GLP-1 gene in hyperglycemia exceeded that of hypoglycemic copy numbers by 4.9 times ($p < 0.014$). Immunocytochemistry confirmed these results showing colocalization of anti-GLP-1 receptor with anti-proinsulin labelling in neocortical interneurons and anti-GLP-1 receptor immunopositivity with markers of neurogliaform cells (NPY, nNOS). Our results provide evidence for GLP-1 receptor expression in neurons known to release insulin in the cerebral cortex. Hyperglycemia increases the expression of GLP-1 receptors in neurogliaform cells suggesting that endogenous incretins and therapeutic GLP-1 receptor agonists might have effects on these neurons similar to that of pancreatic beta cells.

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282-LB

Mice Lacking β-arrestin-1 in AgRP Neurons Show Impaired Glucose Metabolism

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Hunger and satiety are regulated, to a major extent, by the agouti related protein (AgRP)/neuropeptide Y (NPY) and proopiomelanocortin (POMC) neurons residing in the arcuate nucleus of the hypothalamus. During starvation, AgRP neurons are strongly activated to promote hunger. Peripheral hormones and nutrients regulate the function of AgRP neurons, thus ensuring proper glucose and energy homeostasis. Recent studies from various labs, including our group, have shown the importance of G-protein coupled receptors (GPCRs) in regulating the activity of AgRP neurons. GPCR function is modulated by a pair of proteins known as beta-arrestin-1 and -2 (barr1 and barr2, respectively), which can terminate GPCR signaling and/or mediate GPCR-independent signaling. It is well established that barr1 and barr2 are involved in various physiological functions. However, the potential roles of barr1 and barr2 in regulating the function of AgRP neurons remain unexplored. To address this issue, we generated mice that lack barr1 or barr2 selectively in AgRP neurons using Cre/loxP-flex-switch technology. Interestingly, AgRP-barr1-KO mice consuming a high fat diet showed impaired glucose tolerance and insulin sensitivity, while body weight remained unchanged. Moreover, plasma glucose and insulin levels were increased in AgRP-barr1-KO mice. Food intake was not affected by the lack of barr1 in AgRP neurons. In contrast, AgRP-barr2-KO mice showed no obvious metabolic phenotypes. More detailed studies into the mechanisms through which barr1 regulates the activity of AgRP neurons may lead to new strategies to alter the activity of AgRP neurons for therapeutic purposes.

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283-LB

Activation of Hypothalamic Cold-Sensitive Neuron Is Sufficient to Explain the Glucoregulatory Response to Cold Exposure

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Normal glucose homeostasis depends on the capacity of pancreatic β-cells to adjust insulin secretion in response to a change of tissue insulin sensitivity. In cold environments, for example, the dramatic increase of insulin sensitivity needed to meet thermogenic needs is offset by reduced insulin secretion, such that glucose tolerance remains unchanged. We recently reported that the coordinated metabolic responses to cold are blocked by systemic α-adrenergic blockade, suggesting that they are dependent on sympathetic nervous system (SNS) outflow. In the current work, we hypothesized that glucoregulatory responses to cold are mediated by activation of cold-sensitive neurons in the hypothalamic preoptic area (POA, the brain area responsible for transducing cold signals from peripheral thermoreceptors into SNS responses that increase thermogenesis). To test this hypothesis, we employed a frequently sampled intravenous glucose tolerance test to measure insulin secretion, insulin sensitivity and glucose tolerance during POA cooling achieved with a surgically implanted thermode. We found that after just 1 h of POA cooling, glucose tolerance was enhanced by 20% (glucose area under the curve (AUC): 12845±271 vs. 10320±168; P<.05), an effect associated with a trend towards increased insulin sensitivity with no change in the acute insulin response to glucose. By 8 h of POA cooling, however, the glucoregulatory response to cold was fully replicated. Specifically, the insulin sensitivity index was increased by more than 2-fold (S_I: 1.26±0.18 vs. 3.25±0.31 (ml/μU)/(1/min); P<.05), while insulin secretion declined by 43% (Ins AUC: 6614±400 vs. 3770±200; P<.05), such that glucose tolerance was preserved (Glc AUC: 12532±487 vs. 13078±639; P=0.53).

We conclude that activation of cold-sensitive POA neurons is sufficient to explain the effect of cold to increase insulin sensitivity while proportionately reducing insulin secretion to preserve glucose tolerance.

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284-LB

Adipocyte Fatty Acid Synthase Deletion in Adult Mice Enhances Adipose Sympathetic Activity and Browning to Improve Glucose Homeostasis in Obese Mice

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The de novo biosynthesis of fatty acids (DNL) culminating with the enzyme fatty acid synthase (FASN) is one of the most strongly suppressed metabolic pathways in adipose tissue (AT) during fasting and obesity, but its role in systemic glucose metabolism are incompletely understood. Here we investigated the function of DNL in mature white and brown adipocytes (Ad-FASNKO) or only in brown adipocytes (UCP1-FASNKO) by generating mice in which the tamoxifen-inducible Adiponectin-ER-Cre or the UCP1-ER-Cre drivers were used to delete adipocyte FASN. Tamoxifen administration to mature Ad-FASNKO mice induced strong white adipose tissue "browning" with up regulation of UCP-1 and many other thermogenic genes. Importantly, when brown adipocytes in Ad-FASNKO mice were first "whitened" by housing mice at thermo-neutrality (30 degrees C), tamoxifen administration to AdFASNKO mice also induced "browning" of these whitened brown adipocytes. However, this effect was not cell autonomous because tamoxifen failed to have this effect in the UCP1-FASNKO mice at thermo-neutrality and inhibition of DNL in primary white adipocytes in vitro also failed to enhance UCP1. Thus, FASN KO in white adipocytes appears to cause adipocyte browning in WAT and in whitened BAT through a non-cell autonomous mechanism, and an intact animal is required for these "browning" effects. Moreover, we suggest neuronal signaling from WAT mediates browning in response to inducible FASN KO since markedly increased tyrosine hydroxylase and neuropeptide Y content in WAT upon FASN knockout was observed. Accordingly, adipocyte FASN deletion activated beta-3-adrenoreceptor/PKA signaling in WAT and BAT. Moreover, inducible loss of FASN in WAT, but not depletion in BAT, improved glucose homeostasis in obese mice. Thus, fatty acid biosynthesis

in white adipocytes controls thermogenic programming in WAT and BAT and systemic metabolic homeostasis through neuronal regulation.

Supported By: National Institutes of Health

285-LB

WITHDRAWN

INTEGRATED PHYSIOLOGY—INSULIN SECRETION IN VIVO

286-LB

Body-Fat Distribution and Metabolic Correlates of Insulin Resistance in Lean Asians

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Background: Obesity-related insulin resistance (IR) is associated not only with ectopic fat deposition, but also hyperinsulinemia that helps maintain glucose tolerance, at least during the initial stages of development of type 2 diabetes. The phenotype of IR in nonobese people is not well known, particularly among Asians who develop diabetes at low BMI values.

Methodology: We compared the total body fat (DXA), visceral adipose tissue (MRI), intramyocellular and intrahepatic lipids (MRS), insulin sensitivity (4-hr euglycemic clamp), insulin secretion rate and glucose tolerance (3-hr mixed meal with mathematical modeling) of 11 lean (BMI <22.5 kg/m^2) Asian subjects with IR (M value per kg fat free mass (FFM) over steady state insulin=0.10±0.03) and 11 insulin-sensitive (IS) age- and sex-matched controls (M_{FFM}/I=0.26±0.04).

Results: Lean IR subjects had similar BMI but significantly greater percent body fat, visceral adipose tissue, intramyocellular and intrahepatic lipid content when compared with IS subjects (all p<0.05). Despite a ~60% difference in insulin sensitivity, fasting and 2-hr postprandial glucose concentrations and HbA1c did not differ significantly between groups. Fasting and postprandial (clamp and mixed meal) insulin concentrations were 2-3 times greater in IR than in IS subjects, because of 35-70% greater insulin secretion rates and ~35% lower insulin clearance rates (all p<0.05). The disposition index was 40% lower whereas glucose area under the curve was ~15% greater in IR than IS subjects (both p<0.05).

Conclusion: Insulin resistance in lean subjects is associated with increased fat deposition in the visceral area and key metabolic organs (liver and muscle). Increased secretion and decreased clearance of insulin contribute to fasting and postprandial hyperinsulinemia, which largely compensates for peripheral insulin resistance, helping to maintain normal fasting and long-term glycemic control, and preventing significant deterioration in glucose tolerance.

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287-LB

A Novel NDUFAF5 Mutation Associated with β-Cell Dysfunction

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Mitochondrial dysfunction contribute to β-cell failure in type 2 diabetes. The Cohen diabetic sensitive rat (CDs) is a unique model of mitochondrial respiratory chain, complex-IV deficiency. CDs develop hyperglycemia when fed a diabetogenic high-sucrose, low-copper diet (DD) due to a specific β-cell dysfunction and reduced islets complex-IV activity. Copper is crucial for the activity of complex-IV. NDUFAF5 gene encodes a mitochondrial complex I assembly factor. Mutations in this gene are associated with combined complex I and IV deficiency in Leigh-syndrome patients. To elucidate the genetic basis of β-cell dysfunction in diabetic-CDs, complex I and IV activity was measured in islets and fibroblasts. We found that insulin secretion measured in oral glucose tolerance test decreased with time on DD while blood glucose concentration increased. Decreasing glucose stimulated insulin secretion demonstrated a highly significant positive correlation with islets complex IV activity an inverse correlation with increasing blood glucose levels in progression to diabetes (R^2=0.984 and R^2=-0.915, P<0.0001 respectively). Complex I activity was reduced by 30% in CDs islets relative to control islets (P<0.01). Whole genome sequencing identified a novel homozygous missense variant p.P318L (c.C1002T) in the NDUFAF5 gene predicted to be highly pathogenic by in-silico tools. NDUFAF5 protein levels were reduced in CDs islets compared to control islets (P<0.01). Overexpression of wild type NDUFAF5 gene in CDs fibroblasts increased both complex I and complex IV activity (P<0.01). Our results demonstrate a tight correlation between impaired mitochondrial function and β-cell dysfunction in CDs, a model of mitochondrial disorder related diabetes. The novel NDUFAF5 coding variant p.P318L may underlie the CDs mitochondrial defect and genetic susceptibility to develop diabetes, implicating NDUFAF5 as a potential regulator of β-cell function.

Supported By: Cohen Foundation; D Cure Foundation

288-LB

Adapting to Insulin Resistance in Obesity: Role of Insulin Secretion and Clearance

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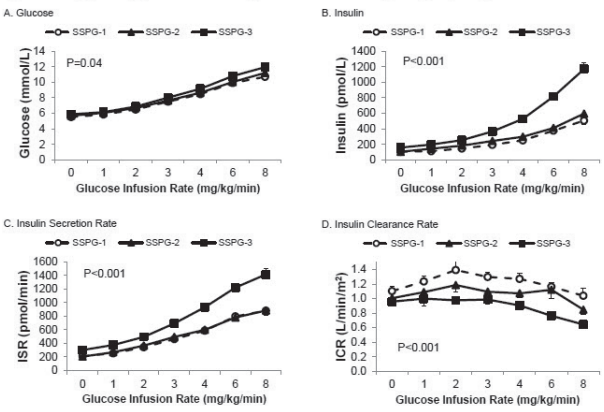
The current view of the pathogenesis of type 2 diabetes (DM2) is that DM2 develops when pancreatic beta cells fail to secrete sufficient insulin to keep up with demand in the context of obesity and/or insulin resistance (IR). While well accepted, this model ignores the role of insulin clearance rate (ICR) in maintaining hyperinsulinemia in IR states. We evaluated the physiologic adaptation to IR in 91 obese (BMI ≥ 30 kg/m^2) individuals without diabetes who had an OGTT and measurements of IR (steady-steady-state plasma glucose concentration, SSPG, during the insulin suppression test), and ISR and ICR (during the graded glucose infusion test). Participants were stratified into tertiles based on their SSPG concentration: SSPG-1 (insulin sensitive); SSPG-2 (intermediate); SSPG-3 (IR). Following oral glucose challenge, there was a progressive increase in total integrated insulin response from the most insulin sensitive to the most insulin resistant tertile (P<0.001). Following IV glucose, only SSPG-3 group had significantly greater integrated glucose and insulin response than SSPG-1 (P≤0.04, Figure). Furthermore, only SSPG-3 group had significant changes in both ISR and ICR (P<0.001). In the intermediate SSPG tertile (SSPG-2) only ICR was significantly decreased compared with SSPG-1. While both increase in ISR and decrease in ICR occur in IR, decrease in ICR may provide the first adaptation to decrease in insulin sensitivity.

Figure. Glucose (A), insulin (B), insulin secretion rate (C) and insulin clearance rate (D) during the graded glucose infusion test



Supported By: National Institutes of Health

INTEGRATED PHYSIOLOGY—LIVER

289-LB

Body-Weight-Lowering Agents and Their Comparative Metabolic and Hepatic Effects in Obese Mouse Models of Nonalcoholic Fatty Liver Disease and Steatohepatitis

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Aim: To compare the body weight lowering effects of the GLP-1 analogue liraglutide and the PPAR α/δ agonist, elafibranor, in diet-induced obese (DIO) and genetically obese mouse models of nonalcoholic steatohepatitis (NASH).

Methods: Male C57BL/6J (DIO-NASH) and Lep$^{ob/ob}$ (ob/ob-NASH) mice with biopsy-confirmed hepatosteatosis and fibrosis were stratified into treatment groups receiving vehicle (PO, QD), liraglutide (0.2 mg/kg, SC, BID) or elafibranor (30 mg/kg, PO, QD) for 8 weeks. At termination, blood and tissue samples were collected for plasma liver enzymes and lipids. Furthermore, a blinded histological evaluation of NAFLD Activity Score (NAS)

(steatosis, inflammation, ballooning degeneration) including Fibrosis Stage was performed.

Results: Liraglutide and elafibranor treatment induced a weight loss of approximately 10% in both DIO-NASH and ob/ob-NASH mice, albeit with differential effect on hepatomegaly, plasma liver enzymes and liver lipids. Based on histopathological analysis, liraglutide reduced composite NAS in DIO-NASH (7/10 animals), but not in ob/ob-NASH (2/10), mainly by reducing steatosis component. In contrast, Elafibranor induced resolution of NAS in both DIO-NASH and ob/ob-NASH (10/10) by improving all three dimensions (steatosis, inflammation and hepatocyte ballooning). Furthermore, only elafibranor reduced liver fibrosis stage in DIO-NASH (6/10) and ob/ob-NASH (10/10).

Conclusions: Pharmacological intervention with liraglutide and elafibranor induced a diverse metabolic and hepatic profile, irrespectively of similar weight-loss inducing effect in diet-induced and genetically obese mouse models of NASH. Notably, both treatments exerted an anti-steatotic action and improved liver histopathology by reducing NAS in DIO-NASH mice. In addition, elafibranor improved steatohepatitis in ob/ob-NASH mice and exerted anti-fibrotic effects in DIO-NASH and ob/ob-NASH mice.

290-LB

WITHDRAWN

291-LB

Spexin Alleviates Insulin Resistance and Inhibits Hepatic Gluconeogenesis via the FoxO1/PGC-1α Pathway in High-Fat Diet-Induced Rats and HepG2 Cells

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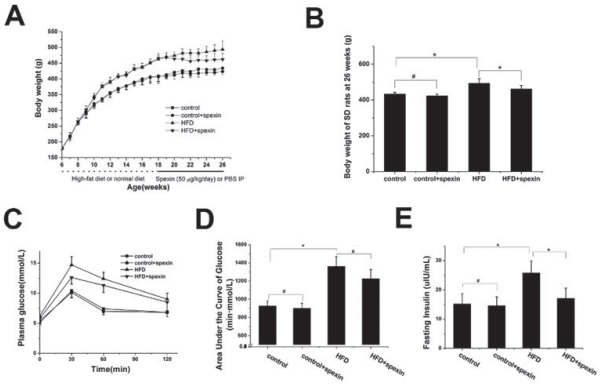
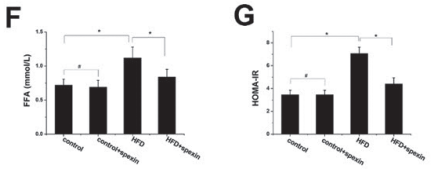
Recent studies demonstrated reduced circulating serum spexin levels in obesity or T2DM patients and may play a role in glucose and lipid metabolism. Indeed, our study showed serum spexin was significantly decreased in newly diagnosed T2DM patients and correlated with HOMA-IR. Consistently, exogenous spexin treatment resulted in weight loss, reduced HOMA-IR in high-fat-diet (HFD)-induced rats. The exogenous glucose infusion rates were higher in the HFD + spexin group than the HFD group. Steady-state hepatic glucose production was also suppressed by ~50% in the HFD + spexin group compared with that in the HFD group. Furthermore, spexin dose- and time-dependently inhibited gluconeogenesis in the insulin-resistant HepG2 cell model (HepG2-IR), and CRISPR/Cas9-mediated disruption of spexin in HepG2 cells activated gluconeogenesis. Moreover, we found that this regulation of spexin may involve the Forkhead box O1 (FoxO1)/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) pathway, both in HFD-induced rats and HepG2 cells. These results indicate that spexin plays an important role in improving insulin resistance in HFD-induced rats and HepG2-IR cells. Thus, preventing the effects of spexin on insulin resistance might hold therapeutic value for metabolic diseases.

Figures.





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292-LB

Dichotomous Effect of Hyaluronan on Glucose and Lipid Homeostasis

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Hyaluronic acid (HA), also known as hyaluronan, is one of the most reliable diagnostic serum biomarkers for nonalcoholic steatohepatitis (NASH). But whether it has a causal role in the pathogenesis of NASH or is simply a byproduct of the disease is unknown. Here we utilized tissue-specific and doxycycline-inducible systems to specific overexpress hyaluronan synthase 2 (Has2) in the liver and adipose tissue to investigate whether changes in HA homeostasis regulate glucose and lipid metabolism.

Overexpression of Has2 increases extracellular HA levels in Met1 cells, suggesting the translation of an enzymatically active protein from the transgene and the sufficiency of the HAS2 enzyme in driving HA production. In vivo hepatocyte-specific Has2 overexpression increased circulating HA levels by 4-6 folds, dependent on the expression levels of the transgene that were controlled by the doses of doxycycline supplemented in the diet. Hepatic Has2 overexpression improved glucose tolerance during high-fat diet (HFD) feeding, without affecting food intake or body weight. Interestingly, hepatic Has2 overexpression leads to significant HA accumulation in the adipose tissue. Adipose tissue Has2 overexpression increased serum HA levels by about 50% and also improved glucose tolerance with an elevated adipose tissue Glut4 expression, but adipose tissue Has2 overexpression impaired oral triglyceride clearance. Adipose tissue Has2 overexpression also enhanced the beta3 agonist CL 316,243's effect on glycerol release, suggesting an enhanced lipolysis after CL 316,243 treatment. Morphologically, lipid droplets in Has2-overexpressing white adipocytes have a multilocular appearance; however transcriptional profiling of Has2-overexpressing white adipose tissue showed a lack of changes in Ucp1 and other beiging genes.

In summary, hyaluronan improves systemic glucose homeostasis, but promotes lipolysis cell autonomously in adipose tissue, contributing to impaired whole-body lipid homeostasis.

293-LB

Hepatic ROCK1 Activation Is Required for the Regulation of Endocannabinoids-Dependent Lipogenesis

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Defects in hepatic lipogenic pathways are often found in pathological states such as obesity and type 2 diabetes, resulting in elevated de novo lipogenesis that could contribute to lipid accumulation and nonalcoholic fatty liver disease (NAFLD). Importantly, obesity-induced NAFLD is characterized by increased levels of the liver-derived endocannabinoids (CBs), anandamide (AEA) and 2-arachidonyl glycerol (2-AG) in animal models and obese humans, both of which are ligands of the CB1 receptor and stimulate CB1 signaling in the liver that accelerates de novo lipogenesis. Our previous study demonstrates that ROCK1 drives obesity-induced fatty liver by stimulating de novo lipogenesis. Thus, we sought to determine whether ROCK1 activation is required for endocannabinoids-CB1 dependent stimulation of hepatic lipogenesis. Treatment with AEA or 2-AG stimulated ROCK1 activity in the liver and HepG2 cells, indicating that ROCK1 is a downstream component of cannabinoid signaling. Concurrently, 2-AG-induced hepatic AMPK activity was greatly suppressed in control mice but unaltered in liver-specific ROCK1-deficient (L-ROCK1$^{-/-}$) mice. In line with these observations, we found that hepatic AMPK activity was increased by ROCK1 deficiency but decreased by ROCK1 activation, further suggesting a negative regulation of ROCK1 on AMPK. Administration of 2-AG led to a significant increase in lipogenic rate and gene expression of lipogenic enzymes in control mice. However, these effects were impaired in L-ROCK1$^{-/-}$ mice. Similar results were observed in isolated primary hepatocytes from L-ROCK1$^{-/-}$ mice. Thus, we establish a novel signaling pathway for cannabinoid-induced hepatic lipogenesis that is regulated through a ROCK1-dependent mechanism, negatively engaged to AMPK.

