Late Breaking Abstracts

July 2018 | Volume 67 | Suppl. 1A | www.diabetes.org/diabetes

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78TH SCIENTIFIC SESSIONS

ORLANDO, FL • JUNE 22 – 26, 2018

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Moderated Poster Discussion: Evolving Concepts in Clinical Management Strategies *(Posters 1-LB to 6-LB)*

1-LB

NGM282 Significantly Reduces Hepatic Steatosis Independent of 2 Diabetes (T2D) Status or Statin Usage—Results from a Phase 2 Trial in Patients with Nonalcoholic Steatohepatitis (NASH)

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Background: NGM282 is an engineered variant of human FGF-19 that retains bile acid and metabolic regulatory activities while eliminating the tumorigenic effects of FGF-19. Multiple preclinical models showed improvements in NASH liver histology similar to those observed post-bariatric surgery. Data from a Phase 2 trial in NASH patients showed significant reductions in hepatic steatosis, liver transaminases and markers of fibrosis that were translated to histologic benefits in NASH. Both T2D status and statin therapy have been variably associated with treatment response in NASH trials. This analysis assessed NGM282 impact on liver fat content by T2D status and statin usage.

Methods: Patients with biopsy-confirmed NASH (n=82) were randomized to NGM282 3 or 6mg or placebo for 12 weeks. The primary endpoint was ≥5% reduction in absolute liver fat content (LFC) by MRI-PDFF. Patients were stratified by T2D status at baseline and categorized as statin/no statin use (3 months prior to screening). Statin therapy was stable during the study. Treatment responses were analyzed using an ANCOVA model; NGM282 treatment arms were pooled (n=53).

Results: T2D and statin use was present in 62% and 45% of the NGM282 treated patients, respectively. There was no significant difference in LFC reduction in patients with T2D vs. no T2D (-10.4% vs.-11.2%, p=0.59) or statin use vs. no statin use (-10.7% vs. -10.7%, p=0.99) at baseline. Absolute LFC was decreased by -9.7% and -11.9% for NGM 282 3 and 6mg (p<0.001 for both), respectively. Reductions in LFC correlated with improvements in C4, HbA1c and triglycerides.

Conclusions: NGM282 is highly effective in reducing LFC, independent of T2D status or statin use. These data support the activity of NGM282 in NASH across a broad patient population. Ongoing studies will evaluate the translation of these effects into improvements in fibrosis and resolution of NASH.

2-LB

Effect and Safety of Oral Semaglutide Monotherapy in Type 2 Diabetes—PIONEER 1 Trial

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Oral semaglutide (sema), the first GLP-1 receptor agonist in a tablet formulation, is in late-stage development for the treatment of T2D. The effect and safety of oral sema (3, 7, or 14 mg once daily) was assessed in this randomized, double-blind, placebo-controlled phase 3a trial in drug-naïve patients with T2D uncontrolled on diet and exercise (n=703). Primary endpoint was change from baseline in HbA_{1c} at week 26. The primary estimand (treatment policy) evaluated the effect regardless of trial product discontinuation or rescue medication use (effectiveness). A secondary estimand (hypothetical) evaluated the effect of trial product while on treatment without rescue medication (efficacy) using a mixed model for repeated measures (MMRM), and is the method used in many previous T2D studies. Oral sema resulted in clinically meaningful reductions in both HbA_{1c} (all doses) and body weight (higher doses) at week 26 (Table). Adverse events (AEs) occurred in 58, 53 and 57% for 3, 7 and 14 mg oral sema, respectively, and 56% with placebo. The most common AE with oral sema was transient mild or moderate nausea. Nausea occurred in 5-16% of patients with oral sema vs. 6% with placebo. Oral sema demonstrated superiority vs. placebo in reducing HbA_{1c} (all dose levels) and body weight (14 mg) and was well tolerated in T2D uncontrolled on diet and exercise (ClinicalTrials.gov NCT02906930).

Table.