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294-LB

Analysis of the Role of AMPK in Metformin Action in Mouse Liver

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The type 2 diabetes drug Metformin inhibits gluconeogenesis in the liver to lower blood glucose levels. Metformin inhibits mitochondrial complex I, causing energetic stress and as a result activates the critical energy sensor AMP activated protein kinase (AMPK). Upon activation, AMPK attempts to restore energetic balance via promotion of energy generating processes and repression of energy utilizing processes in the cell. Although several studies have focused on understanding the role of AMPK in Metformin action, the overall molecular mechanism of Metformin's therapeutic effects remain poorly understood, and the relative contribution of AMPK to any particular output of Metformin action also is not well-delineated. In order to elucidate how Metformin is mediating its effects we analyzed Metformin's ability to regulate ATP levels, mTOR signaling, and transcriptional events in wild type and AMPK deleted primary hepatocytes. To further compare and contrast the role of AMPK in Metformin action, we utilized a small molecule allosteric activator of AMPK called 991. While Metformin activates AMPK through an indirect mechanism 991 directly binds to an AMPK subunit to activate the kinase complex.

Our results show that both Metformin and 991 activate AMPK and inhibits mTOR signaling in wild type primary hepatocytes. In the case of Metformin, but not 991, this is accompanied by a reduction in ATP levels. Metformin and 991 have no effect on mTOR inhibition in AMPK deleted primary hepatocytes except at later time points when Metformin suppress mTOR in an AMPK independent manner while 991 is still incapable of reducing mTOR signaling. Metformin and 991 give rise to different transcriptional profiles in wt and AMPK deleted primary hepatocytes. These results indicate that Metformin function through both AMPK dependent and independent pathways, which we will begin to examine in tissue-specific mouse knockout studies as well.

Supported By: National Institutes of Health (R01DK080425, P01-CA120964)

295-LB

Hepatic NFIL3 Is a Negative Regulator of Gluconeogenesis in Liver via Transcriptional Regulation

GEON KANG, HYE-SOOK HAN, SEUNG-HOI KOO, *Seoul, Republic of Korea*

Nuclear factor interleukin-3 regulated (NFIL3, also known as E4BP4) has been identified as an important factor in the immune system, in which it is critical in the development of NK cell and IgE class switching. However, the role of NFIL3 in energy metabolism has not been extensively studied. Here we show that hepatic NFIL3 represses gluconeogenesis in liver by regulating the expression of key gluconeogenic enzymes. The mRNA level of gluconeogenic enzymes was decreased by NFIL3 overexpression in mouse primary hepatocytes. Through luciferase assay, we also observed that NFIL3 suppress the transcription of gluconeogenic genes; this regulation is contingent on the cAMP response elements (CRE) of gluconeogenic gene promoter. Experiments performed with several mutants of NFIL3 revealed that the bZIP domain of NFIL3 is important for regulating the transcription of gluconeogenic genes. Furthermore, we unveiled that NFIL3 hinder the binding of CREB on CRE of gluconeogenic genes by binding on the same region itself. Surprisingly, the amount of NFIL3 protein is reduced in livers of both genetic and diet-induced obesity mouse models. Adenovirus mediated expression of NFIL3 showed decreased hepatic gluconeogenesis and improved glucose metabolism in diet-induced obesity (DIO) mice. We also found that overexpression of NFIL3 in ob/ob mice repress an abnormal increase of gluconeogenic gene expression and improve whole body glucose metabolism. On the other hand, knock-down of NFIL3 in mice caused the up-regulation of hepatic gluconeogenesis. Therefore, these results suggest that hepatic NFIL3 has a role in energy metabolism and acts as a negative regulator of gluconeogenesis in liver by repressing expression of key gluconeogenic enzymes.

296-LB

The Role of PRMT1 in the Regulation of Hepatic FGF-21 Regulation

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The fibrosis growth factor-21 (FGF-21) is a hepatokine, which plays an important role in the browning of subcutaneous white adipose tissue (sWAT) in response to cold or adrenergic stimulation. Recent studies have shown that hepatic FGF-21 is induced under metabolic stress caused by starvation, steatosis, and obesity. Here, we provide the evidence that protein arginine methyltransferase 1 (PRMT1), a major arginine methyltransferase in mammals, controls hepatic FGF-21 as a stress responsive hepatokine. To understand the physiological and pathophysiological roles of PRMT1 in liver, we generated the liver-specific PRMT1 knockout (PR1-LKO) mice by crossing PRMT1 floxed mice with Alb-cre mice. Depletion of the hepatic PRMT1 induced fat accumulation and macrophagy infiltration into the liver. Interestingly, because these metabolic stress strongly induced hepatic and serum FGF-21, PR1-LKO mice was protected against high-fat diet-induced metabolic disorders, such as body weight gain, fat accumulation of adipose tissues, and insulin resistance. Actually, an increased hepatic FGF-21 in the high-fat fed PR1-LKO mice contributed to the increased energy expenditure via inducing uncoupling protein 1 (UCP1) in the brown adipose tissue (BAT) and sWAT without cold stimulation. We observed the similar results in diabetic ob/ob mice with liver-specific depletion of PRMT1. Overall, these data suggest a critical role for PRMT1 in the regulation of hepatic FGF-21 under the metabolic stress.

297-LB

Simultaneous Modeling of Glucose and Glycerol Rates of Appearance in Youth With and Without Type 1 Diabetes

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Hepatic and peripheral insulin resistance (IR) contribute to hyperglycemia in type 1 diabetes (T1D). Interactions between glucose and lipid metabolism are complex, and adipose IR is increasingly recognized in T1D. Thus, simultaneous measurements of lipid and glucose metabolism from multiphase hyperinsulinemic euglycemic clamps with isotopic tracers may provide unique insights into alterations of metabolism in T1D, but have not been combined in a single statistical model. We have described methods for analyzing data from clamps in participants requiring overnight insulin, which complicates measures of basal glucose and glycerol rate of appearance (Ra) and prevents use of measures such as percent suppression. We applied those methods to 4 phase clamps (basal, 10, 16 and 80 mU/m^2/min) in 57 participants, 35 with T1D and 22 without diabetes. The groups were similar in age [median (25th percentile, 75th percentile) 16 yrs (14, 17) T1D; 14 (12, 17) control] and BMI percentile [82 (55, 96) T1D; 72 (51, 97) control], but not HbA1c [8.3% (7.3, 9.4) T1D, 5.4% (5.2, 5.5) control]. In youth without T1D, 10 mU/m^2/min suppressed glycerol Ra, and 16 mU/m^2/min suppressed glucose Ra. In separate models, glucose Ra was 1.09 mg/kg/min higher at 16 mU/m^2/min (p=0.0008), and glycerol Ra was 2.42 mmol/kg/min higher at 10 mU/m^2/min (p=0.0005) in T1D, confirming that youth with T1D have hepatic and adipose IR. We then used a doubly repeated measures model, with measures over tissue (adipose, hepatic) and phase, controlling for serum insulin concentration and T1D status, to simultaneously model glucose and glycerol Ra and examine relationships between hepatic and adipose IR. The interaction of tissue, T1D, and phase was significant (p=0.0063), indicating different trajectories of glycerol and glucose Ra in T1D compared to controls. These models are useful in describing interactions of tissue-specific IR in patients without diabetes, as well as those with diabetes who require overnight insulin and have no clear basal phase.

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298-LB

SGLT2 Inhibitor Canagliflozin Triggers Hepatic Transcriptional Reprogramming and Impacts Systemic Metabolism in Mice with Diet-Induced Obesity

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To determine the impact of SGLT2 inhibition and reduction in plasma glucose on transcriptional and metabolic responses, we fed normoglycemic C57BL/6J mice a 60% HFD for 4 weeks prior to assignment to one of 3 groups (n=12/group): (1) HFD ad libitum (HFD), (2) HFD ad libitum with canagliflozin (CANA, 30mg/kg/day), and (3) HFD weight-matched to CANA-treated mice via caloric restriction (CR). Fasting plasma glucose was reduced by 68 mg/dl (p<0.001) and body weight reduced by 5 g (p<0.001) in CANA vs. HFD. Fat mass was reduced in CANA vs. HFD (Δ-2 g by DEXA, p=0.03). Mice were sacrificed after an overnight fast after 4 weeks. Severe hepatic steatosis was reduced in CANA vs. HFD (Grade 3, >66% of parenchyma, X^2 p=0.056) but no change in triglyceride content (4.3 ± 1.7 vs. 3.7 ± 1.2 mg/g tissue, p=0.85).

To evaluate transcriptional responses to resolution of glucotoxicity, RNA was extracted from liver and processed for microarray analysis (Mouse Gene 2.0 ST). 2048 genes were differentially expressed between CANA and HFD (p<0.05). Pathway analysis revealed downregulation of de novo lipogenesis, glycolysis and steroid biosynthesis, and upregulation of TCA cycle and electron transport chain (p<0.05). Parallel targeted metabolite profiling (LC/MS) revealed significant changes in 31 metabolites and 59 lipid species (p<0.05). Among these, deoxycholic acid, C3 malonyl-canitine, malonic acid, and the

ketones acetoacetate and β-hydroxybutyrate were significantly higher in CANA. Moreover there were significant increases in polyunsaturated fatty acids within triglyceride fractions.

Collectively, these data indicate that SGLT2 inhibition and sustained reduction in plasma glucose trigger altered hepatic transcriptional programs, inducing not only ketogenesis and oxidative catabolism but also reduced de novo lipogenesis, potentially via reduced activation of key lipid and carbohydrate regulatory transcription factors SREBP2 and ChREBP.

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299-LB

Inhibition of the Estrogen-Related Receptor Alpha Blocks Liver Steatosis and Tumorigenesis Induced by Pten Loss

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Mitochondrial dysfunction has been attributed to be a major cause for fatty liver development and also underlies tumor development. Using a liver-conditional Pten deletion model where the activation of its downstream PI3K/AKT signaling led to fatty liver, steatohepatitis, fibrosis and finally liver cancer development, we reported previously that the fatty liver and liver cancer is accompanied by elevated mitochondrial bioenergetics and a dramatic induction of estrogen-related receptor α (ERRα), a master regulator that orchestrate mitochondria response to modulate metabolism. In this project, we intended to investigate whether blocking ERRα expression and inhibiting mitochondrial respiration can attenuate tumor growth and lipid accumulation in the Pten null livers and human liver cancer cells. Using a genetic knockdown approach with siERRα and chemical genomic approach with a small molecular polyamide compound that binds to the ERRα consensus binding site, we showed that ERRα knockdown suppressed mitochondrial function and impeded cell proliferation in human liver as well as prostate cancer cell lines lacking Pten. In addition, blocking ERRα transcriptional activity with ERRα specific polyamide err-PA significantly reduced tumor growth in xenograft models. Furthermore, err-PA administration in vivo in 1.5-month old liver-specific Pten null mice remarkably prevented the development of fatty liver morphology and quantitatively reduced the hepatic triglyceride level.

In summary, our study highlights ERRα's crucial role in regulating mitochondrial bioenergetics and underscores its therapeutic potential in cancer and lipid disorders.

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300-LB

Glucagon-Receptor Signaling Regulates Hepatic Leptin Receptor Expression

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Glucagon is an essential regulator of glucose and lipid metabolism that also promotes weight loss. Investigation of downstream GcgR targets elucidated potent and previously unknown regulation of liver leptin receptor (LepR) expression. Previous reports of LepR regulation are limited to its ligand, leptin, and food deprivation. Intriguingly, we found GcgR agonism induces hepatic LepR expression in vivo and in vitro. Chronic administration of a selective GcgR agonist (IUB288) in diet-induced obese male mice significantly increased both total hepatic LepR mRNA expression and the signaling isoform, LepR-b. This effect is ablated in $GcgR^{\Delta Liver}$ mice, suggesting hepatic GcgR signaling is necessary for this increase. To examine whether this effect was influenced by IUB288-stimulated fat mass loss, we evaluated LepR mRNA following an acute single-dose treatment in chow-fed mice. LepR expression was induced 3 hours post treatment with a return to baseline at 24 hours. To explore potential sex differences, we treated female mice with IUB288 and observed a similar increase in LepR and LepR-b mRNA expression, reinforcing GcgR agonism as the regulator of LepR expression. Moreover, total LepR and LepR-b mRNA increased in IUB288-treated primary hepatocytes in a time-dependent manner, suggesting cell autonomous regulation. Consistent with these results, phosphorylation of Stat3 was increased in IUB288-treated hepatocytes, indicative of enhanced LepR signaling. Taken together, these data reveal that GcgR agonism induces hepatic LepR expression independent of diet, sex, or negative energy balance. While the functional role of hepatic LepR has not been well characterized, $LepR^{\Delta Liver}$ mice have increased hepatic lipid deposits, an effect also observed in $GcgR^{\Delta Liver}$ mice, suggesting a link between hepatic GcgR signaling and LepR in regulation of hepatic lipid content. This aspect of glucagon biology has implications for the use of GcgR agonism in therapeutic strategies for nonalcoholic fatty liver disease.

301-LB

Hepatic Insulin Resistance Causing Metabolic Dysfunctions in Brown Adipose Tissue and Skeletal Muscle

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LDKO (hepatic Irs1/Irs2 double knockout) mice develop glucose intolerance, hyperinsulinemia and other features of diabetes. However, the metabolic phenotype in these mice might also involve peripheral resistance. The liver releases different hormonal factors (hepatokines) into the circulation, which can affect other tissues to dysregulated nutrient homeostasis. The liver is the major source for FGF-21 (fibroblast growth factor-21). Circulating FGF-21 decreased significantly in LDKO-mice compared against control mice. FGF-21 plays an important role in the development of BAT (brown adipose tissue). The BAT in LDKO-mice was less brown and enlarged, and displayed less glucose uptake during a [^{14}C]2-DOG glucose uptake assay under both basal and insulin-stimulated conditions. Various muscle subtypes also displayed less glucose uptake in LDKO-mice, which contributed to the diabetes. Injection of $AdV^{FGF\text{-}21}$ (adenovirus encoding FGF-21) to increase hepatic FGF-21-expression improved insulin and glucose tolerance in LDKO-mice, and improved glucose uptake into BAT. Consistent with this result, FGF-21 injections restored glucose uptake into muscle of LDKO-mice. During HFD (high fat diet) feeding for 2 weeks LDKO-mice displayed severe hyperglycemia (300-500 mg/dl); however FGF-21 injections lowered the glucose to the concentrations measured in HFD control mice. The deletion of hepatic Irs1 and Irs2 by infection with $AAV^{TBG\lozenge Cre}$ (adeno-associated virus encoding hepatocyte-specific Cre) of 8 week old $Irs1^{L/L}Irs2^{L/L}$-mice avoided low FGF-21 levels during BAT development. These mice displayed normal BAT tissues, and glucose tolerance was slightly improved compared with LDKO-mice. Circulating FGF-21 contributed to dysregulated glucose metabolism in LDKO-mice. Thus, dysfunctional BAT and skeletal muscle are linked to an insulin resistant liver via dysregulated FGF-21, and in combination with uncontrolled gluconeogenesis promotes the severe diabetic phenotype in LDKO-mice.

302-LB

Hepatic Iron Regulation in Two Models of Insulin Resistance

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Recent work has linked elevated tissue iron levels to insulin resistance and type 2 diabetes. Poorly chaperoned iron is a catalyst for producing reactive oxygen species, and excess iron may exacerbate insulin resistance. Different models of iron restriction have demonstrated improved insulin sensitivity; however, it is unknown if insulin sensitivity influences iron metabolism. The purpose of this study is to evaluate iron regulation using two different animal models of insulin resistance. In one model, rats were fed either normal chow or a high fat diet. Rats fed a high fat diet exhibited a 23±18% (p=0.043) increase in total hepatic iron, but did not exhibit changes in hepatic labile iron. High fat diet increased ferritin heavy chain expression by over 2-fold (p=0.02) and ferritin light chain expression by 80±15% (p=0.008), and decreased transferrin receptor by 52±15% (p=0.048). In the second animal model, Zucker Diabetic Fatty rats were compared against lean controls. A group of ZDF rats were also supplemented with the insulin sensitizer Rosiglitazone for six weeks. ZDF rats exhibited a 37±7% (p=0.009) increase in total hepatic iron, and a 36±7% (p=0.04) increase in hepatic labile iron. Rats treated with Rosiglitazone prevented increases in total and labile iron and reduced hydroxyl radical potential by 27.5±4% (p=0.004) compared to ZDF. Sample treatment with the iron chelator Deferoxamine confirmed that the capacity for hydroxyl radical formation was attributable to iron availability. ZDF rats showed decreased expression of ferritin heavy chain by 50±10% (p=0.006) and decreased ferritin light chain by 26±4% (p=0.003). Rosiglitazone treatment prevented decreased expression of ferritin heavy chain while increasing expression of transferrin receptor by 2-fold (p=0.043). Our findings demonstrate changes in iron regulation in two models of insulin resistance, and that Rosiglitazone treatment improves the management of intracellular iron, reducing a source of oxidative stress.

INTEGRATED PHYSIOLOGY—MACRONUTRIENT METABOLISM AND FOOD INTAKE

303-LB

Metabolic Changes after Overfeeding Differ According to Macronutrient Content

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Background: In obese rats, a high-fat diet (HFD) supplemented with branched-chain amino acids (BCAA) induces insulin resistance compared to HFD alone, despite lower weight gain. Using controlled feeding protocol, we studied the metabolic effects of a short-term overfeeding HFD with and without BCAA supplementation and high-carbohydrate (HCD) diet in overweight/obese males.

Methods: This was a randomized controlled study of 75 normoglycemic males (mean age 27.5±5.6 yrs and BMI 26.1±1.9 kg/m2). We provided 20% above total daily calorie and added 0.1g/kg/day BCAA in caplets to HFD with BCAA group. Insulin sensitivity (ISI) was measured by hyperinsulinemic euglycemic clamp. Phosphorylated IRS, AKT and mTOR, and key gene expression for metabolic enzymes were measured from human primary myoblasts. Tandem mass spectrometry profiled plasma amino acids, acylcarnitines (AC) and ceramides.

Results: Body weight and BMI increased significantly on all diets. HOMA-IR increased on all diets, with the greatest increase on HFD. ISI decreased on all diets, with the greatest decrease on HCD. Fasting protein levels for pIRS1ser307, pAKTser473 and p-mTOR did not change significantly on all diets. Fasting gene expressions for fatty acid oxidation, BCAT2, hexokinase and citrate synthase were upregulated, being more marked on HCD. PDK4 was upregulated on HCD but downregulated on HFD. Fasting alanine and glycine decreased, and proline increased significantly on HCD. Fasting BCAA levels did not change on all diets. Fasting C3-C5 AC was significantly higher on HFD and HCD. Fasting plasma C2, medium- and long-chain AC, total ceramide and sphingomyelin levels were higher on HCD but not on HFD.

Discussion: Two-week overfeeding induces weight gain and worsens ISI. Metabolic responses show differential adaptation to the macronutrient composition; increased fat storage on HFD, and enhanced fatty acid oxidation on HCD. Higher ceramide content and mitochondrial overload might explain the greater decline in ISI after HCD.

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304-LB

Novel Roles of HER3/ErbB3 in Adipocyte Metabolism

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Adipose tissue is a key regulator of systemic metabolism an insulin sensitivity. "Healthy" expansion of adipose through adipogenesis rather than hyperplasia, and expansion of subcutaneous rather than visceral depots correlate with preserved glucose tolerance and insulin sensitivity. Additionally, thermogenic beige and brown adipocytes are capable of increasing energy expenditure and preserve metabolic function in the context of high fat diet exposure.

Here, we report that an unexpected factor, the EGFR family member HER3/ErbB3, is capable of promoting healthy adipose depots and preserve systemic metabolism. Utilizing an inducible transgenic mouse model, we describe a protective role for HER3: overexpression of the protein leads to a surprising increase in subcutaneous adipose adipogenesis and a concomitant upregulation of the master adipogenic factor, PPARγ. In a lean mouse, this pro-adipogenic response leads to an increased number of beige adipocytes within the subcutaneous depot, and subsequent improvements in thermogenesis. In an obese mouse, increased adipogenesis stimulated by adipocyte-specific expression of HER3 blunts diet-induced glucose intolerance. Preliminary data suggests HER3 is able to effect these changes through upregulation of the outer mitochondrial membrane protein, mitoNEET specifically in the subcutaneous adipose of these mice. These observations reveal an exciting, thus uncharacterized role for HER3 and EGFR-family receptors in metabolism, and reveal the potent antidiabetic actions of beige adipose tissue.

INTEGRATED PHYSIOLOGY—MUSCLE

305-LB

Reduced Circulating Levels of Soluble Receptor for Advanced Glycation End Products and Low Muscle Mass

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Context: Accumulation of advanced glycation end products (AGEs) in skeletal muscle is associated with aging, both in diabetic and nondiabetic subjects. Soluble receptor for AGEs (sRAGE) might exert a protective role against development of sarcopenia by neutralizing the action of AGEs.

Objectives: We investigated the associations between circulating levels of sRAGE and low muscle mass in nondiabetic Korean subjects.

Methods: This cross-sectional study included 390 subjects recruited within the framework of the Korean Sarcopenic Obesity Study, an ongoing prospective cohort study. Low muscle mass was defined as below the sex-specific lower 20% of the distribution of appendicular skeletal muscle mass (ASM) divided body mass index (BMI) (ASM_{BMI}), as proposed by the Foundation for the National Institutes of Health Biomarkers Consortium Sarcopenia Project in the study population.

Results: The ASM_{BMI} was significantly and positively associated with sRAGE in both men and women. After correction for other confounding parameters, low circulating levels of sRAGE was an independent risk for the presence of low muscle mass in the study population (P=0.001) as well as HOMA-IR (P=0.005). Furthermore, sRAGE levels were an independent determinant of ASM_{BMI} (P=0.002) in addition to HDL-cholesterol, regular exercise, HOMA-IR, and systolic blood pressure.

Conclusions: The present study suggests that decreased circulating levels of sRAGE was an independent risk factor for low muscle mass in Korean men and women without diabetes. This result may provide a novel insight into the mechanism linking between sarcopenia and AGEs/RAGE system.

306-LB

Role of HDAC11 in Myogenic Differentiation

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Abnormal differentiation of muscle is closely associated with aging (sarcopenia) and diseases including cancer and type 2 diabetes. Thus, understanding the mechanism that regulates muscle differentiation is useful in treating and preventing these conditions. Protein lysine acetylation and methylation are major post-translational modification mechanisms that regulate key cellular processes. To elucidate the relationship between myogenic differentiation and protein lysine acetylation/methylation, we performed a PCR array of enzymes related to protein lysine acetylation/methylation during myoblast differentiation of C2C12 cells. HDAC11 was found as a factor with a greatly increased expression pattern during myoblast differentiation. Ectopic expression of HDAC11 completely inhibited myoblast differentiation, concomitant with reduced expression of key myogenic transcription factors. However, its catalytically inactive mutant (H142/143A) did not impede myoblast differentiation. Furthermore, wild type HDAC11, but not the inactive HDAC11 mutant, suppressed the MyoD-induced promoter activities of MEF2C and MYOG (Myogenin), indicating that HDAC11 could suppress myoblast differentiation via its enzymatic activity. These data demonstrate HDAC11 as a novel critical target for controlling the myoblast differentiation.

307-LB

Effects of Meal Ingestion on Intramyocellular Ceramide Concentrations and Fractional De Novo Synthesis in Humans

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We investigated the effects of meal ingestion on intramyofibrillar (IMF) and subsarcolemmal (SS) ceramide metabolism in lean and obese volunteers. Thirty-eight women and men underwent a steady-state meal ingestion protocol that included a 6.5 h infusion of [U-^{13}C] palmitate and muscle biopsies 1.5 h and 6.5 h after starting the tracer infusion. We measured IMF and SS sphingolipid concentrations and the contribution of plasma palmitate to intramyocellular C16:0 ceramide using LC\MS\MS. In response to meal ingestion SS C24 ceramide concentrations increased significantly, whereas C14-C20 concentrations tended to decrease or did not change. IMF ceramide concentrations did not change. The increases in SS C24 ceramides were negatively related to parameters of insulin resistance. The fractional contribution of plasma palmitate to intramyocellular C 16:0 ceramides in both IMF and SS fractions was inversely related to overweight status (β=-0.447, p=0.0071 and β=-0.467, p=0.0036, respectively). These data indicate that meal ingestion has differing effects on SS ceramide subspecies and sug-

gest that the fractional, de novo synthesis of intramyocellular ceramide from plasma palmitate in the postprandial condition is reduced in those who are overweight.

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308-LB

Skeletal Muscle O-GlcNAc Transferase Regulates Muscle Energy Homeostasis and Whole-Body Insulin Sensitivity

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Skeletal muscle tissue is metabolically demanding and must instantaneously integrate inputs from a variety of cues to ensure proper function. Because cellular protein O-GlcNAcylation level is a real-time measure of cellular nutrient status, we evaluated the role of O-GlcNAcylation in skeletal muscle. Muscle-specific knockout of O-GlcNAc transferase (OGT), the enzyme that mediates O-GlcNAcylation, resulted in decreased adiposity. As a result, skeletal muscle-specific OGT null mice (mKO) are lean. Chromatin immunoprecipitation analyses showed that OGT controls epigenetic-mediated production of muscle IL-15 (mRNA upregulated 5 fold $p<0.001$ and plasma levels 3 fold $p<0.001$ in mKO), which enters the circulation and results in a reduction in adipose tissue 50% ($p<0.01$) and adipocyte size 60% ($p<0.001$). We show that extracts from mKO muscle inhibits SVF cell adipogenesis as evidenced by reduced lipid droplet formation compared with muscle extracts from WT mice. However, this inhibition is released when an IL-15-neutralizing antibody is introduced into the media. In hyperinsulinimic-euglycemic clamp experiments glucose infusion rates were increased 1.5-fold ($p<0.001$) in mKO indicating improved whole body insulin sensitivity. Moreover, glucose uptake was increased two fold in both muscle ($p<0.01$) and white adipose tissue ($p<0.05$). A metabolomics analysis of the gastrocnemius muscle from the clamped mice showed that lack of OGT induces a change in fuel utilization in response to insulin. mKO mice display decreased levels of glycolytic metabolites fructose-1,6 bisphosphate (50% $p<0.01$) and PEP (70% $p<0.01$). Collectively, our data suggest that OGT is an important energy sensor in skeletal muscle, and our working hypothesis is that OGT controls IL-15 expression that in turn signals to adipose tissue to provide fuel in response to energy stress.

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309-LB

The Roles of PRMT1 in Skeletal Muscle Homeostasis

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Protein arginine methyltransferase 1 (PRMT1) is a principal enzyme that methylates arginine residues of histone and non-histone proteins, and have important roles in cancer and energy metabolism. Muscle phenotypes such as mass, fiber size are influenced by balance between the muscle growth and its wasting, and their abnormal changes are associated with a metabolic dysfunction. Here, we utilized muscle specific PRMT1 knockout mice (PRMT1 MKO) to understand the functions of PRMT1 in muscle metabolism. PRMT1 MKO mice showed myopathy phenotypes including a reduction of fiber size and muscle mass, and an increase in centralized nuclei and muscle fatigue. In addition, deficiency of PRMT1 in skeletal muscle caused fiber type switch, alteration of metabolic properties and reduction of whole-body energy expenditure. Interestingly, we found that Forkhead box O (FoxO) transcription factors and their atrophy related target genes were up-regulated in both chronic deletion and acute knockdown of PRMT1 in muscle cells. Our data show that PRMT1 may contribute to suppression of atrophy related signal and maintain normal metabolic conditions in the skeletal muscle.

310-LB

Unique Role of the p110α Isoform of PI 3-Kinase in the Regulation of Mitochondrial Homeostasis and Muscle Metabolomics

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The class I_A phosphatidylinsositol 3-kinases (PI3Ks) mediate many metabolic and the growth-promoting actions of insulin and IGF-1. To determine the precise role of the p110α catalytic subunit of PI3K in skeletal muscle, we created mice in which p110α was specifically deleted in muscle by Cre-lox recombination. By 3 months of age, M-p110αKO mice displayed elevated mitochondrial mass as evidenced by an 83% increase in average mitochondrial size in EDL muscle on electron microscopy and a 1.5-fold increase in mitochondrial volume per fiber area measured by intravital imaging in quad muscles transfected with Mito-GFP, as well as 30-60% increases in expression of citrate synthase and mitochondrial complexes I to V proteins in gastrocnemius muscle. This was accompanied by 60-96% increases in CO2 production and oxygen consumption rate in isolated mitochondrial of M-p110αKO mice, suggesting increased capacities of TCA cycle and electron transport chain in these mice. Metabolomic analysis of gastrocnemius and TA muscles from M-p110αKO mice by gas chromatography/mass spectrometry (GC-MS) revealed 18-55% increases in TCA cycle metabolites and 10-44% decreases in glycolytic metabolites (glucose, glucose-6-P and ribose-5-P), suggesting higher TCA activity and a shift of muscle metabolism towards higher fatty acid oxidation. A similar pattern was also observed in oxidative muscles (soleus) of M-p110αKO mice with 51-90% decreases in glycolytic metabolites, and increased fatty acid oxidation, as evidenced by lower levels of medium and long chain acyl-carnitines, but a 2-fold increase in short chain (C4) acyl-carnitine. Together these data show that loss of the p110α regulatory subunit of PI3K elevates mitochondrial biogenesis and increases mitochondrial respiration in skeletal muscle, indicating that in addition to its classical function in insulin/IGF-1 signaling, p110α plays a novel role in the regulation of mitochondrial homeostasis in skeletal muscle.

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311-LB

Cysteine and Glycine-Rich Protein 3 Regulates Glucose Homeostasis in Skeletal Muscle

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Obesity-induced chronic inflammation is a key component in the pathogenesis of insulin resistance. Skeletal muscle is the major site of postprandial glucose uptake and is dysregulated in insulin resistant states, such as in type 2 diabetes where insulin-stimulated glucose disposal is markedly impaired. In this study we used RNA-seq to discover differentially expressed genes between lean and obese/diabetic muscle that were also conserved across species in both mouse and human samples. We found that expression of cysteine and glycine-rich protein 3 (Csrp3) was reduced in both mouse and human muscle from obese/diabetic samples compared with control, lean muscle. We hypothesized that Csrp3 contributes to muscle insulin sensitivity and that Csrp3 deletion may impair glucose homeostasis. To this end, we used Csrp3 whole body knockout mice (CSRP3-KO) to examine glucose homeostasis in normal chow-fed lean and high fat-fed obese mice. Although there is no difference in glucose tolerance between genotypes under normal lean conditions, diet-induced obese CSRP3-KO mice have higher glucose intolerance and increased insulin resistance compared to wild type. This phenotype in CSRP3-KO mice is attributable to impaired insulin sensitivity as measured by euglycemic-hyperinsulinemic clamps. Additionally, CSRP3-KO mice displayed higher expression of the inflammatory markers F4/80 and cd11c. We further examined the contribution of Csrp3 to glucose regulation under inducible conditions, such as in fasting and exercise. An impairment in glucose tolerance was observed in normal chow-fed CSRP3-KO mice under 24h fasting and 1h acute exercise. These studies suggest that Csrp3 plays a role in the development of obesity-induced insulin resistance.

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INTEGRATED PHYSIOLOGY—OTHER HORMONES

312-LB

Control of Thermogenic Adipocyte Differentiation by the Conserved Long Noncoding RNA Blnc1

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Brown and beige adipocytes convert chemical energy into heat through uncoupled respiration to defend against cold stress. Beyond thermogenesis, brown and beige fats engage other metabolic tissues via secreted factors to influence systemic energy metabolism. How the protein and long noncoding RNA (lncRNA) regulatory networks act in concert to regulate key aspects of thermogenic adipocyte biology remains largely unknown. We previously discovered Brown fat lncRNA 1 (Blnc1) as an inducible lncRNA that promotes

brown and beige adipogenesis through its interaction with EBF2. Blnc1 is highly conserved in mice and humans at the sequence and function levels, both capable of stimulating thermogenic gene expression. A conserved RNA domain was identified to be required and sufficient for the biological activity of Blnc1. Further, we identified hnRNPU as an RNA-binding protein that facilitates the assembly and augments the transcriptional function of the Blnc1/EBF2 ribonucleoprotein complex. These studies illustrate Blnc1 as a conserved lncRNA regulator of thermogenic adipocyte development through interfacing with the protein regulatory network.

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313-LB

Intravenous Arginine Has No Effect on the Secretion of Gut-Derived Glucagon in Totally Pancreatectomized Subjects

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We recently provided evidence that glucagon also is secreted from extrapancreatic tissues in totally pancreatectomized (PX) patients-most likely from enteroendocrine L cells. The regulation of gut-derived glucagon secretion is unknown. In order to establish whether arginine (a strong stimulus for pancreatic glucagon secretion) stimulates gut-derived glucagon secretion, we performed an intravenous (iv) arginine test in PX patients and nondiabetic control subjects (CTRL) and employed a recently validated and highly sensitive and specific glucagon assay. Plasma glucagon and glicentin (a product of the enteroendocrine L cell) concentrations were measured at baseline (in the fasting state) and at 2, 5, 10, 15 and 30 minutes following iv infusion of 5 grams of arginine (administered over 5 minutes) in 12 PX patients (age [mean±SEM] 65±2.7 years; BMI 22.9±1.1 kg/m^2) and 12 matched CTRL (age 64.4±2.4 years; BMI 24.0X±0.8 kg/m^2). PX patients exhibited significantly lower fasting plasma glucagon compared to CTRL (2.5±0.4 vs. 8.2±0.9 pmol/l, P<0.0001). In the CTRL group we observed an abrupt and significantly larger glucagon response following iv arginine (baseline-subtracted area under the curve (bsAUC) 347±32 pmol/l × min) compared to the PX patients (P<0.001) in whom no change in plasma glucagon was observed (bsAUC 0±7 pmol/l×min). In the CTRL group, no glicentin response was found (bsAUC -43±32 pmol/l×min), whereas a small response was observed in the PX group (136±70 pmol/l×min) (P<0.0001). Iv infusion of arginine, often used to evaluate maximal pancreatic glucagon secretion, has no effect on gut-derived glucagon secretion in totally pancreatectomized patients.

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314-LB

Oxyntomodulin (OXM)-XTEN: A Pharmaceutical Protein with Extended Half-Life ($t_{1/2}$) that Improves Glucose Metabolism and Decreases Body Weight in Diet-Induced Obese (DIO) Mice

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OXM is a gut peptide with short half-life. It is a balanced agonist at both GLP-1 and glucagon receptors. Dual GLP-1R/GCGR agonists have been shown not only to improve glycemic control via GLP-1R, but also induce profound weight loss through dual agonism in mice. The unstructured recombinant polypeptide, XTEN, has been shown to extend the $t_{1/2}$ of numerous peptides with short $t_{1/2}$. We had previously performed a cysteine scan of OXM to determine optimal sites to chemically conjugate two OXM peptides to XTEN, to increase the $t_{1/2}$ of this OXM-XTEN homodimer, Cpd. A. Cpd. A has EC_{50}s of 1.8±0.3 and 3.0±1.0 nM on mouse GLP-1R and GCGR, respectively. A single dose, dose-dependently decreases net AUC during an IPGTT as well as food intake and body weight, and increases FGF-21 in DIO mice with minimally efficacious doses of 1, 10, and 3 nmol/kg, respectively. In ex vivo human plasma stability studies, 70% remains at 7 days. Its in vivo IV $t_{1/2}$ is 22, 15, and 62 hours in mouse, rat, and cynomolgus monkey, respectively. Dosing Cpd. A every other day in DIO mice for 9 days dose-dependently decreased body weight up to 20% at 30 nmol/kg. Cpd. A dosed in rats at either 0.2 or 2 mg/kg QW for 4 weeks resulted in no decrease of exposures (except in 1 rat at 2 mg/kg). Cpd. A is a dual GLP-1R/GCGR agonist that has an extended $t_{1/2}$ enabling QW dosing, and significantly improves glucose metabolism and weight loss in DIO mice.

315-LB

Glucagon Elimination Is Increased in Patients with Type 2 Diabetes

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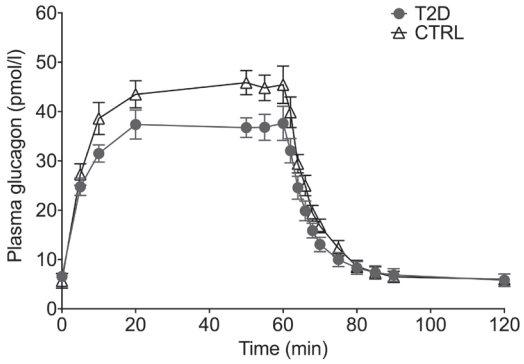
Type 2 diabetes (T2D) is characterized by hyperglucagonemia, which contributes significantly to the hyperglycemic state of the disease. The etiology behind the hyperglucagonemia is complex and thought to involve hypersecretion of glucagon from the pancreas. We investigated whether a decreased metabolic clearance rate (MCR) of glucagon could contribute to the hyperglucagonemia in patients with T2D. Glucagon was infused intravenously for 1 hour (4 ng/kg/min) to 16 patients with T2D (age [mean±SD]: 59±8 years, BMI: 31±6 kg/m^2, HbA_{1c}: 52±16 mmol/mol (6.9±1.4%), estimated glomerular filtration rate (eGFR): 89±12 ml/min/1.73 m^2) and 16 age-, gender- and BMI-matched nondiabetic controls (age: 59±9 years, BMI: 31±6 kg/m^2, HbA_{1c}: 34±4 mmol/mol (5.3±0.4%), eGFR: 83±13 ml/min/1.73 m^2). Plasma glucagon was measured frequently before, during and after the 1-hour infusion (Figure 1). Compared to the controls, the MCR of glucagon was higher (40.6±2.7 vs. 29.7±1.2 ml/kg/min, p=0.02) and elimination half-life (T½) of glucagon lower in the T2D group (4.4±0.3 vs. 5.5±0.4 minutes, p=0.02). From these accurate estimates of the MCR and T½ of glucagon in patients with T2D and matched nondiabetic controls, we conclude that glucagon elimination is increased in our cohort of patients with T2D, suggesting that increased secretion rather than diminished MCR of glucagon contributes to the hyperglucagonemic state of T2D.

Figure 1. Plasma Glucagon (Mean ± SEM) Following Infusion of Glucagon (4 ng/kg/min) from 0-60 Minutes in 16 Patients with Type 2 Diabetes (T2D) and 16 Matched Nondiabetic Control Subjects (CTRL).



316-LB

Downregulation of Renal SGLT2 Expression after Duodenal Jejunal Bypass: Evidence for a Gut-Kidney Axis in Glucose Metabolism

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Background: Both sodium glucose co-transporter 2 (SGLT2) inhibitors and Roux-en-Y gastric bypass (RYGB), a bariatric surgery procedure, cause glucose lowering, weight loss and reduced cardiovascular risk in patients with type 2 diabetes. Both are also associated with increased renal glucose excretion (case reports show glycosuria during oral glucose tolerance test post RYGB) and a paradoxical postprandial increase in glucagon.

Aim: To investigate the impact of gastrointestinal bypass surgery on renal SGLT2 expression.

Methods: Seventeen Wistar rats underwent either duodenal-jejunal bypass-DJB (n: 9), an experimental, stomach-sparing model of RYGB that excludes the duodenum and part of the jejunum from the transit of food, or a sham operation (n: 8). Kidneys were harvested in fed animals 2-4 weeks after surgery. Quantitative real-time PCR (qRT-PCR) and Western Blot were used to measure SGLT2 gene expression and protein levels. Food intake and body weight were also measured.

Results: DJB rats had markedly reduced renal SGLT2 gene expression (P=0.0002) compared to sham-operated controls. Western blot also showed lower SGLT2 protein levels in kidneys of DJB animals compared to controls. No differences in food intake and weight gain were observed between groups.

Conclusions: Gastrointestinal bypass surgery down-regulates SGLT2 expression in the kidney. These findings suggest a previously unappreciated gut-kidney axis in the regulation of glucose metabolism, which may contribute to the metabolic benefits of bariatric surgery.

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317-LB

Differentiating Familial Partial Lipodystrophy from Truncal Obesity and Type 2 Diabetes: Making Use of the Mixed-Meal Test and Support Vector Machines

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Familial Partial Lipodystrophy (FPLD) is a rare heterogeneous disorder associated with a paucity of extremity fat and hypertrophy of central depots. This leads to insulin resistance, hypertriglyceridemia and steatohepatitis. Differential diagnosis (DDx) of FPLD and type 2 diabetes (T2DM) with truncal obesity may be challenging. We compared mixed meal test (MMT) results of 12 patients with FPLD (3M/9F; 34-64 years old) and an age and gender matched group of 20 patients with T2DM, truncal obesity and nonalcoholic fatty liver disease (6M/14F, 34-67 years old). Our hypothesis was that metabolic and hormonal parameters in FPLD would differ from common T2DM. Patients ingested 474 ml of Optifast (320 kcal, 50% carbohydrate, 35% protein, 15% fat) after a 10-hour fast. Blood was collected for metabolic and hormonal measurements at baseline, 30, 60, 90, 120 and 180 minutes. Baseline and post-meal triglycerides and the post-MMT glycemic peak was significantly higher in FPLD. Physiological suppression of FFA at 120 min. was also attenuated in FPLD. Using Support Vector Machines (SVM), we developed a linear model to differentiate between groups with 92% sensitivity and 95% specificity using 5 MMT parameters (Table 1, *: Excluding GLP-1).

In conclusion, metabolic and hormonal responses to MMT in FPLD are quite different compared to common T2DM and may be useful in DDx.

Table 1. Mixed Meal Test Results.

Measurement (mean±SEM)	T2DM	FPLD	p-value		True negative	True positive
60 min Glucose (mg/dl)	194 ± 8	272 ± 23	0.0039	**SVM Prediction**	**T2DM, n=20**	**FPLD, n=12**
60 min Insulin (uU/ml)	89.3 ± 7.7	133.6 ± 23.4	NS	**T2DM**	19	1
60 min GLP-1 (pg/ml)	26.5 ± 5.6	18.7 ± 3.0	NS*	**FPLD**	1	11
60 min GIP (pg/ml)	197 ± 16	325 ± 48	0.025		95%	92%
AUC for Triglycerides (mg*h/dl)	529 ± 66	1619 ± 316	0.0057			
FFA % suppression (%)	63.0 ± 4.3	40.0 ± 6.8	0.0097			

318-LB

Direct and Indirect Regulation of Camp-Dependent Transcriptional Pathway Involved in GPCR-Mediated GLP-1 Release from L Cell

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Glucagon-like peptide-1 (GLP-1) is major incretin hormone produced by L cells through a proglucagon processing, it is a potent insulinotropic agent that increases insulin release from the pancreatic islet b-cells in a glucose-dependent manner. The elevation of intracellular cyclic AMP (cAMP) can stimulate activation of proglucagon (gcg) transcription and the production of GLP-1. Activation of G-protein coupled receptor (including bile acid receptor GPBAR1) that increases intracellular cAMP levels upon activation resulted in GLP-1 release. However, the role of cAMP mediated transcription in the process remains obscure. Using a combination of pharmacological and genetic studies, we show here that activation of gcg transcription and the production of its encoded hormone GLP-1 was mediated via cAMP-dependent induction of the CREB regulated transcriptional coactivator (CRTC) 2. Depletion of CRTC2 or CREB inhibitor A-CREB expression significantly inhibited forskolin- and TGR5 agonist INT-777-induced gcg expression and GLP-1 release. Furthermore, as in the case for other metabolic tissues, expression of peroxisome proliferator activating receptor coactivator 1 alpha (PGC-1α) was also reduced by depletion of CRTC2 in L cells. Indeed, several key genes involved in the oxidative phosphorylation were downregulated in CRTC2-knockdown cells compared with the control, leading to the reduced ATP levels in the cells. Although, glucose did not induced the activation of CRTC2, disruption of CRTC2 resulted in reduction of glucose-induced GLP-1 secretion, suggesting that CRTC2 also regulate glucose mediated GLP-1 release through the PGC-1a indirectly. Finally, we showed that in vivo treatment with INT-777 increased proglucagon mRNA levels in the small intestine in wild type but not in CRTC2-deficient mice.

In summary, our study identifies CRTC2 as an important regulator of GLP-1 synthesis and secretion in intestinal L cells.

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The Role of PIASy in Cold-Induced Browning of Subcutaneous Adipose Tissue in Mice

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Increase in obesity is a principal cause of development of a metabolic syndrome. Activation of brown adipose tissue promotes a lean and healthy phenotype and improves insulin sensitivity. Recently, ever increasing attention has been paid to the existence of active brown and beige fat in humans for attractive therapeutic challenge. Our previous study showed that Protein Inhibitor of Activated Stat γ (PIASy) is involved in the hepatic lipogenesis through sumoylation of Sterol Regulatory Element Binding Protein 1c (SREBP1c) upon Protein Kinase A (PKA) activation during nutritional deprivation. In this study, we analyzed PIASy-/- mice and these mice showed enhanced BAT activation but there was no change in any other tissues. PIASy-/- mice showed reduced fasting blood glucose levels and improved glucose tolerance. Despite these metabolic advantages, when these mice were exposed to cold environment, PIASy-/- mice were intolerant to cold and had hypothermia. They did not show any difference in BAT but in subcutaneous adipose tissue, UCP1 expression in response to cold is severely impaired in the absence of PIASy. Therefore, cold intolerance in PIASy-/- mice was attributed to the impaired cold-induced thermogenesis and browning of subcutaneous adipose tissue. These findings provide a novel function of PIASy in browning of white adipose tissues and important insights into the mechanism of thermoregulation.

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320-LB

Neural Circuit Mechanisms Underlying Hunger

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AgRP neurons are a specialized neural cell type that monitors nutritional signals that circulate in the blood, such as leptin and ghrelin, and then transforms those signals into the motivation to eat. How this transformation is performed remains unclear. I will discuss recent work from my lab investigating the dynamics of AgRP neurons and the mechanisms by which they control feeding. By recording the activity of these neurons in awake, behaving mice, we have shown that AgRP neurons are rapidly regulated by sensory cues associated with food, such as its sight and smell, and that this rapid sensory input effectively anticipates the nutritional value of a forthcoming meal. The consequence of this anticipatory regulation is that the activity of AgRP neurons is paradoxically "reset" before a meal begins. Consistent with these anticipatory dynamics, we have shown that AgRP neurons control feeding through an unusual delayed mechanism, in which the firing of AgRP neurons before food availability is sufficient to drive intense feeding behavior that persists for tens of minutes after AgRP neurons have shut off. We have shown that these sustained behavioral effects of AgRP neuron activity are responsible for alliesthesia, the everyday phenomenon whereby food deprivation makes food seem more palatable. Finally, I will discuss the neural circuit mechanisms underlying the ability of AgRP neurons to potentiate the rewarding properties of food and specifically the distinct anatomic pathways by which AgRP neurons transmit information to brain centers involved in appetitive and consummatory behaviors.

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321-LB

Niacin Improves Gut Function and Microbiota Composition in High-Fat Diet-Fed Mice

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High-fat diet (HFD) consumption has been reported to alter the intestinal structure, morphology and the gut microbiota composition, leading to the development of intestinal inflammation, inflammatory bowel disease and colorectal cancer. Niacin, also known as vitamin B3 and nicotinic acid, has been demonstrated to suppress intestinal inflammation and colon cancer through activation of its receptor, HCA_2. Therefore, we hypothesized that the beneficial effects of niacin might be due to its ability to prevent HFD-induced changes in the gut microbiota composition. To test our hypothesis, 32 three-week-old male B6129SF2/J mice were randomized into four groups: chow/vehicle, chow/niacin, HFD/vehicle, and HFD/niacin. They were placed on either a chow or HFD for 20 weeks. In the niacin treatment groups, niacin

(360 mg/kg/day) was added to the drinking water from day 32 till the end of the study, when mice were sacrificed and tissues collected. As expected, HFD-fed mice gained significantly more weight than chow fed mice. Surprisingly, niacin treatment suppressed body weight gain by 23% in HFD-fed mice, but not chow fed mice. This niacin-induced change in body weight gain was not associated with changes in food or water consumption. However, colon length was significantly increased in HFD/niacin mice compared to three other groups of mice. In the gut microbiota, niacin treatment lowered the aerobe/anaerobe ratio in both chow and HFD-fed mice compared to vehicle. Niacin also significantly lowered haemolytic bacteria and increased Bifidobacteria and Bacteroides in HFD-fed mice. In addition to the microbiota, Paneth cell number was significantly increased in HFD/niacin mice. The number of goblet cells was elevated with HFD feeding. Niacin increased goblet cell number in chow fed mice but decreased it in HFD-fed mice.

In conclusion, mice fed a HFD displayed disrupted gut microbiota composition and abnormal number of two principal cell types in the intestine, both of which were improved by niacin treatment.

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322-LB

Long-Acting GLP-1/Glucagon Dual Agonist SP-1373 Shows Superior Body and Liver Weight Loss in DIO Rodent Models Relevant to Diabetes and NASH

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Obesity and diabetes are primary indicators associated with NAFLD/NASH and, although the etiology is complex, weight loss is associated with improvements in liver status. Treatment of patients with GLP-1 agonists results in improved BMI and NAFLD Activity scores. A recent approach focuses on the use of multi-receptor co-agonists (GLP-1/glucagon; GLP-1/GIP, etc.) in order to achieve more rapid, larger impacts on weight and lipids. We report initial results with a EuPort-modified, highly potent and long-acting GLP-1/glucagon receptor dual agonist (SP-1373) in DIO rodent models of glucose intolerance and obesity. SP-1373 treatment resulted in superior body weight loss vs. semaglutide (lit. standard) following parallel, equimolar doses (12 nmole/kg; QD sc) to DIO rats (weight loss -40% vs. -13% respectively). SP-1373 also caused significant decreases in liver weight vs. vehicle (-52%, $p<0.001$) and vs. semaglutide treatment (-20% vs. vehicle; SP-1373 vs. semaglutide, $p<0.001$). Importantly, the decrease in body and liver weight with SP-1373 was greater than that of pair-fed rats (pair-fed to SP-1373, -17.7% BW, -23.2% liver; $p<0.001$ vs. SP-1373) indicating an additional mechanism of weight loss in the dual agonist. In diabetic DIO mice, a similar profile of substantial body weight loss (SP-1373, -25%; semaglutide -10%) was seen, as well as a clear improvement in glucose tolerance (IPGTT). SP-1373 showed a more favorable pharmacodynamic profile (delayed onset to maximal effect) compared to semaglutide, but with similar efficacy to reduce plasma glucose. Based on these data, SP-1373 appears to be an attractive new candidate for the treatment of diabetes, obesity and NAFLD/NASH by QW injection.

323-LB

Cavefish as a Natural Model for Insulin Resistance

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Understanding the genetic basis of adaptation has broad implications not only for a basic understanding of evolution, but also for human pathologies given that many human diseases are a consequence of mis-adaptation to modern societies. The emerging model system Astyanax mexicanus has become an important species to address adaptation to extreme environments due to its unique ecology and the availability of genetic and genomic tools. Cave environments are typically dark and nutrient deprived. Cavefish have acquired impressive adaptations such as hyperphagia, starvation resistance and fatty liver to cope with these conditions. Here, we have focused on symptoms reminiscent of diabetes these fish develop. We show that cavefish display insulin resistance due to a mutation in the insulin receptor. Notably, the same mutation is found in human cases of Rabson Mendenhall syndrome. In contrast to human patients, however, cavefish live long and symptom-free lives and display normal levels of advanced glycation end products. On the contrary, we show that the presence of the mutation is sufficient to provide these fish with an advantage and is selected for in nature. Our findings are probing the question whether cavefish have co-evolved factors to mitigate the otherwise detrimental effects of diabetes allowing them to cope with extreme nutritional levels. We propose strategies to identify these mechanisms, thereby providing potential new insights into human health.

Figure.

324-LB

Administration of NAPE Expressing Probiotic Bacteria Inhibits Weight Gain by Increasing Sensitivity to CCK

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Food intake triggers biosynthesis of the anorexigenic lipids N-acylphosphatidylethanolamines (NAPEs) in the intestinal tract. Previous studies showed decreased intestinal NAPE biosynthesis in animals on high fat diet (HFD) and we have demonstrated that administration of recombinant E. coli Nissle 1917 (EcN) expressing a NAPE acyltransferase gene (pNAPE-EcN) generate NAPEs and compensate for reduced intestinal biosynthesis of NAPE. The precise mechanism that NAPEs reduce food intake and body weight gain requires further elucidation. NAPEs may reduce food intake by increasing the sensitivity to CCK and leptin, which are key short term and long term regulators of food intake, respectively. To test if pNAPE-EcN increased sensitivity to leptin, C57BL6 mice were fed a high-fat diet (HFD; 60% kcal fat) for 4 weeks; then continued on HFD while given vehicle (0.125% Gelatin), control bacteria (pEcN) or pNAPE-EcN for 4 weeks; then osmotic pumps implanted to administer either vehicle (HBSS) or leptin (5mg/kg) for 1 week. When combining all mice treated with vehicle vs. leptin, leptin significantly reduced 7 day food intake ($p=0.010$) and increased weight loss ($p=0.049$). However mice treated with pNAPE-EcN had no greater reductions in food intake or body weight compared to control mice. To test if pNAPE-EcN increased sensitivity to CCK, C57BL6 mice were fed a low fat diet (10% kcal fat) for 10 days; then on HFD while treated with vehicle, pEcN, or NAPE-EcN for 2 weeks; then fasted for 12 h, then injected with CCK (20 µg/kg) 30 min prior to restoring food, and food intake measured over 16 h. In mice injected with saline did not significantly reduce 16 h food intake regardless of treatment. In mice injected with CCK, previous pNAPE-EcN administration significantly reduce 16 h food intake compared veh ($p=0.004$) or pEcN ($p=0.043$). Therefore, pNAPE-EcN reduces food intake and adiposity on a HDF in part by increasing sensitivity to CCK.

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325-LB

Arginase Promotes Hypertension and Insulin Resistance in Obese Rats

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The obese Zucker rat (ZR) is a genetic model of obesity that exhibits hypertension and insulin resistance (IR). We recently reported that the enzyme arginase, which converts arginine to ornithine, is elevated in 12 week old obese ZR, and that its blockade reverses hypertension by competing with endothelial nitric oxide (NO) synthase for the substrate arginine. In the present study, we investigated the temporal activation of arginase in obese ZR, and determined if arginase inhibition prevents the development of hypertension and IR in these animals. At 4 weeks of age, there was no difference in body weight, vascular or plasma arginase activity, mean arterial blood pressure (BP), or whole body IR, as estimated by the homeostasis model assessment of IR, between obese and lean ZR. However, at 8 weeks of age a significant increase in plasma and vascular arginase activity was detected in obese relative to lean ZR that was paralleled by an increase in body

weight and IR. BP was similar between obese and lean ZR. A further rise in vascular and plasma arginase activity was noted in obese but not lean ZR at 12 weeks of age and this was associated with an increase in BP, an additional rise in body weight and IR, and a decline in circulating arginine and NO, as measured by its major oxidative metabolites nitrite and nitrate. Finally, administration of arginine (2%) to the drinking water of obese ZR beginning at 8 weeks of age for 4 weeks attenuated the rise in BP and augmented circulating levels of arginine and NO without correcting body weight or IR. In contrast, chronic intraperitoneal delivery of the arginase inhibitor, N-hydroxy-L-arginine (25μg/h) for 4 weeks improved BP, body weight, IR, and plasma arginine and NO levels in obese ZR.

In conclusion, the present study found that arginase inhibition prevents the development of hypertension and IR while L-arginine administration only blocks the increase in BP in obese ZR. Arginase represents a promising therapeutic target in mitigating vascular and metabolic dysfunction in obesity.

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326-LB

miR-150 Influences Body Weight, Insulin Sensitivity, and Systemic Metabolism in Mice

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Background: Obesity, insulin resistance, and prediabetes affect large segments of the population and are responsible for rising rates of T2DM. Short non-coding micro-RNAs (miRNAs) are post-transcriptional factors that directly regulate protein expression by degrading or inhibiting target mRNAs; however, the role of miRNAs in metabolic disease remains unclarified. Based on our earlier data demonstrating that miR-150 influences adipocyte metabolism, we have studied the effects on systemic metabolism and body weight in miR-150 knockout mice.

Methods: Weight, body composition, glucose tolerance (GTT), and insulin sensitivity (ITT) were assessed in WT and global miR-150 KO male mice fed a high fat diet, and epididymal adipose tissue (EAT) was obtained for RT-PCR and Western blotting.

Results: KO mice showed lower body weight, with lower % fat and higher % lean mass, compared with WT. Global KO of miR-150 also enhanced systemic metabolism with KO mice exhibiting improved insulin sensitivity and glucose tolerance. In adipose tissue, KO mice were found to have higher protein level of pgc-1α with increased expression of genes involved in both the degradation and synthesis of fatty acid and triglyceride (TG) such as PPARα and glycerol kinase.

Conclusion: miR-150 strongly influences body weight, body composition, and systemic metabolism. When compared with WT, miR-150 KO mice were found to have reduced body weight and fat mass as well as enhanced insulin sensitivity and glucose tolerance. Increased pgc-1α in adipose tissue promoted changes in gene expression indicative of a futile cycle involving breakdown and synthesis of TG, which consumes energy and prevents export of free fatty acid to the circulation. miR-150 may represent both a biomarker and novel therapeutic target regarding obesity and insulin resistance.

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327-LB

Bofutsushosan, an Oriental Herbal Medicine, Induces Akkermansia Muciniphila and Improves Glucose Metabolism in Diet-Induced Obese Mice

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Bofutsushosan (BFT), an oriental herbal medicine, has been clinically used for obese patients. However, the effect of BFT on glucose metabolism has not been fully elucidated.

To explore the impact of BFT on glucose metabolism, male C57BL6 mice were fed on high-fat diet (HFD) for 12 weeks and administered either BFT (25 mg/day) or saline for the last 8 weeks. BFT did not alter daily food intake and body weight compared to control group. Oral glucose tolerance test and insulin tolerance test revealed improved glucose metabolism with improved insulin sensitivity in BFT treated mice, which was associated with decreased inflammatory gene expressions in the liver and adipose tissue. Whereas the weight of liver and adipose tissue was not changed, cecum weight was significantly increased by BFT. 16S rRNA sequence analysis of fecal samples showed that microbial community structure was markedly changed. BFT reduced the relative abundance of Bacteroidetes from 52% to 34%, whereas it increased Verrucomicrobia from 3.4% to 24%. We found that an increase in Verrucomicrobia was mainly associated with Akkermansia mucuniphila (Akk). QPCR analysis showed that the bloom of Akk was observed at one week of treatment and continued for 10 weeks. When the bedding of BFT-treated mice were transferred to non-treated HFD-fed mice, insulin sensitivity was significantly improved with increased Akk level in the feces. Consistent with the previous reports that Akk improves gut barrier function and prevents from metabolic endotoxemia in obese subjects, hepatic lipopolysaccharide binding protein expression was significantly decreased in BFT group. These data demonstrate that BFT increases Akk in the gut, which may contribute to improving gut barrier function and preventing metabolic endotoxemia, leading to improved diet-induced inflammation, thereby controlling glucose metabolism.

328-LB

Tetrahydrobiopterin Activates Brown Adipose Tissue and Regulates Energy and Glucose Metabolism

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Brown adipose tissue (BAT) is a central organ that acts to increase energy expenditure; its regulatory factors could be clinically useful in the treatment of obesity and diabetes. Tetrahydrobiopterin (BH4) is an essential co-factor of tyrosine hydroxylase and nitric oxide synthase (NOS). Although BH4 is involved in known regulatory factors of BAT such as noradrenaline (NA) and nitric oxide (NO), participation of BH4 in BAT function remains unclear. In the present study, we investigated the role of BH4 in the regulation of BAT using a mouse model of BH4 deficiency. Hph-1 mice, in which GTP-cyclohydrolase I (GTPCH I), a rate-limiting enzyme of BH4 syntheses, is deficient, exhibited a marked reduction in BH4 levels and impaired BAT functions including lower thermogenesis and reduction of thermogenesis-related gene expression. Hph-1 mice also exhibited obesity, adiposity, glucose intolerance, and insulin resistance. Supplementation of BH4 ameliorated BAT function as well as glucose intolerance. BAT transplantation from BH4-sufficient mice (control mice) into BH4-deficient mice (hph-1 mice) ameliorated BAT dysfunction together with related systemic metabolic disturbances, strongly suggesting that BH4-induced BAT has a critical role in the regulation of systemic energy metabolism. Both NA and NO levels were decreased in BAT of hph-1 mice. In addition, a direct effect of BH4 in the stimulation of brown adipocytes is implicated. BH4 increased the expression levels of thermogenesis-related genes including Ucp1, Pgc1a and Dio2 as well as the mitochondrial respiration rate in brown adipocytes. The proton leak level was increased, which induced elevation of the uncoupling rate. Furthermore, GTPCH I inhibitor suppressed the differentiation of brown adipocytes and thermogenesis-related gene expression. Taken together, BH4 activates BAT and regulates energy and glucose metabolism, suggesting a novel approach for metabolic disorders such as obesity and diabetes.

329-LB

The EndoBarrier in a Canine Lean Model of Normal Glucose Homeostasis

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Gastric bypass surgery has been shown to reduce body weight in obese patients and improve glucose homeostasis in type 2 diabetes (T2D). Placed endoscopically, the EndoBarrier covers the first 60 cm of the small intestine with a nonpermeable liner and mimics the intestinal bypass portion of surgery. In a large animal model, we are exploring the mechanisms by which bariatric surgery might drive the improvement in glucose homeostasis in T2D. In our first approach we examined the effects of placing the EndoBarrier in lean, male mongrel hounds with normal glucose homeostasis (n=7). Testing included an intravenous glucose tolerance test (IVGTT) as well as an oral mixed-meal tolerance test (MMTT) at baseline and week 1 and week 6 while the barrier was in place. All dogs lost weight post-procedure with an average weight loss of 8% at week 1 that was maintained through week 6. From baseline to week 1, all 7 dogs showed a significant decrease in glucose tolerance as reflected in the 10-19 min Kg value from the IVGTT (3.18 to 2.12%/min, $p<0.01$) was maintained at week 6 in 5/7 dogs for both glucose tolerance (2.23%/min). As an index of counter-regulation during the IVGTT, we also calculated the rate at which glucose levels returned to baseline (40-70 min) following the nadir after the insulin bolus. This rate of return was retarded after placement of the barrier at weeks 1 and 6 (baseline: 1.22, week 1: 0.16, week 6: 0.30 mg/dL/min, $p=0.001$). From the MMTT the insulin value measured at 120 minutes (baseline: 19.4 μU/mL) and the insulin

AUC above basal (baseline: 3795 µU/mL/min) were significantly increased at week 1 (52.4 µU/mL, p=0.04 and 7625 µU/mL/min, p=0.02, respectively) but returned to basal by week 6 (13.0 µU/mL and -197 µU/mL/min). These data show that the EndoBarrier has measurable effects on glucose homeostasis in nonobese animals and include reduced counter-regulation during the IVGTT and hyperinsulinemia during the MMTT. The significance of these findings in relation to changes in obese animals after surgery remain to be further elucidated.

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Protein Carbonylation Is a Novel Redox-Regulated Histone Modification that Accumulates in Obesity and Aging and Informs the Adipocyte Epigenome

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Post-translational modification (PTM) of histones is a dynamic epigenomic regulatory mechanism that controls transcription in every mammalian cell type. Mitochondrial oxidative stress and the resultant chemical synthesis of reactive lipid aldehydes is positively correlated with obesity, type 2 diabetes and aging. Using a variety of proteomic approaches, we have identified the core histones as targets of carbonylation, a PTM that results from the covalent modification of lysine, cysteine, and histidine residues by reactive aldehydes such as 4-hydroxy-nonenal (4-HNE) and 4-hydroxy-hexenal (4-HHE). Using affinity purification coupled with mass spectrometry, we identified 13 sites of carbonylation including H3K4, H3K36, H4K31, and H2BK4. Intriguingly, 4-HNE and 4-HHE modify distinct sites despite their chemical similarity. Importantly, carbonylation of histones in visceral white adipose tissue was 3 fold higher in high-fat fed mice and ob/ob mice compared to lean controls. In contrast, there was no change in histone carbonylation in subcutaneous adipose tissue. Carbonylation of histones also increased in chow-fed mice as a consequence of aging. In the 3T3-L1 cell culture system, treatment with inflammatory cytokines or increased oxidative stress resulted in a 2-5 fold increase in histone carbonylation. This effect was ameliorated by overexpression of the mitochondrial antioxidant GSTa4. This work has led to the identification of a novel class of redox-regulated histone modifications in adipose tissue that are linked to oxidative stress. These results suggest that carbonylation of histones may play a critical role in epigenomic regulation of transcription in the obese state.

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331-LB

Divergent Roles in the Control of Food Intake for Leptin Receptor and Calcitonin Receptor Neurons of the Nucleus of the Solitary Tract

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Neurons in the nucleus of the solitary tract (NTS) integrate multiple signals of gut status (including distention and nutrient content) to control satiety and subsequent feeding, as well as the aversive response to gastrointestinal (GI) distress. The roles for specific types of NTS neurons involved in satiety and aversion have not been defined previously, however. Here, we show that leptin receptor (LepRb) and calcitonin receptor (CalcR) expression define distinct subsets of NTS neurons. Activation of NTS^{LepRb} cells in mice using the Designer Receptors Exclusively Activated by Designer Drugs-hMD3q (DREADD-hMD3q) inhibited acute (2 hour and 4 hour) food intake during the dark cycle, as well as blunting refeeding following an overnight fast by approximately 20% over 6 hours. Furthermore, chronic activation of NTS LepRb promoted a sustained decrease (approximately 25%) in daily food intake and 5% body weight loss over 4 days. While the DREADD-hM3Dq-mediated activation of NTS^{CalcR} neurons produced a similar acute reduction in food intake, the activation of these cells suppressed food intake upon refeeding following overnight fast by approximately 75% over 6 hours. Additionally, activation of NTS^{CalcR} cells reduced feeding by approximately 50% and decreased body weight by approximately 10% over 4 days, suggesting greater anorectic potential of NTS^{CalcR} cells compared to NTS^{LepRb} cells. In contrast, activation of NTS^{LepRb} neurons, but not NTS^{CalcR} neurons, promoted a robust conditioned taste aversion (CTA). These findings suggest that NTS^{CalcR} neurons mediate satiety, while NTS^{LepRb} neurons contribute to the aversive response to GI distress. Thus, NTS^{CalcR} neurons represent a potential target for the suppression of food intake and body weight in obesity.

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332-LB

Endothelial Deletion of Carcinoembryonic Antigen-Related Cell Adhesion Molecule 1 in Mice Preserves Insulin Clearance, but Increases Food Intake and Promotes Obesity

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Insulin resistance is the hallmark of type 2 diabetes, and clearance of insulin is becoming more recognized as an important regulator of insulin sensitivity. Carcinoembryonic antigen-related cell adhesion molecule 1 (Ceacam1) has been shown to improve the rate of insulin clearance in the liver. When Ceacam1 is deleted globally from mice ($Cc1^{-/-}$), insulin clearance is impaired, resulting initially in hepatic insulin resistance that progresses with age to peripheral insulin resistance, increased adiposity, and other signatures of metabolic syndrome and nonalcoholic fatty liver disease (NAFLD). With high fat diet $Cc1^{-/-}$ mice exhibit features of nonalcoholic steatohepatitis (NASH). Ceacam1 has also been identified in a number of metabolically relevant tissues such as the pancreas, brain, intestine, and endothelium. To determine the relative contribution of endothelial Ceacam1, we used cre/lox technology to create an endothelial specific Ceacam1 knockout mouse (Endo-$Cc1^{fl/fl}$). These Endo-$Cc1^{fl/fl}$mice are insulin sensitive with normal insulin and glucose tolerance, yet they develop obesity and have higher levels of plasma leptin. ICV injection of leptin results in normal signaling in the hypothalamus, but with IP injection leptin response is impaired. These studies indicate endothelial Ceacam1 may play an important role in the transport of leptin into the brain.

333-LB

Challenging the Adipocyte Color Barrier—TR Activation Elicits White-to-Beige Transdifferentiation Independent of Beta-Adrenergic Signaling

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An alluring possibility to combat diabetes and metabolic disease is to activate beige adipocytes, brown-like adipocytes that reside in white adipose tissue, with the capacity to conduct adaptive thermogenesis, an action often referred to as "beiging." Currently, the most potent and well appreciated beiging agents are beta-adrenergic receptor (b-AR) agonists. While these agonists care capable of inducing beiging in select adipocytes, they are largely incapable of doing so in adipocytes within or derived from visceral depots or in white adipocyte cell lines. Here we show that, unlike beta-adrenergic agonism, pharmacologic activation thyroid hormone receptor (TR) signaling is sufficient to markedly induce beiging in a variety of viscerally derived white adipocytes, as well as 3T3-L1 adipose cells. TR activation is also sufficient to induce the expression of key intracellular mediators of adaptive thermogenesis, such as ATGL and HSL, lipases known to be necessary for the activation of Ucp1 mediated uncoupling and thermogenesis. Loss of b-AR signaling does not affect the ability of TR activation to elicit beiging, indicating that TR mediated beiging is independent of beta-adrenergic signaling. Finally, TR activation, unlike b-AR stimulation, appears to elicit beiging of these recalcitrant adipocytes, not via the maturation (or differentiation) of beige adipocyte precursor cells, but largely via the direct interconversion or "transdifferentiation" of mature adipocytes into Ucp1+ beige adipocytes. Thus, select TR agonists can markedly elicit beiging in a fashion that appears to be mechanistically distinct from perhaps all other known beiging agents (nearly all of which require b-AR signaling), making them important tools in assessing the therapeutic potential of beige fat activation to treat diabetes and metabolic disease.

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334-LB

Amygdalar AMPK Has a Crucial Role in the Regulation of Energy Homeostasis

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The CeA (central nucleus of the amygdala) is part of the reward system and participates, with the hypothalamus in the control of food intake (FI) and body weight (BW). Hypothalamic AMPK (AMP-activated protein kinase) controls the energy balance. However, there is a lack of research regarding the expression and action of AMPK in the CeA. Thus, we aimed to determine whether AMPK: 1.) is expressed and 2.) is an energy sensor in the CeA of control rats. Prolonged fasting (24h) increased and refeeding (2h) decreased AMPK phosphorylation (AMPK thr172) in the CeA. Infusion of ghrelin into CeA of fed rats increased FI, enhanced AMPK thr172 and NPY mRNA in this region. In contrast, chronic melanocortin agonist (MTII) infusion in the CeA

decreased AMPK thr172, FI and BW. Infusion of 2-deoxyglucose into the CeA began to increase food intake after 10 and lasted until 60 minutes. An increased AMPK thr172 accompanied this result at the same time and started to decrease after 60 minutes. Further, knocking down Alpha 1/2 AMPK in the CeA for 14 days (mini pump) was sufficient to decrease BW and fat mass until the fourteenth day after 4 days. FI was not different, but the oxygen consumption and UCP1 gene expression in the brown adipose tissue was increased at the end. The mRNA levels of NPY were reduced and oxytocin levels were enhanced in the CeA of fasted rats.

In summary, our results suggest that AMPK in the CeA is regulated via nutritional status, hormones and neuroglucopenia. In addition, AMPK in the CeA has a critical role in the regulation of adiposity, mainly through increased energy expenditure. Our results indicate that AMPK may have a major role in extra-hypothalamic regions, such as the CeA, participating in the complexity of the control of energy balance.

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OBESITY—HUMAN

335-LB

A Smartphone-App-Based Lifestyle Intervention Program for Weight Loss: Interim Analysis of a Randomized Controlled Trial

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Despite widespread use of smartphones and wearables, we have limited evidence that they aid weight loss or behavior change. Here, we report interim results at the halfway point of a 6-month, prospective, randomized study of our smartphone app-based lifestyle intervention vs. standard of care (in-person weight management visits at 0, 3, and 6 months) in a cohort of overweight or obese subjects.

The smartphone app downloads objective data of physical activity from 3-axis accelerometers and daily weights from smartscales. The technology allows peer social networking and remote professional coaching employing behavior modification techniques delivered via group and private messaging, emoticons, shared activity and weight data, shared photographs of meals, and a virtual reward system for behavior modification. The pre-specified primary outcome is weight loss at 6 months.

The intervention group is n=13, no drop-outs, 85% F, age 39.5± 3.71 y, initial weight 94.3 ± 3.42 kg, BMI 34.5 ± 1.3 kg/m^2 (means ± SE). We observed a clinically and statistically significant weight change of -4.9 kg ± 1.49 (95% CI -8.19 to -1.69, p=0.0062), % weight change was -5.4% ± 1.72 (95% CI -9.16 to -1.66, p=0.0085) after 3 months of our smartphone app-based lifestyle intervention. Spearman's correlation (rho) showed that weight loss significantly associated with median step counts (rho=-0.74, p=0.0036), numbers of text messages from each subject (rho=-0.82, p=0.0006), and numbers of diet photos shared (rho=-0.86, p=0.0002).

This interim analysis suggests that our technology-based lifestyle intervention delivered via a smartphone app produces clinically meaningful and statistically significant weight loss at 3 months. The strongest correlations with weight loss were physical activity (step counts) and evidence of subjects' engagement in behavior modification coaching on the app (messages and diet photos).

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336-LB

Adaptive Changes in Pancreas Volume, Composition, and Function after RYGB-Induced Weight Loss

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Background: Obesity has been shown to trigger adaptive increases in pancreas parenchymal and fat volume as significant determinant of insulin resistance and β-cell failure. It is unknown whether, in reverse, the pancreatic tissue components decrease with weight loss. RYGB is associated with a dramatic increase in GLP-1. Considering the modulating effects of GLP-1 on the endocrine and exocrine pancreas, we investigated the impact of RYGB-induced weight loss on pancreatic volume and function.

Methods: This study included 11 patients eligible for RYGB. Before and 6 months after surgery, GLP-1 was measured during a standard oGTT. Volumetric MR imaging (Dixon method) was performed. HbA1c, FPG and insulin with C-peptide were measured to assess ß-cell function. HOMA-IR levels were calculated to quantify insulin resistance. Amylase and lipase levels were evaluated indicative of pancreatic injury. Fractional ß-cell area was estimated by the C-peptide-to-glucose ratio, ß-cell mass was calculated by the product of ß-cell area and parenchymal weight.

Results: 30 min after glucose ingestion, peak GLP-1 levels increased from 32.3±3.7 to 117.2±17.8 (mean±SEM, p<0.001). Total pancreas volume decreased from 83.8±3.7 to 70.5±5.3 cm^3, which was associated with a decrease in fat volume from 17.6±3.1 to 9.6±2.4 cm^3 (mean±SEM, p=0.001). Changes in parenchymal volume showed a similar, though not significant trend. Fasting concentrations of insulin and C-peptide were significantly lower after RYGB (p<0.05). HOMA-IR levels significantly decreased from 7.7±4.5 to 2.5±0.7 (mean±SD, p<0.05). This was consistent with a significant mean reduction in the estimated ß-cell mass (p<0.05). Lipase levels significantly decreased after RYGB (p<0.05).

Conclusion: Pancreatic volume adaptively decreases with weight loss. Obesity-driven ß-cell expansion can be reversed by RYGB, which is accompanied by improved insulin sensitivity. Despite high levels of GLP-1, no increase in parenchymal volume was present.

337-LB

Adipose Tissue Fibrosis Is Linked to Visceral Adiposity and Glucose Control in Chinese Adults

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Diabetes type 2 (DM2) presents at a lower BMI in Chinese than Caucasians people, suggesting that rising BMI marks a more metabolically harmful form of adiposity in Chinese individuals. However, what functional differences in adipose tissue contribute to DM2 risk in Chinese individuals is unknown. We investigated the relationship between BMI, percent body fat and insulin resistance, and the extent to which subcutaneous adipose tissue (SCAT) fibrosis is a determinant of glucose control, in 23 Chinese and 28 Caucasian men and women. Subjects underwent body composition (DXA), fasting plasma glucose, and insulin analyses, and 38 underwent gene expression analysis in abdominal SCAT (qPCR). BMI and total adiposity (DXA) were strongly correlated in Caucasians (r=0.76, p <0.01), whereas there was a striking lack of correlation among Chinese (r=0.36, p >0.05). Interestingly, BMI correlated positively with visceral adipose tissue (VAT) mass in both groups (Caucasian r=0.9 and Chinese r=0.84; p <0.01 for both). However, whereas both total body fat and VAT masses correlated with rising HOMA-IR in Caucasians (r=0.73 and r=0.55, p < 0.01 for both), only VAT mass did so among Chinese (r=0.87, p < 0.01), suggesting that the link between VAT accrual and insulin sensitivity, at least in Chinese, may occur through a mechanism partly independent of adiposity per se. By contrast, mRNA levels of fibrosis genes [COL1A1, COL3A1, COL6A1, FN1 (Fibronectin)] in the SCAT had a significant, positive correlation with both BMI and VAT in Chinese individuals, but not in Caucasians. Moreover, SCAT mRNA levels COL3A1, COL6A1 and FN1 mRNA levels correlated significantly with HOMA-IR in Chinese, but this was less evident in the Caucasians. Together, our findings dissociate BMI and adiposity in Chinese, and instead link visceral adiposity to SCAT fibrosis, the development of which worsens glucose homeostasis in this group. Probing these fat-intrinsic functional differences may reveal ethnically precise mechanisms of DM2 risk.

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338-LB

Exendin-4 Modifies Adipogenesis of Preadipocytes Isolated from Human Omentum through Multiple Mechanisms

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Abdominal obesity is considered a major factor in the development of metabolic disorders. Glucagon-like peptide-1 (GLP-1) has been reported to have positive effects on improving body metabolism and to reducing insulin resistance. However, it remains less clear whether GLP-1 plays a role in the adipogenesis process of visceral fat. Here we demonstrated that, Exendin-4, a GLP-1 receptor agonist, improved cell viability via promoting proliferation and inhibiting apoptosis in preadipocytes isolated from human omentum. Mechanistically, the activation of MAPK/ERK1/2, Akt/GSK-3β, and PKA/CREB pathways and downstream consequences induced (elevated expression of Cyclin D3, CDK4, c-fos and c-myc, as well as inhibited expression of P21 and P27) are involved in the proliferative and anti-apoptotic roles of Exendin-4. More intriguingly, Exendin-4 could promote the differentiation of preadipocytes isolated from human omentum. Underlying mechanisms of the differentiation of omental preadipocytes are associated with the up-regulation of the expression of pro-adipogenic genes (such as PPARγ, C/EBPα, C/EBPβ, FABP4, FASN, IRS2, LPL, PPARGC1A, SREBF1and Wnt5b) and

down-regulation of the expression of anti-adipogenic genes (which include FoxO1, SIRT1, SIRT2, GATA3, Wnt3a and Wnt10b).

In conclusion, our data demonstrate that Exendin-4 modifies adipogenesis of preadipocytes isolated from human omentum through multiple mechanisms, those effects could contribute to the protective actions of GLP-1 receptor agonist body metabolism and insulin sensitivity.

339-LB

Metabolic Derangements Contribute to Reduced sRAGE Isoforms in Subjects with Impaired Cognition

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Receptor for advanced glycation end products (RAGE) has been implicated in the pathogenesis of diabetes and Alzheimer's disease, whereas soluble RAGE (sRAGE) isoforms (endogenous secretory: esRAGE, and cleaved: cRAGE) attenuate RAGE signaling by acting as ligand decoys. Obesity, diabetes and cognitive impairment (CI) all present reduced circulating sRAGE; however, the effects of concurrent metabolic and cognitive derangement are unknown. We examined the interactions between determinants of metabolic health and CI on circulating sRAGE isoforms in 135 older adults (60-89 y) stratified by the Clinical Dementia Rating (CDR; 0=normal cognition (NC), ≥0.5=CI). Total sRAGE and esRAGE were assayed via ELISA and cRAGE and cRAGE:esRAGE ratio were calculated. Apolipoprotein ε4 (APOE4) genotype, diabetes status, fasting glucose status (FGS), insulin, amylin, HOMA-IR, BMI status and fat mass were also assessed and used for sub-stratification. Friedman's test was used to evaluate group differences in sRAGE isoforms (Table). Where significance is identified, the CI group displayed reduced sRAGE compared to NC. These findings are the first to show that obesity and insulin resistance superimposed upon CI, display aberrant sRAGE profiles, thus reinforcing metabolic disturbances may drive CI in some individuals.

Table.

Group Comparison	df	sRAGE	cRAGE	esRAGE	cRAGE: esRAGE
NC vs. CI (Mann Whitney U-test)	1	0.154	0.056	0.840	**0.023**
Cognitive status vs. APOE4 genotype	3	0.350	0.184	0.908	0.083
Cognitive status vs. age (decade)	5	0.708	0.882	0.562	0.544
Cognitive status vs. type 2 diabetes status	3	0.586	0.392	0.329	0.105
Cognitive status vs. FGS by ADA criteria	5	0.127	0.197	**0.044**	0.563
Cognitive status vs. median insulin (6.8mIU/L)	3	0.118	0.184	0.069	**0.008**
Cognitive status vs. median amylin (6.8pM)	3	**0.047**	**0.005**	0.868	**0.001**
Cognitive status vs. median HOMA-IR (1.7AU)	3	**0.009**	**0.008**	0.114	**0.020**
Cognitive status vs. BMI status (lean vs. overweight vs. obese)	5	**0.044**	**0.047**	0.205	0.823
Cognitive status vs. median fat mass (29kg)	3	**0.035**	**0.044**	0.576	0.291

df=degrees freedom; data=Friedman's p-value.

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340-LB

Does Hyperinsulinemia in Obesity Elicit Brain Responses that Provoke Greater Motivation for Food?

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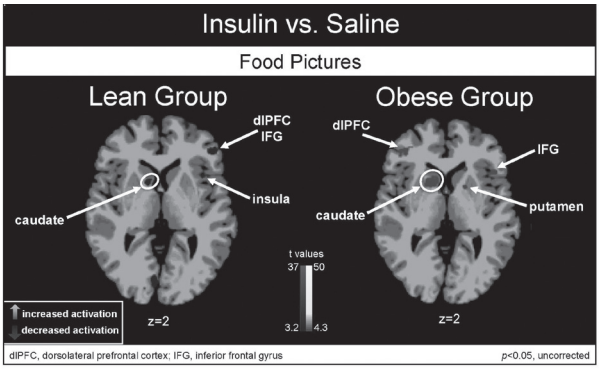
Markedly elevated insulin levels in response to eating are a hallmark of insulin resistance in obese individuals. Although the effects of insulin have been studied extensively in the body, less is known about the effects of high insulin levels on the brain, specifically neural regions that regulate eating behavior. We studied 5 Lean (LN) (BMI 22 kg/m^2, age 31, A1c 5.3%) and 6 Obese (OB) subjects (BMI 32 kg/m^2, age 30, A1c 5.5%) who underwent functional MRI scans while viewing food and non-food pictures during hyperinsulinemic-euglycemic clamp (insulin 2mU/kg/min, glucose maintained at 90mg/mL) vs. saline-euglycemic control on 2 separate random order days after an overnight fast. As shown below, in response to viewing food pictures during Insulin vs. Saline infusion, LN exhibited decreased blood-oxygen-level dependent (BOLD) responses in the caudate, insula, dorsolateral prefrontal cortex (dlPFC) and inferior frontal gyrus (IFG), brain regions involved in reward-motivation, taste perception, decision making and working memory. Conversely, OB demonstrated increased responses in the caudate, putamen, dlPFC and IFG ($p<.05$), brain regions involved in reward-motivation, decision making and working memory. These data suggest that increases in plasma insulin reduce neural responses to food pictures in lean but not in obese individuals, thereby potentially impacting motivation to eat in obese individuals.

Figure.



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341-LB

Incidence of Hypoglycemia after Gastric Bypass vs. Sleeve Gastrectomy—A Randomized Trial

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Background and Aim: Conversion of Roux-en-Y Gastric-Bypass (RYGB) to sleeve-gastrectomy (SG) is currently used as an alternative to pancreatectomy to treat severe reactive-hypoglycemic complication. Prospective, randomized-trials (RT) are however lacking. We compared the incidence of reactive hypoglycemia (<3.1 mmol/l) after RYGB vs. SG in a single-center, two-arm, parallel, randomized, open-label trial at the Catholic University in Rome, Italy.

Results: Of 175 eligible patients, 120 were randomized 1:1to RYGB or SG. One-hundred and twelve (93%) completed the 12-months follow-up. Hypoglycemia (<3.1 mmol/l) was detected in 14% and 29% of SG and RYGB patients (P=0.079). Daily hypoglycemic episodes (≤3.1 mmol/l) during continuous-glucose-monitoring did not differ between groups. Glucose levels ≤3.3 mmol/l were 36.2% after SG and 61% after RYGB, respectively (P=0.012). Four out 59 RYGB subjects (6.8%) had 1 to 3 hospitalizations for symptomatic hypoglycemia. The association between hypo- and hyperglycemic peaks independently of treatment was not significant. The static β-cell glucose-sensitivity-index calculated by the minimal-model increased after both treatments [from (50.99±33.68·to 120.43±98.90)·10^9 min^{-1}, P<0.001], but the dynamic β-cell glucose-sensitivity-index increased significantly in SG [(from 323.93±480.87 to 933.32±1063.86)·10^9 min^{-1}, P=0.008] and decreased in RYGB [(from 645.69±733.21 to 414.90±469.87)·10^9 min^{-1}] (P=0.004 for time×treatment interaction). Whole-body insulin-sensitivity increased about 10 times in both groups.

Conclusion: SG is not a safer option than RYGB in leading reactive hypoglycemia 1 year after surgery. However, RYGB overall induced a higher number of hypoglycemic episodes than SG. This might be due to the lack of improvement of β-cell sensitivity to changes in circulating glucose, which determines an inappropriately high insulin-secretion in the face of a dramatically improved peripheral insulin-sensitivity.

342-LB

Norepinephrine Transporter Availability in Imaging Brown Fat Is Reduced in Obesity: A Human Pet Study with [^{11}C]MRB

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There is growing interest in harnessing the energy-dissipating properties of brown adipose tissue (BAT) to combat diabetes and obesity. BAT activity is tightly regulated by the sympathetic nervous system (SNS), and basal sympathetic tone of BAT is critical to all aspects of BAT function. Most studies have overlooked the importance of basal, room temperature (RT) BAT activity, focusing instead on activation of BAT using cold stimulation, in part, because the standard imaging modality for BAT, ^{18}F-FDG-PET, shows low tracer uptake at RT. We have shown previously that BAT can be reli-

ably and equally detected in humans under both RT and cold conditions with ^{11}C-MRB (S,S)-^{11}C-O-methylreboxetine), a PET ligand for the norepinephrine transporter (NET), suggesting that ^{11}C-MRB labels an intrinsic property of the BAT tissue, the degree of SNS innervation. In this study, we sought to determine whether obesity alters human BAT labeling. Twelve healthy, non-diabetic Caucasian women (7 lean, age 25.7±0.8 years; BMI 21.8±0.6 kg/m^2 and 5 obese, age 29.4±4.0 years; BMI 39.4±2.8 kg/m^2) underwent PET/CT imaging of the neck/supraclavicular region using [^{11}C]MRB under RT conditions. The distribution volume ratio (DVR) for [^{11}C]MRB (the magnitude of tracer binding to NET) was estimated via MRTM2 referenced to the occipital cortex, an area with minimal NET. Two women (1 lean and 1 obese) had no detectable BAT. Of the women who had detectable BAT, obese women had lower [^{11}C]MRB DVR compared to lean women (lean BAT DVR 1.12±0.2 (mean±SEM) vs. obese BAT DVR 0.82±0.1, P=0.03). Furthermore, BAT DVR correlated inversely with BMI (r=-0.77, P=0.009). Our preliminary findings are consistent with reports that NET is decreased in obesity and suggest that the sympathetic innervation of BAT is altered in obesity. These findings may have implications for understanding the role of basal BAT activity in obesity.

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343-LB

Six-Month Lorcaserin Administration Decreases Body Weight and Improves Cardiometabolic Parameters

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Lorcaserin (Belviq) is a serotonin 2c receptor agonist which has been shown to be effective at inducing weight loss. Preclinical and clinical fMRI studies have shown that lorcaserin exerts its weight loss actions in the brain, although its full effect on circulating hormones regulating metabolism and energy homeostasis remains unknown. We performed a randomized, placebo-controlled, double-blind trial to evaluate the effect of lorcaserin on weight loss, metabolic and hormonal changes in 37 obese adults. After 6 months, lorcaserin-treated subjects demonstrate a placebo-subtracted weight loss of 6 kg (p<.001), a BMI reduction of 2.24 kg/m^2 (p<.001), and a waist circumference reduction of 13.5 cm (p<.001). Importantly, fat mass was reduced (p<.001), particularly visceral adipose tissue (p<.001), while lean mass was unchanged (p<.98). Leptin (p<.04), oxyntomodulin (p<.05) and insulin (p<.05) decreased with lorcaserin treatment but GLP-1 and glucagon did not change significantly. Patients on lorcaserin showed a significant improvement of lipid parameters, including reduction in LDL (p<.04), particularly in small LDL subfractions (p<.03), triglycerides (p<.001) and also an increase in HDL (p<.02), large HDL subfractions (p<.04), HDL mean size (p<.008) and ApoA1 (p<.03). A trend in the reduction of the nonalcoholic fatty liver disease fat score and lipoprotein insulin resistance score was also observed with lorcaserin (p<.05). These data suggest that lorcaserin effectively reduces body weight while preserving lean mass which is crucial to maintain energy homeostasis during weight loss. Changes in appetite-regulating hormones suggest that counter-regulatory hormonal mechanisms are activated, potentially curbing weight loss and suggesting the need for future combination therapies. Regardless, lorcaserin improved the cardiometabolic profile. Longer-term studies are needed to determine potential reductions in overall risk.

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ISLET BIOLOGY—APOPTOSIS

344-LB

The PET Ligand Florbetapir Binds Pancreatic Islet Amyloid Deposits In Vivo in Mice

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Islet amyloid contributes to β-cell death in the majority of individuals with type 2 diabetes. However, no non-invasive method is available to determine whether islet amyloid is present in individuals with the disease. We therefore determined whether florbetapir, a radiopharmaceutical used for detection of amyloid in the brain, also allows in vivo identification of islet amyloid in hIAPP transgenic mice. In vitro, florbetapir bound hIAPP amyloid fibrils with a Kd of 7.9nM. When applied ex vivo to archived mouse pancreas sections, autoradiographs showed significantly greater florbetapir binding to amyloid-containing vs. amyloid-free islets (16475±5581 arbitrary units in hIAPP transgenic vs. 5762±575 in non-transgenic control pancreas; p<0.05, n=4-5). hIAPP transgenic mice fed a 60% fat diet for one year developed significant islet amyloid deposition compared to control mice (9.3±3.0% vs. 0±0% amyloid area/islet area, assessed histologically p<0.01, n=11). After high fat diet feeding, florbetapir was administered intravenously to hIAPP transgenic and control mice and 90-minute positron emission tomography (PET) scans were performed. Pancreatic florbetapir PET signal peaked 10 minutes post injection but did not differ between genotypes at that time point (2.1±0.3 vs. 2.8±0.3 standardized uptake, p=0.17, n=8-10) or any other throughout the scan. To determine whether in vivo administered florbetapir bound endogenous islet amyloid in these animals, pancreata were excised and florbetapir uptake was determined ex vivo by gamma counting. Pancreatic uptake of florbetapir was highly correlated with the degree of islet amyloid deposition as assessed by histochemistry (r^2=0.84, p<0.001, n=22). Thus, although current methods for PET detection are unable to identify islet amyloid-bound florbetapir in vivo, florbetapir does bind islet amyloid deposits in a specific and quantitative manner. Advances in imaging sensitivity and resolution may allow in vivo detection of islet amyloid in the future.

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345-LB

PREDICT T1D Study: Plasma RNA and Insulin cfDNA Evaluation for Diagnosis of Islet-Cell Death and Progression to Type 1 Diabetes

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Background: Islet β-cell death is central to the development of type 1 diabetes (T1D). We currently lack tools to assess β-cell death prior to clinical onset of T1D. Insulin-coding cell-free (cf) DNA as well as microRNAs have been proposed to be minimally invasive biomarkers of T1D. Profiling of miRs in i) developing human pancreas; ii) plasma of individuals without or with T1D, and iii) in 526 human tissues (including 155 cadaveric donor islets), led to identification of a panel of 50 microRNAs ("PREDICT panel") associated with T1D progression.

Methods: We assessed the expression of insulin-coding cfDNA and PREDICT panel of miRNAs in five different cohorts of individuals at risk of T1D (N=19), at clinical diagnosis of T1D (N=199), within 6 weeks (N=57) or 12-months (N=19) of clinical T1D diagnosis or after 20 years of clinical diagnosis of T1D (N=220). Unmethylated/methylated insulin cfDNA was measured using ddPCR and microRNAs measured using OpenArray™ platform. Sample information was masked.

Results: Although levels of unmethylated and methylated insulin cfDNA were significantly higher in individuals at risk of T1D, these decreased in samples from individuals at clinical diagnosis. In individuals at 6 week and 12 months, the abundance of cfDNA increased to those in high T1D risk group, resulting in a highly significant quadratic trend for unmethylated (p=0.000004) and methylated (p=0.0007) insulin cfDNA. GAD autoantibody titres showed a linear trend with 23 miRNA candidates; their abundance increasing with GADA titres, reflective of islet cell death. Methylated and unmethylated insulin cfDNA, as well as eight candidate miRNAs demonstrated a significant association with HbA1c levels.

Conclusions: The abundance of these circulating molecules shows significantly different profiles in individuals before, during and after T1D diagnosis. They also demonstrate relationships with clinical parameters at diagnosis, including GADA titres and HbA1c.

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346-LB

Transcriptome Analysis of Human Pancreatic Islets and Alpha Cells from Donors with Type 1 Diabetes

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Little is known about biology and pathophysiology of pancreatic islets in type 1 diabetes (T1D) mainly due to the limited availability of human pancreatic tissue for research. To comprehensively define molecular properties of the T1D islets, we performed RNA-sequencing (RNA-seq) analysis on whole islets (n=2; ages 14-20 yrs, 2-7 yrs T1D duration), purified alpha cells (n=3; ages 14-30 yrs, 2-20 yrs T1D duration), and compared them with controls (n=5; ages 26-55 yrs). We focused on alpha cells, since they constitute the majority of T1D islet cell types, and individuals with T1D have impaired glucagon secretion in response to hypoglycemia. In whole islets, RNA-seq analysis revealed upregulated expression of genes associated with immune response, apoptosis and viral defense, whereas genes critical to metabolic processes, ECM formation, cell adhesion, angiogenesis, and neuronal development were downregulated suggesting persistent islet inflammation and

alterations in islet structural, vascular, and neuronal components. T1D alpha cells had increased expression of genes important for the unfolded protein response and tight and adhesive junction formation. Furthermore, T1D alpha cells showed dysregulated expression of several islet-enriched transcription factors (TFs) constituting alpha cell identity (ARX, MAFB, and NKX6-1). RFX6, lying upstream of these TFs, was the most reduced (7.2 fold) and its direct targets including voltage-gated calcium channels (CACNA1A, CACNA1C, CACNA1D), and sulfonylurea receptor 1 (ABCC8) had reduced expression. In addition, T1D alpha cells had reduced expression of GCG, potassium and sodium ion channels, vesicle trafficking proteins, and cAMP signaling molecules.

Our results indicate significant changes at both islet and alpha cell level which collectively may lead to the altered alpha cell glucagon production and secretion in T1D.

347-LB

Identification of Circulating Markers for the Development of Type 1 Diabetes

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Discovery of markers of beta-cell stress provide an opportunity for targeted interference to delay or even prevent impaired beta-cell function or death in diabetes. However, it is unclear if currently available biomarkers, including antibodies or DNAs released by stressed or dead beta cells during the development of type 1 diabetes (T1D), have the necessary sensitivity for early detection of subtle beta-cell abnormalities. In an effort to develop new biomarkers of beta cell dysfunction or death, we utilized NOD mice, NSG-DTR (NOD-scid IL2Rgnull Diphtheria Toxin receptor) mice with human islet transplants, and human plasma to test whether circulating miRNA or metabolites can detect the presence of beta-cell stress. We examined the expression of miRNA in normal and stressed mouse and human islets via RNAseq. These analyses revealed ~60 miRNA molecules (e.g., Let7, Mir7d, Mir22, Mir122, Mir144, Mir185, Mir186, Mir320, Mir375, and Mir486), that were enriched in normal or stressed mouse and human islets. We then utilized PCR to analyze the abundance of these candidate miRNAs in the plasma of NOD mice, in mice with transplanted human islets, and in human subjects who were autoantibody positive, nondiabetic and those with T1D, and found several miRNAs whose level correlated with the development of T1D. For metabolite analyses, we have identified several hundred chemical candidates via Mass-Spectrometry. Interestingly, the increased metabolites of glucose, arginine, and butyrate positively correlated with diabetes development. These findings provide a list of molecules that may serve as biomarkers for onset of T1D.

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348-LB

NAD^+ Enhancement Improves Viability and Function of Pancreatic Beta Cells and Primary Islets

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Loss of pancreatic beta cell mass and function is a key underlying cause for both type 1 and type 2 diabetes. Maintaining NAD^+ level in the beta cell could be key to improve beta cell viability and function during cell stress. Nicotinamide riboside (NR), a Vitamin B3 derivative and a NAD^+ precursor, has been shown to improve metabolic health and glucose tolerance in prediabetic and type 2 diabetic mice. Recently, our lab synthesized novel NR derivatives (NR-Ds) to identify compounds potentially more active than the parent NR. A specific NR-D exhibited pronounced NAD^+ enhancing effects which surpassed the NR effect at the same concentration in beta-cell lines. We further showed that this NR-D could substantially enhance the cellular and mitochondrial NAD^+ levels in beta cells, activate mitochondrial biogenesis and protect the cells from oxidative stress-induced apoptosis. In this study, immortalized beta cell lines and primary islets were used as models. Treatment of NR-D increased NAD^+ level by 3 fold in INS1 cells, and 4 fold in MIN6 cells compared to untreated controls. NAD^+ level was also elevated by NR-D in mitochondria by 4 fold. The NAD^+ enhancement improved beta cell survival when INS1 cells were exposed to the oxidative stress in the form of hydrogen peroxide. In glucose-stimulated insulin secretion tests, both NR and NR-D maintained the insulin secretion level, which was depleted by hydrogen peroxide in INS1 cells. Moreover, NR-D exerted beneficial and protective effects in primary islets. In primary pancreatic islets isolated from rat, treatment of NR-D improved insulin secretion in a dose dependent manner.

In conclusion, our data identifies a specific NR-D that is more potent than NR in enhancing NAD^+ in beta cells, resulting in improved beta cell survival and improved insulin secretion under oxidative stress. We propose that novel NR-Ds could have potential to be developed as therapeutic agents in the prevention and treatment of diabetes.

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ISLET BIOLOGY—BETA CELL—DEVELOPMENT AND POSTNATAL GROWTH

349-LB

Endocrine Plasticity in the Pancreatic Islets of Diabetic Mouse Models

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Lineage tracing studies have revealed that β cells can be dedifferentiated into progenitor-like state or reprogrammed into α-like cells in certain knockout mouse models with diabetes. In addition, it was reported that there were polyhormonal cells, expressing both insulin and glucagon, observed in diabetic mouse models treated with alloxan, a compound to ablate β cells. Although these studies have shown the plasticity of adult β cells under diabetic conditions, the underlying molecular mechanisms remain to be elucidated. To investigate where polyhormonal cells arise from in alloxan-induced diabetic mice, we used a reporter mouse model "βGFP" in which green-fluorescent protein (GFP) is expressed in β-cell lineage after Cre-mediated recombination, and administered alloxan into adult βGFP mice. Immunostaining with alloxan-treated βGFP mice revealed that insulin/glucagon or insulin/somatostatin double-positive cells were co-stained with GFP, showing that these polyhormonal cells were derived from β cells. Furthermore, there were some GFP-expressing cells were positive for glucagon but negative for insulin, suggesting that β-to-α conversion was induced by alloxan. There were no polyhormonal endocrine cells observed in control mice treated with vehicle (saline). It is noted that there were no insulin/glucagon double-positive cells in db/db obese diabetic mice and $Ins2^{Akita}$ insulin-deficient mice. These findings suggest that adult β cells in alloxan-treated mice have a plasticity that allows them to be reprogrammed into polyhormonal cells or to be converted into α-like cells.

350-LB

Prenatal Exposure to Diesel Exhaust $PM_{2.5}$ Programs Offspring Pancreatic Islet Mass and Glucose-Induced Insulin Secretion

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Background: Environmental stressors in early-life causing abnormal fetal and/or neonatal development have been well-known to increase susceptibility to diabetes, known as developmental programming. Rapidly increasing studies have shown that maternal exposure to ambient fine particles ($PM_{2.5}$) correlates to various abnormalities in fetus and neonates as a programming stressor. However, its long-term effect on offspring glucose homeostasis has not yet been systemically investigated. In the present study, we therefore assessed whether maternal exposure to diesel exhaust $PM_{2.5}$ (DEP) programs offspring glucose metabolism.

Methods and Results: Intraperitoneal glucose tolerance test revealed that the adult male offspring of DEP-exposed dams had markedly impaired glucose tolerance (AUC, area under curve: $2.92\pm0.11\times10^4$ vs. $3.71\pm0.21\times10^4$, $p<0.01$, PBS vs. DEP). Unexpectedly, insulin tolerance test did not observe any insulin resistance in these mice (AUC: $1.12\pm0.10\times10^4$ vs.$1.03\pm0.07\times10^4$, $p=0.45$, PBS vs. DEP), suggesting that their glucose intolerance may result from deficits in insulin secretion. Consistent with this, glucose-induced insulin secretion (GIIS) in the adult male offspring of DEP-exposed dams was significantly decreased (AUC: 10.57±0.62 vs. 6.80±0.71, $p<0.01$, PBS vs. DEP). This deficit in GIIS was corroborated by arginine tolerance test (AUC: $3.50\pm0.35\times10^3$ vs. $2.45\pm0.12\times10^3$, $p<0.01$, PBS vs. DEP). The pancreatic weights of PBS and DEP-exposed offspring were comparable (0.136±0.006g vs. 0.145±0.008g, $p=0.36$, PBS vs. DEP). However, histological analysis demonstrated that both number ($2.10\pm0.08\times10^{-7}/\mu m^2$vs. $1.28\pm0.15\times10^{-7}/\mu m^2$, $p<0.01$, PBS vs. DEP) and size ($5.53\pm0.61\times10^4$ μm^2 vs. $3.51\pm0.37\times10^4\mu m^2$, $p<0.05$, PBS vs. DEP) of islets in DEP-exposed offspring were significantly decreased.

Conclusion: Prenatal DEP exposure programs offspring glucose metabolism through impaired insulin secretion, marked with decreased-size islet.

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351-LB

Evaluation of Pancreatic Hormone Expression in Patients with Cystic Fibrosis

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Background: Cystic fibrosis-related diabetes (CFRD) is the most common co-morbidity in people with CF, occurring in 40-50% of adults. Islet destruction, secondary to fibrosis, is associated with significant reductions in endocrine cell mass. In addition, autopsy studies and observations in the null-CFTR ferret model support intrinsic ß-cell-specific pathology. The specific mechanisms underlying ß-cell dysfunction and any potential regeneration remain unclear. Given the primary ductal pathology in CF and accumulating evidence for pancreatic cell plasticity in human diabetes, we aimed to determine the presence and distribution of degranulated endocrine cells (Chromogranin A (ChrA)$^+$/hormone negative (CPHN)) in human CF pancreas.

Methods: Expression of ChrA, insulin and non-ß-cell islet hormones (glucagon, somatostatin and pancreatic polypeptide) was assessed by immunofluorescence staining of pancreatic tissue from 11 deceased donors (1 month-19 years) with CF; and 5 age-matched controls. CPHN cells were characterised as ChrA$^+$/hormone$^-$ and ductal regions confirmed by cytokeratin 19 (CK19) expression.

Results: ChrA$^+$ cells, including CPHN cells, were identified in and around the pancreatic ducts in tissue sections from all patients with CF, a phenotype largely absent in control tissue. All ChrA$^+$ cells were CK19$^-$. Whilst insulin positive cells were infrequent within these ductal regions, a number of endocrine cells (ChrA$^+$) expressed non-ß-cell hormones. Positive glucagon expression in serial sections confirmed an alpha-cell-like phenotype in these duct-associated hormone-positive cells.

Conclusions: Analysis of post mortem human CF pancreatic tissue confirmed abnormal endocrine cell distribution within ductal regions. These cells consist largely of glucagon-positive and CPHN cells, implying possible attempted regeneration. This is in line with recent studies demonstrating ductal derived neo-ß-cell generation via a glucagon-positive intermediate.

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352-LB

Are Alpha, Delta-Cell Mantles around Beta-Cell Clusters Common in Human Pancreatic Islets?

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Pancreatic islets of Langerhans contain endocrine cells, e.g., α, β, and δ cells, that regulate glucose homeostasis. β cells in clusters have 2-fold increased insulin secretion compared to isolated β cells. The precise arrangement of non-β cells around β-cell clusters in large human islets is debated. This architecture has been described variously as mantle-core lobules, mantle-core subunits, random, cloverleafs, and trilaminar plates, among others. Here we quantify this architecture with graph theory to determine how often α,δ cell mantles surround β cell clusters in human islets. The dataset consisted of ~150,000 islets and 2,000,000 α, β, and δ cells imaged from 139 human organ donor pancreata ranging in age from gestation to adult. Graphs consisting of vertices and edges were created for each islet with vertices representing endocrine cells and edges determined by the distance between neighboring cells. Edge existence was based on pair correlation functions, an approach used in crystallography to study distances between atoms. From these graphs we determine if cycles of α,δ cells surround β cells and quantify their occurrence. Our results show subject-specific conserved distances between β cells. The existence of cycles and the number of cycles was dependent on both islet size and cell fraction. Very few islets in our dataset exhibited α,δ cell loops around β cell clusters. It follows that, statistically, most human islets do not show β cell clusters enclosed by α,δ cell loops.

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353-LB

The Role of the Transcription Factor Glis3 in Directing Pancreatic β-Cell Development and Function

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Pancreatic β-cells play a central role in regulating glucose homeostasis, through sensing glucose in the blood and responding to high levels of glucose via insulin secretion. One prominent regulator of both β-cell fate and function is Glis3, a transcription factor with both co-activating and co-repressive roles. Both humans and mice lacking a functional copy of Glis3 are diabetic from birth, with a near complete absence of β-cells. Furthermore, postnatal deletion of Glis3 also results in hyperglycemia, suggesting Glis3 as a critical regulator of postnatal function. Yet, while much is known about the phenotype of Glis3 deletions, little is known about its molecular function. My research focuses on how Glis3 regulates β-cell development and function. To determine which genes are regulated by Glis3, a mouse model with a pancreas-specific deletion of Glis3 was utilized. Microarray analysis of their pancreatic islets revealed 516 genes upregulated and 160 genes downregulated upon deletion of Glis3, and ChIP-seq is under investigation to identify direct targets. However, several genes regulated by Glis3 lack a known function. Prominent among these novel genes were a series of long non-coding RNAs (LncRNAs). LncRNAs are transcribed RNAs >200 nucleotides that are not translated into protein, but have a variety of functions. One particular lncRNA, which we refer to as Glis3 Regulated 1 (G3R1), is restricted in expression to the pancreatic β-cells and the brain. Similarly, an apparent human homolog of G3R1 also exists, and displays the same expression pattern in human tissues. Both Luciferase assays and Chromatin Immunoprecipitation experiments indicate direct regulation of G3R1 by Glis3. We therefore generated a G3R1 knockout mouse for further study. Taken together, our studies of Glis3 gene regulation and of novel lncRNAs within the pancreatic β-cell will lead to a better understanding of how β-cell fate is controlled and maintained, and which genes are essential for postnatal function.

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354-LB

AKT1 Mediates Pancreatic Beta-Cell Growth and Survival upon Mitotic Stimuli

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Diabetes currently affects nearly 10% of U.S. population. Loss of β cell population is featured in diabetic patients. However, the mechanisms regulating β cell population in diabetes, specifically the signaling affecting β cell proliferation and cell death, are not fully understood. We previously found enhanced PI3K/AKT signaling causes enlargement of islet area and better β cell survival upon Streptozotocin (STZ) injury. Here, we further show that one of the protein kinase B (AKT) isoforms, AKT1 but not AKT2, controls β cell growth and death upon mitotic stimuli. We studied rodents with Akt1 and Akt2 gene deletion in β cells and our data shows only AKT1 is required for injury or high fat diet-induced β cell proliferation. Specifically, mice with AKT2 specific deletion in β cells presented normal β cell proliferation after STZ injury but mice with AKT1 deletion showed dramatic β cell regenerative function after STZ injury. Additionally, AKT1 deficient mice have lower islet mass and less β cell proliferation after 8 weeks of high fat diet. However, the cell apoptosis event in AKT1 deficient mice is significantly higher than control mice after 16 weeks of high fat diet. Furthermore, we discovered AKT1 deficiency in β cells increased unfolded protein response (UPR) in β cells at a basal level which is linked to increased β cell death after high fat diet. Inhibiting PI3K/AKT pathway in vitro also caused increased p-eIF2a level and increased cell death upon tunicamycin treatment. Thus, our data shows AKT1 is a key molecule controlling cell proliferation. Also, the deficiency of AKT1 in pancreatic β cells increases the UPR burden and further enhances cell apoptosis.

Supported By: National Institutes of Health; California Institute of Regenerative Medicine

355-LB

WITHDRAWN

ISLET BIOLOGY—BETA CELL—STIMULUS-SECRETION COUPLING AND METABOLISM

356-LB

Molecular Mechanisms of Diabetes Associated with Chronic Arsenic Exposure

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Chronic exposure to inorganic arsenic (iAs), a common drinking water contaminant, has been associated with impaired glucose homeostasis in humans and mice. However, mechanisms underlying these effects remain

unclear. Our previous studies have shown that exposure of isolated murine pancreatic islets to arsenite (iAs^{III}) or its methylated trivalent metabolites, methylarsonite (MAs^{III}) and dimethylarsinite ($DMAs^{III}$), leads to an inhibition of glucose-stimulated insulin secretion. The goal of the present study was to assess the molecular mechanisms underlying these effects. INS-1 823/13 pancreatic β-cells and isolated murine islets were exposed to iAs^{III}, MAs^{III} or $DMAs^{III}$ for 24 or 48 hours. Following exposure, glucose-stimulated insulin secretion was measured, along with mitochondrial oxygen consumption rates (OCR) and calcium influx using Seahorse XF analyzer and fluorescence imaging, respectively.

Glucose-stimulated insulin secretion by INS-1 832/13 cells was significantly inhibited by both iAs^{III} and MAs^{III} at non-cytotoxic doses. OCR was decreased in both INS 832/13 cells and murine islets. Consistent with these findings, iAs^{III} and MAs^{III} also inhibited calcium influx in glucose-stimulated islets. In all assays, methylated arsenics were more potent inhibitors than iAs^{III}.

Mitochondrial respiration, coupled with ATP production, and calcium influx are essential steps in the activation of downstream mechanisms regulating insulin secretion. Our findings suggest that inhibition of mitochondrial respiration and inhibition of calcium influx may be responsible for the impairment of insulin secretion previously observed in pancreatic islets exposed in vitro to iAs^{III} or its methylated metabolites. These results, which are consistent with β-cell dysfunction reported previously in human studies, have potential implications for treatment of arsenic-associated diabetes.

Supported By: National Institutes of Health

357-LB

Gnao Allocates Granules for Storage vs. Secretion via Microtubules

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Beta cells secrete insulin to maintain euglycemia. Yet constant high insulin secretion results in beta-cell failure, partially attributed to insulin biosynthesis-related ER stress. Interestingly, newly synthesized insulin vesicles are preferably secreted for unknown reasons. This results in accumulation of older vesicles that need to be degraded and replenished, further demand extra insulin biosynthesis and exacerbate beta-cell stress. Here we show that inhibitory G alpha protein, Gnao, regulates the secretion rate of new vs. old insulin vesicles. Gnao mutant beta cells secrete a higher portion of older insulin vesicles during GSIS. Consequently, Gnao mutant beta cells maintain a low ER stress despite its potentiated GSIS in normal, high-fat diet fed, and db/db mice. This leads to the preservation of functional beta cells in the prediabetic/diabetic models even at older ages (>15 months) and the prevention of their glucose intolerance and overt diabetes. Moreover, the increased beta-cell function coincides with the preserved proliferation ability of the Gnao mutant beta cells even after one and half-year of age, suggesting delayed senescence in these mutant beta cells. Mechanistically, Gnao inactivation disrupts the normal microtubule network, particularly those that run parallel to the plasma membrane, while chemically induced MT disruption enhances the secretion of older vesicles as well. These results, together with our recent findings that intact microtubule networks reduce insulin secretion by withdrawing vesicles away from the plasma membrane, suggest that Gnao allocates insulin vesicles for storage or release via regulating the beta-cell cytoskeleton. Manipulating its signal can be utilized to enhance beta-cell function while avoiding the hyper insulin secretion-induced cellular stress and failure.

Supported By: National Institutes of Health; JDRF

358-LB

Blockade of Cannabinoid 1 Receptor Improves Pancreatic Beta-Cell Function

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Cannabinoid 1 receptors (CB1Rs) are expressed in peripheral tissues, including islets of Langerhans, where their function(s) is under scrutiny. Using mouse β-cell lines, human islets, and CB1R-null (CB1R-/-) mice, we have now investigated the role of CB1Rs in modulating adenylyl cyclase activity and insulin secretion. We also examined the effect of CB1R on insulin secretion and glucose clearance in CB1R+/+ and CB1R-/- mice by performing an oral glucose tolerance test. Synthetic CB1R agonists diminished GLP-1-mediated cAMP accumulation and insulin secretion as well as glucose-stimulated insulin secretion in mouse β-cell lines and human islets, and genetic blockade of CB1R resulted in an increase of insulin secretion and improved glucose tolerance in response to a glucose load, when compared to control mice. Furthermore, CB1R-/- mice had increased glucokinase and glucose transporter 2 expression in β cells. Our results suggest that CB1R signaling in pancreatic islets may be harnessed to improve β-cell glucose responsiveness and preserve β-cell function in type 2 diabetes. Now, our findings show that blocking peripheral CB1Rs would be beneficial to β-cell function.

359-LB

Cumulative Autophagy Deficiency Causes Progressive β-Cell Failure

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Autophagy has been demonstrated to play a pivotal role in intracellular quality control through degradation of damaged organelles and components. The "βAtg7KO" mice, deficient for Atg7 specifically in β cells, exhibited impaired glucose tolerance, demonstrating the importance of cellular autophagy in β-cell homeostasis and its function. Because βAtg7KO mice lacks Atg7 throughout their lives once insulin promoter was activated in embryonic β cells, their phenotype is a consequence of life-long autophagic failure. Therefore, it was difficult to clarify when and how autophagy deficiency affects β-cell homeostasis. To address this issue, we have generated β-cell specific and inducible knockout mice, MIP-CreER^{TM}: $Atg7^{f/f}$ (iβAtg7KO), by crossing mice carrying an Atg7flox allele with the MIP-CreER^{TM} mice that induce Cre-mediated recombination under the control of mouse insulin promoter (MIP). In iβAtg7KO, autophagy deficiency can be induced in a tamoxifen-inducible manner specifically in β cells. When tamoxifen was administered into 6-week-old iβAtg7KO mice, accumulation of p62 was observed specifically in β cells at the age of 8 weeks, two week after the first tamoxifen injection, suggesting that autophagy failure was induced by tamoxifen as designed. It is noted that these iβAtg7KO mice showed normal glucose intolerance, comparable with control littermates. However, iβAtg7KO mice exhibited severe glucose intolerance with impaired insulin secretion at the age of 12 weeks, 6 weeks after the first tamoxifen injection. Thus, short-term (less than 2 weeks) autophagy deficiency in β cells does not affect glucose profiles, but cumulative defect causes β-cell dysfunction over the course of several weeks, suggesting that cellular autophagy is required for long-term maintenance of β-cell homeostasis.

360-LB

A Novel Multiplex Solution for Islet Hormones

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Most existing multiplex solutions lack the specificity, sensitivity and reproducibility that is needed to generate accurate results. The major benefit of multiplex panels is that you can measure multiple biomarkers with limited sample volume, which is especially beneficial when screening large groups of patients. An accurate multiplex diabetes panel can provide a method to better map the complexity and dynamics of protein levels correlating to the health status of the patient. Our aim was to develop a multiplex diabetes panel to include glucagon, insulin, C-peptide and proinsulin that shows insignificant cross-reactivity and high sensitivity and can be used as a tool to further understand the physiological function and relationship of the islet hormones as biomarkers in diabetes research. The assay should have an easy-to-use format, require a low sample volume and the results should correlate well to established measurement methods. We succeeded in developing a multiplex assay on the Quansys platform that only requires 25 µL of sample volume. Less than 3% cross-reactivity was shown for all of the analytes in the panel. The assay showed dynamic ranges of 5-414 pg/mL (1.4-120 pmol/L) for glucagon, 65-8200 pg/mL (1.5-190 mU/L) for insulin, 300-10500 pg/mL (83-2900 pmol/L) for C-peptide and 7-1181 pg/mL (0.8-130 pmol/L) for proinsulin.

Conclusion: This novel multiplex assay is sensitive and specific for determination of insulin, C-peptide, proinsulin and glucagon. It is an easy-to-use technology that requires a relatively low initial investment in equipment compared to many existing multiplex assays. This is a novel solution for scientists in the metabolic field as it will help them further understand the physiological functions and relationships between four of the most important biomarkers within the field of diabetes.

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Loss of STIM1 and Impaired Beta-Cell Store-Operated Calcium Entry (SOCE) Leads to Decreased ER Ca^{2+} Storage and Insulin Secretion and Increased Beta-Cell ER Stress

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Pancreatic β cell endoplasmic reticulum (ER) Ca^{2+} dyshomeostasis contributes to the pathogenesis of diabetes, however identification of pathways leading to this phenotype remains incomplete. SOCE is a process that serves to refill ER Ca^{2+} stores through reversible gating of plasma membrane Ca^{2+} channels by the ER Ca^{2+} sensor, STIM1. To test whether impaired SOCE contributed to altered regulation of β cell ER Ca^{2+}, we measured β cell STIM1 expression in human and rodent models of diabetes. Results showed reduction of STIM1 mRNA and protein in human islets from donors with T2D, islets from hyperglycemic Akita and streptozotocin-treated mice, and INS-1 cells treated with proinflammatory cytokines and palmitate. To determine how loss of STIM1 impacted β cell function, CRISPR/Cas9 genomic editing was used to create an INS-1 STIM1 knock-out (STIM1KO) cell line. Ca^{2+} imaging revealed significantly impaired SOCE and reduced ER Ca^{2+} levels in STIM1 KO cells compared to wild type INS-1 cells, while glucose-stimulated insulin secretion was reduced by ~50% in STIM1 KO cells. Next, to define whether loss of STIM1 increased β cell ER stress, wild type and STIM1 KO cells were treated with 10 uM tunicamycin (TM). In response to TM, the spliced/unspliced XBP-1 ratio and cleaved caspase-3 expression were significantly increased in STIM KO cells, suggesting that impaired SOCE rendered the β cell more susceptible to ER stress and cell death. Finally, we tested whether STIM1 restoration was sufficient to rescue cell death in response to TM and cytokine stress. Results revealed that adenoviral STIM1 overexpression was sufficient to reduce cleaved caspase-3 levels in response to both cytokines and TM. Together, these results indicate that loss of STIM1 and impaired SOCE lead to ER Ca^{2+} dyshomeostasis and pancreatic β cell dysfunction under diabetic and ER stress conditions.

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Mitochondrial GTP Links Beta-Cell Nutrient Sensing with Differentiation, Health, and Insulin Secretion

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Mechanisms coordinating the metabolism of glucose to the release of insulin in pancreatic beta-cells are intimately related to glucose homeostasis. In vitro deletion of genes involved in the metabolism of mitochondrial GTP (mtGTP) previously identified an important mtGTP-dependent metabolic coupling mechanism. ATP- and GTP-dependent isoforms of the TCA cycle enzyme succinyl-CoA synthetase (SCS-ATP and SCS-GTP) compete for succinyl-CoA that is consumed during substrate-level synthesis of mitochondrial ATP (mtATP) or mtGTP, respectively. To further assess the energy-sensing role of mtGTP in beta-cells, in vitro and in vivo overexpression strategies were developed. Transient, constitutive, and inducible expression of either the SCS-ATP or SCS-GTP isoform in insulinoma cells confirmed a dependence on mtGTP synthesis for both the triggering and amplifying pathways of insulin secretion. The role for mtGTP in insulin secretion was further validated in vivo and in perifused islets via two isoform-specific transgenic models we have termed "tetracycline regulated beta-cell specific succinyl CoA synthetase" (TaBaSCo) mice. Insulin secretion was enhanced in insulinoma cells overexpressing SCS-GTP in the presence of various nutrients, metabolites and pharmacological agents. In addition, elevated mtGTP synthesis increased total insulin content, promoted cellular differentiation and protection from glucolipotoxicity, in vitro. This relationship between insulin secretion and SCS-GTP expression did not correlate with the cellular redox potential or oxidative phosphorylation, but was associated with increases in cytosolic calcium. Taken together, these data highlight an important mtGTP-dependent role in beta-cell nutrient sensing and for maintaining islet health.

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ER Calcium Dyshomeostasis and ER Stress Lead to Impaired Proprotein Convertase Subtilisin/Kexin Type 1 (PC1/3) Maturation in the Pancreatic β Cell

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Impaired proinsulin processing is observed in type 1 and type 2 diabetes. We have previously reported that proinsulin processing is altered in islets from SERCA2b haploinsufficient mice (S2Het) and SERCA2KO INS1 cells (S2KO), however the relationship between ER calcium dyshomeostasis and impaired proinsulin maturation remains incompletely understood. Proinsulin is processed sequentially within the secretory granules by the enzymes, PC1/3, proprotein convertase 2 (PC2), and carboxypeptidase E (CPE). We first tested whether expression of these enzymes was altered in islets from S2Het mice and in S2KO cells. Our results identified a specific loss of PC1/3 mRNA and protein without alterations in the expression of PC2 or CPE. Furthermore, immunoblot analysis revealed decreased expression of the 66 kDa high active form of PC1/3 and increased levels of the 87 kDa low active form in S2KO cells. Moreover, restoration of SERCA2b via adenoviral transduction in S2KO cells was sufficient to restore PC1/3 processing and increase expression of the 66 kDa high active form. To test this in a second model of ER stress, wild type INS-1 cells were treated with 10 μM tunicamycin, which led to a time-dependent loss of ER calcium and activation of ER stress signaling as well as increased expression of the 87 kDa active form and reduced expression of the 66 kDa form of PC 1/3. Taken together, these data indicate that ER stress arising from alterations in ER calcium reduces proinsulin processing through decreased PC1/3 maturation and expression.

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Imaging Whole-Pancreas Insulin Secretion Live after Liraglutide Treatment of Mice

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Liraglutide (a GLP-1 analogue) is known to stimulate glucose-dependent insulin secretion. However, technical limitations have made it difficult to say whether this effect is spread across all pancreatic β-cells or whether there are specific populations that are particularly responsive in vivo. We used a recently described CpepSfGFP transgenic mouse, which expresses a Superfolder-GFP embedded within the C-peptide of human proinsulin. This allows for visualization of C-peptide molecules co-stored with insulin in individual islets in vivo in live animals. This reporter can be monitored in real time after a glucose challenge. Sedated mice (n=5) were pretreated with either liraglutide (800 μg/kg) or saline. The tail and body of the pancreas were externalized and placed on a warmed slide for imaging under a microscope. 75 mg of glucose was then administered by gastric infusion. Insulin content per islet was followed over time through the CpepSfGFP fluorescence by imaging every 5 minutes. The changes in relative fluorescence intensity within each individual islet allowed the quantification of the effects of the glucose challenge from up to ~100 individual islets per mouse. Circulating insulin was also measured in paralle at 15 minutes. We found that liraglutide treatment increased plasma insulin 3 fold (p=0.029, t-test). Interestingly, a proportion of the large islets in the liraglutide treated mice showed increased fluorescence over time resulting in less overall decrease in insulin content in these mice (p=0.0482 for effect of treatment, 2 way ANOVA with % of baseline insulin content and quartile start content as parameters). This surprising result may imply that liraglutide is capable of inducing insulin synthesis causing the islets to increase their content over short timespans even while secretion is taking place.

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Angiopoietin-1 Contributes to the Glucose Homeostasis by Regulating Insulin Secretion in Diet-Induced Obesity Mice Model

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Background and Objective: Islet is composed not only of endocrine cells but also of blood vessels. The vessels are key contributors of endocrine cell development and the islets are highly vascularized in response to the body glucose change, resulting in prompt insulin secretion. Angiopoietin-1 (Ang1) is a potent angiogenic and antiinflammatory factor that drives its signal via the Tie2 receptor on endothelial cells. Here, we investigated the role of Ang1 on glucose homeostasis and the mechanism underlying it.

Methods: We used inducible systemic Ang1 knockout (KO) mice (Rosa26-Cre^{ERT2}/$Ang1^{fl/fl}$, $Ang1^{KO}$) and ß-cell-specific Ang1 KO mice (Rip-Cre/$Ang1^{fl/fl}$,

Ang1$^{\Delta\beta\ cell}$). We analyzed the insulin secretion from islets and the islet morphology after 24 weeks of high fat diet.

Results: High fat diet for 24 weeks after systemic deletion of Ang1 induced glucose intolerance in Ang1^{KO} compared to wild type mice but no change of insulin sensitivity. The serum insulin level after glucose challenge was lower in the Ang1^{KO} mice, suggesting a defect in insulin secretion in the Ang1^{KO} mice. These glucose homeostasis features were identical in Ang1$^{\Delta\beta\ cell}$ mice in vivo and in isolated islets of Ang1$^{\Delta\beta\ cell}$ mice after 24 weeks of high fat diet. On morphometric analysis, the insulin-positive area and the vasculature density was similar between the Ang1$^{\Delta\beta\ cell}$ and the control mice. However, the pericyte-covered area was significantly sparse in the islets of Ang1$^{\Delta\beta\ cell}$ mice, which was associated with defective penetration and increased caveolae of the endothelial cells. There was also significant infiltration of inflammatory cells in the islets of Ang1$^{\Delta\beta\ cell}$ mice.

Conclusion: Ang1 is a key molecule that regulates insulin secretion from islets in response to glucose by modulating endothelial cell microstructure/function and by protection from inflammation.

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366-LB

Glucose Uptake within Intact Islets Is Significantly Impaired in Type 2 Diabetes

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The ability to sense and respond to glucose is a hallmark of pancreatic beta cell function that breaks down in diabetes. Studying glucose transporter (GLUT)-mediated glucose uptake in pancreatic islets is therefore of great interest. However, this has never been directly measured in intact islets; past efforts have focused on beta cell lines or single beta cells in culture. To overcome this barrier, we devised a method to detect glucose uptake within intact pancreatic islets in real-time with subcellular resolution. To quantify glucose uptake within the islet, we apply the green fluorescent derivative 6-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino]-2-deoxy-D-glucose (6-NBDG) as a tracer to mIns1-H2b-mCherry transgenic reporter islets, where all beta cells are labelled with a red nucleus. The interstitial space is filled instantly upon 6-NBDG addition, gradually followed by the cytoplasm of beta cells. Uptake of 6-NBDG is inhibited dose-dependently by glucose and the GLUT2 inhibitor phloretin, which validates the specificity of our approach. We confirmed our hypothesis that glucose uptake by beta cells of leptin-deficient (ob/ob), type 2 diabetic beta cells is significantly impaired, compared to beta cells within lean control islets. Furthermore, we observe a substantial degree of functional heterogeneity in lean islets, with regards to their rate and quantity of glucose uptake. To our surprise, this degree of functional heterogeneity is significantly smaller in beta cells of islets from diabetic mice, with beta cells that take up glucose rapidly becoming sparse.

We conclude that the ability to study glucose uptake is a powerful readout of beta cell function that can be applied in real-time to assess beta cell function within intact rodent and human islets.

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Glucose-Lowering Effects of DPP-4 Inhibitors Require β-Cell Incretin Receptors

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Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are released from the intestine after eating and stimulate insulin secretion. However, oral glucose tolerance (OGT) is not impaired by single elimination of either incretin receptor in β cells, consistent with compensation by one incretin for the other. To test this possibility β cell-specific double incretin receptor knockout (βDIRKO) mice were given glucose gavages and OGT compared to controls. βDIRKO mice significantly increased glucose excursions in response to oral glucose, suggesting that both β cell incretin receptors are required for normal postprandial homeostasis. Dipeptidyl peptidase-4 inhibitors (DPP-4i) are new drugs for diabetes that prevent inactivation of the incretins and prolong their insulinotropic effects. Previous work showed that elimination of the incretin receptors singly did not affect the glucose lowering action of DPP-4i; this effect also implies mutual incretin compensation. A DPP-4i (sitagliptin) lowered glucose levels during an OGTT in control mice, but had no impact on glycemia in βDIRKO mice, further supporting cooperative actions of the incretins. Surprisingly, these findings were replicated when the DPP-4i was administered prior to an IPGTT, a setting in which GIP and GLP-1 levels are low and unchanging. This result suggests that incretin release from the intestine is not necessary for the glucose-lowering effects of DPP-4i and that protection of the incretins at an extra-vascular site accounts for this action. One possibility is GLP-1 produced locally within the islet. In support of this, islets from WT mice perifused with sitagliptin had increased insulin production in response to high-glucose alone, and with GLP-1, compared to islets not receiving DPP-4i. These findings indicate that parallel activity of β cell incretin receptors is essential for normal OGT and the response to DPP-4 inhibition, and support islet DPP-4 as an effective target to promote GLP-1 activity.

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In Vivo Loss of Beta-Cell Drp1 Impairs Insulin Secretion and Mitochondrial Content

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Mitochondria are dynamic organelles that rely on a balance between the reciprocal processes of mitochondrial fission and fusion to maintain normal mitochondrial morphology. Mitochondrial fission is initiated by binding of the GTPase dynamin related protein 1 (Drp1) to receptor proteins on the outer mitochondrial membrane in response to various stimuli, where Drp1 then oligomerizes and constricts to produce two daughter mitochondria. Prior studies using chemical inhibitors, dominant negative proteins and/or transformed cell lines have shown that pancreatic beta-cells appear to require Drp1-dependent mitochondrial fission to carry out proper glucose-stimulated insulin secretion (GSIS), and to undergo apoptosis in response to various noxious stimuli. However, the role of Drp1 in maintaining beta-cell function in vivo remains unexplored. In this study, we utilized the Ins1(Cre) knock-in line to generate mice lacking beta-cell Drp1 expression (Drp1β-KO mice). Drp1β-KO mice became glucose intolerant and had drastically reduced plasma insulin levels in response to glucose challenge when compared to Drp1β-WT littermates. Drp1β-KO islets displayed normal gross morphology, but contained highly fused beta-cell mitochondria. In vitro, Drp1β-KO islets secreted reduced amounts of insulin in response to glucose stimulation, but showed a normal secretory response to depolarizing stimuli. In contrast to previous studies using chemical inhibitors, Drp1β-KO islets had reduced mitochondrial DNA content and showed reduced expression of electron transport chain components. Oxygen consumption by Drp1β-KO islets was higher than littermate controls due to increased proton leak. Unexpectedly, we observed an intermediate glucose tolerance phenotype in female, but not male Drp1β-Het mice. These results indicate an important role for Drp1 in regulating beta-cell insulin secretion and mitochondrial content in vivo.

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Comparison of Plasma Glucagon Kinetics between RIA and ELISA Platforms

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Method comparisons were performed for glucagon between Mercodia ELISA, Millipore RIA, and Luminex. Kinetic responses were compared between endogenous glucagon (meal or fatty acid challenge) and infused glucagon with somatostatin suppression. Time course patterns between RIA and ELISA were superimposable. However, RIA concentrations were greater by an average of 16 to 76%. The greatest differences were with endogenous glucagon as compared to exogenous glucagon. Exogenous glucagon was 16 to 38% greater with RIA compared to ELISA, whereas endogenous glucagon was 69 to 76% greater with RIA. In addition, the spread of values for a given time point was greater with RIA vs. ELISA and these differences were greatest for endogenous vs. exogenous glucagon. For instance, the average max/min difference across all time points was 66.5 (meal challenge) and 102 (fatty acid challenge) with RIA vs. 30.5 (meal challenge) and 59 (fatty acid challenge) with ELISA: a percent difference between assays of 54.2% (meal challenge) and 43% (fatty acid challenge). The exogenous glucagon average min/max difference across all time points was 76 for RIA vs. 64.6 for ELISA: a percent difference between assays of 15%. These data imply that a glucagon-like peptides generated in vivo cross react to a greater extent in the RIA than in the ELISA. In support, dilutional linearity is obtainable with ELISA but not with RIA. Furthermore, a significant concentration of apparent glucagon is detected in a commercially available QC material in the RIA but not in the ELISA, but this material is not supplemented with glucagon. Lastly, the Luminex assay, which incorporates extraction, shows better correlation with the ELISA than with RIA. These differences could not be attributed to the standard curves between the assays. When RIA calibrators are included as "unknowns" on the ELISA, observed concentrations are virtually identical with target concentrations. Furthermore, QC from each kit report target values when assayed by the opposing kit.

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ISLET BIOLOGY—SIGNAL TRANSDUCTION

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11beta-Hydroxysteroid Dehydrogenase (HSD11b1) Revealed by Comparative Transcriptomics as a Novel Pancreatic Islet "Disallowed" Gene

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Transcriptomic comparisons have been useful in identifying genes which are selectively repressed, or "disallowed", in pancreatic islets compared to other tissues. In order to explore the possibility that distinct disallowed gene sets may exist in separate islet cell types, we have analyzed massive parallel sequencing (RNASeq) data from purified mouse and human islet endocrine cells. This approach demonstrates firstly that Igf1, Yap1 and Igfbp4 are expressed at substantially lower levels in beta vs. alpha cells. As these genes are involved in cell growth, their absence may contribute to the low rates of proliferation usually seen in adult beta cells, with relatively higher rates in alpha cells. Moreover, the monoacylglycerol (MAG) lipase LgIl is expressed at low levels in both beta and alpha cells, consistent with a role for MAG in stimulation-secretion coupling. Unexpectedly, we identify mRNA encoding 11β-hydroxysteroid dehydrogenase (Hsd11b1) as strongly repressed in all three islet endocrine cell types examined (alpha, beta, delta), suggesting that within the intact islet this enzyme is largely expressed in islet non-endocrine cells. HSD11b1 converts an inactive precursor (cortisone in man or 11-dehydroxycortosol in rodents) to active cortisol (or corticosterone, respectively). The absence of HSD11b1 may therefore limit the deleterious actions of glucocorticoids on the secretion of insulin or other islet hormones by preventing the local activation of precursors. However, since modest over-expression of Hsd11b1 in beta cells promotes islet growth (Turban et al Diabetes 10.2337/db11-1054) we suggest that low levels of this enzyme may also restrict adaptive responses to beta cell stress. Hsd11b1 and other disallowed genes may therefore provide novel targets for intervention in T2D.

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371-LB

Estradiol-17Beta-Induced Beta-Cell Proliferation in Human Islets Is Foxo1 Dependent

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Estradiol-17beta (E2) via its cognate receptor ERα and the Foxo1 transcription factor have been implicated, individually, in β-cell development and proliferation. Association between Foxo1 and ERα has been shown to affect cell cycle in classic E2 responsive tissues, but has not been studied in β-cells. We therefore examined the Foxo1 dependent proliferative effect of E2 in rodent cell lines and human islets. Effect of E2 on β-cell proliferation was assessed by 3[H]-thymidine incorporation in the insulinoma cell lines INS1-E and MIN6 (rat and mouse respectively) and in human islets (n≥4). Treatment with E2 for 24h induced a 3 fold increase in ^{3}[H]-thymidine incorporation in INS1-E cells ($p<0.001$) and a 2 fold increase in MIN6 cells and in human islets ($p<0.01$). Knock down (KD) of Foxo1 expression in INS1-E cells (by siRNA; 60% reduction) increased basal proliferation by 38±16% ($p<0.05$), but abrogated the proliferative effect of E2. High glucose (HG; 25mM) maintained its proliferative effect in the KD cells, suggesting that Foxo1 KD does not impair or saturate INS1-E proliferative capacity. In human islets, transcriptional activity of endogenous Foxo1 was inhibited using a selective Foxo1 inhibitor (AS1842856; 0.033μM). Foxo1 inhibition did not change basal proliferation but prevented E2 induced proliferation (proliferation in treated vs. control islets increased by 22 ± 17%, $p=0.14$). Foxo1 inhibition did not hamper HG induced proliferation ($p< 0.01$). Activity of Foxo1 is regulated by its phosphorylation state. In order to further support an E2-Foxo1 pathway in β-cells we examined the effect of E2 30nM on Foxo1 phosphorylation. In INS1-E and human islets, E2 increased the ratio of pFoxo1 to total-Foxo1 by 4 and 1.6 folds respectively ($p<0.05$). Our findings support a novel co-operation in β-cells, between E2 and Foxo1. This may have implications on the interaction between diabetes and the estrogen status, such as encountered in gestational and postmenopausal DM and on cell targeted therapy.

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372-LB

Elevated Levels of miR-21 in Circulating Extracellular Vesicles Predate Onset of Type 1 Diabetes

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Early detection of developing type 1 diabetes (T1D), before widespread loss of β cell mass, is needed for improved outcomes of T1D prevention strategies. MicroRNAs (miRNAs) released in extracellular vesicles (EVs) have been proposed as ideal biomarkers due to their stability and feasibility of detection. Previous studies from our lab showed increased miR-21 expression in rodent β cells and cultured human islets exposed to inflammatory cytokines, and miR-21 was found to be overexpressed in the islets of diabetic NOD mice as compared to NOR controls. miR-21 was also increased in the EVs from the β cells and cultured human islets in response to cytokine treatment, and elevations in the levels of circulating EV miR-21 were found to precede onset of diabetes in NOD mice. We hypothesized that, as with our preclinical data, elevations in EV miR-21 may be present in the circulation of T1D patients at the time of diagnosis. EVs were isolated from serum of pediatric new-onset T1D patients (n=19) and age-matched healthy controls (n=16) using ExoQuick reagent, and quantified using RT-qPCR. Statistical analyses of miR-21 levels in patient samples were performed using non-parametric Mann-Whitney U test. Spearman's correlation analyses were used to measure monotonic relationships between miR-21 relative quantity and age or BMI. We found that the levels of miR-21 were significantly increased in circulating EVs from T1D patients compared to age-matched controls. Intriguingly, the levels of total serum miR-21 were significantly higher in the serum from healthy patients, suggesting that elevations in miR-21 levels are specific to circulating EVs. Serum EV miR-21 levels were negatively correlated with age of healthy subjects ($p=0.0474$, $r=-0.506$), but no such correlation was discovered with T1D samples, and no correlations with BMI were found. Ongoing studies will further define relationships between EV miR-21 content and β cell inflammation and death and verify our findings in additional human samples.

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373-LB

Effect of High-Fat Diet (HFD) on Beta-Cell Proliferation in Mice

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Hyperglycemia and hyperlipidemia are two major hallmarks of type 2 diabetes. Pancreatic β cells are exposed to high levels of free fatty acids (FFAs)/lipids along with glucose during diabetes development. 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 lipids influence islet mass by using High Fat Diet (HFD) mice model and Palmitic Acid (PA) treatment in INS-1 cell line. My data indicates that β cell proliferation is significantly upregulated after short-term exposure of HFD, which is accompanied by both hyperglycemia and hyperlipidemia. This β cell proliferation is due to up-regulation of Cyclin D2 in mice islets. Our in vitro PA treatment results further demonstrated that Cyclin D2 induction is regulated by the lipid mediated activation of mTOR pathway. RNA seq analysis of the islets from HFD vs. control fed mice support significant enrichment of the genes involved in the mTOR pathway. Additionally, treatment of mice with rapamycin (mTOR inhibitor) abolished HFD mediated proliferative effect. Together, our data identifies mTOR as the regulator of HFD mediated β cell proliferation.

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