	Oral semaglutide			
	3 mg (n=175)	7 mg (n=175)	14 mg (n=175)	Placebo (n=178)
KEY BASELINE CHARACTERISTICS				
Female, n (%)	86 (49.1)	82 (46.9)	89 (50.9)	89 (50.0)
Age, y	55	56	54	54
Diabetes duration, y	3.8	3.6	3.4	3.4
HbA_{1c}, %	7.9	8.0	8.0	7.9
Body weight, kg	86.9	89.0	88.1	88.6
ENDPOINTS AT WEEK 26 BY ESTIMAND				
	PRIMARY / SECONDARY	PRIMARY / SECONDARY	PRIMARY / SECONDARY	PRIMARY / SECONDARY
Change from baseline in HbA_{1c}, %-points ± SE (primary endpoint)	-0.9 ± 0.1 / -0.8 ± 0.1	-1.2 ± 0.1 / -1.3 ± 0.1	-1.4 ± 0.1 / -1.5 ± 0.1	-0.3 ± 0.1 / -0.1 ± 0.1
HbA_{1c} (%-points) treatment difference vs placebo [95%CI]	-0.6‡ [-0.8; -0.4] / -0.7‡ [-0.9; -0.5]	-0.9‡ [-1.1; -0.6] / -1.2‡ [-1.5; -1.0]	-1.1‡ [-1.3; -0.9] / -1.4‡ [-1.7; -1.2]	
Change from baseline in body weight, kg ± SE (secondary confirmatory endpoint)	-1.5 ± 0.3 / -1.7 ± 0.3	-2.3 ± 0.4 / -2.5 ± 0.3	-3.7 ± 0.3 / -4.1 ± 0.3	-1.4 ± 0.3 / -1.5 ± 0.3
Weight (kg) treatment difference vs placebo [95%CI]	-0.1 [-0.9; 0.8] / -0.2 [-1.0; 0.6]	-0.9 [-1.9; 0.1] / -1.0* [-1.8; -0.2]	-2.3‡ [-3.1; -1.5] / -2.6‡ [-3.4; -1.8]	
Proportion of subjects with HbA_{1c} <7%, %	55.1‡ / 59.1‡	68.8‡ / 71.9‡	76.9‡ / 80.3‡	31.0 / 33.8
Proportion of subjects with weight loss ≥5%, %	19.6 / 21.3	26.9* / 28.7*	41.3‡ / 44.3‡	14.9 / 15.7

n, number of randomized subjects in the full analysis set; SE, standard error; *p<0.05; ‡p<0.001 vs placebo. Baseline data are means unless specified otherwise. Changes and treatment differences are LSmeans; proportions are observed. The primary and confirmatory secondary endpoints were controlled for multiplicity for the primary estimand. The primary estimand (treatment policy) was evaluated by a pattern-mixture model using multiple imputation to handle missing data. The secondary estimand (hypothetical) was evaluated by a MMRM.

3-LB

Liraglutide as an Additional Treatment to Insulin in Patients with Type 1 Diabetes Mellitus—A 52-Week Randomized Double-Blinded Placebo-Controlled Clinical Trial

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We have previously demonstrated that a 12-week addition of liraglutide to insulin therapy in patients with type 1 diabetes (T1D) results in an improvement in glycemic control, weight loss and a reduction in systolic blood pressure (SBP). We have now conducted a 1 year randomized study investigating effects of liraglutide in patients with T1DM. All patients had T1D for at least one year, were on insulin therapy and had no detectable c-peptide in plasma (mean BMI: 28.9±1.4kg/m^2, mean HbA1c: 7.82±0.16%, mean age: 46.7±1.9 years, mean age of T1D diagnosis: 22.3±1.7 years). They were randomized to receive placebo, (n=20) or 1.8mg Liraglutide (n= 26) daily for 52 weeks. Continues glucose monitoring (CGM) was performed for 4 weeks before and at end of treatment. At the end of 52 weeks treatment with liraglutide, placebo adjusted HbA1c fell significantly by 0.57±0.17% (p=0.006 vs. placebo) from 7.920.15± to 7.45±0.12% (p=0.009). Weekly placebo adjusted average blood glucose fell by 15±4mg/dl (p=0.014 vs. placebo) from 174±5 to 156±6mg/dl (p=0.021) and fasting weekly glucose fell by 8±7mg/dl (p=0.075 vs. placebo) from 165±7 to 153±9mg/dl (p=0.032). There was no change in reported incidences of hypoglycemia and no change in percent time spent below 70mg/dl based on CGM. Total insulin dose did not alter. There was a significant weight loss by 2.5±0.9kg (placebo adjusted, p=0.041 vs. placebo) from 83.6±4.1 to 80.5±4.0kg (p=0.01) in the liraglutide group. Placebo corrected SBP also fell following liraglutide treatment by 9±3mmHg (p=0.031) from 128±3 to 122±3 mmHg while placebo adjusted diastolic BP fell by 5±1mmHg from (79±2 to 75±2mmHg). We conclude that the addition of liraglutide to insulin treatment in type 1 diabetes significantly reduced HbA1c, mean and fasting blood glucose, blood pressure and body weight without significant increase in hypoglycemia.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases

4-LB

Canagliflozin (CANA) vs. Other Antihyperglycemic Agents on the Risk of Below-Knee Amputation (BKA) for Patients with T2DM—A Real-World Analysis of >700,000 U.S. Patients

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Sodium glucose co-transporter 2 inhibitors (SGLT2i) are indicated for treatment of T2DM; some SGLT2i have reported a CV benefit and some reported a risk of BKA. U.S. claims databases were analyzed using a prespecified protocol to examine CANA-associated effects on BKA and hospitalization for heart failure (HHF) vs. other SGLT2i and non-SGLT2i. Analyses used a propensity score adjusted new user design with numerous sensitivity analyses. The 4 databases included 142K new users of CANA, 110K of other SGLT2i, and 460K of non-SGLT2i AHAs. Meta-analysis results are reported when heterogeneity across databases was not substantial (I^2 <0.4). There was no evidence of increased risk of BKA with CANA vs. non-SGLT2i or other SGLT2i in on-treatment or ITT analyses (Table). HHF benefits were demonstrated in

these analyses, consistent with clinical trials. Similar BKA and HHF results were seen in a subgroup with established CV disease. In this large comprehensive analysis, neither CANA nor other SGLT2i showed an increased risk of amputation vs. non-SGLT2i. Because on-treatment median exposure was <6 months, future observational studies with longer duration are needed. This study helps to further characterize the potential benefits and harms of SGLT2i as observed in routine clinical practice to complement the evidence from clinical trials and prior observational studies.

Table. Risk of BKA and HHF in the overall population.*

				On-treatment†					Intent-to-treat (ITT)‡				
		Exposure (n/PY)		Outcomes, n					Outcomes, n				
Outcome	Comparison	CANA	Comp	CANA	Comp	HR (95% CI)	p value	Cal p value§	CANA	Comp	HR (95% CI)	p value	Cal p value§
BKA	CANA vs non-SGLT2i	111,332/ 53,125	445,367/ 256,646	60	481	0.75 (0.40-1.41)	0.25	0.30	295	1,308	1.01 (0.93-1.10)	0.71	0.51
	CANA vs other SGLT2i	69,554/ 31,369	98,169/ 41,666	40	53	1.14 (0.67-1.93)	0.48	0.53	171	209	1.13 (0.99-1.29)	0.06	0.06
HHF	CANA vs non-SGLT2i	111,332/ 53,116	445,367/ 255,504	124	2,979	0.39 (0.26-0.60)	0.01	0.00	810	7,081	**	–	–
	CANA vs other SGLT2i	69,554/ 31,363	98,169/ 41,667	56	73	0.90 (0.71-1.13)	0.22	0.28	352	381	1.07 (0.95-1.20)	0.16	0.32

PY, patient-years; Comp, comparator; Cal, calibrated; HR, hazard ratio; CI, confidence interval.
*Time-to-first-post-index-event analysis using variable-ratio propensity score matching.
†'On treatment' period was defined as the time from 1 day after exposure to all days through the period of persistent exposure allowing for 30 day gap between successive exposures until the final exposure record. The time will be censored if the patient starts a non-metformin antihyperglycemic agent other than the cohort defining drug(s).
‡'Intent-to-treat' (ITT) period was defined as the time from 1 day after exposure to the last day of observation available in the database.
§A set of negative control outcomes were used to calibrate p values to control for any potential systematic errors after propensity score adjustment.
**Meta-analytic estimate was not imputed due to observed heterogeneity (I^2 = 0.59). HR (95% CI) in the 4 databases were: 0.63 (0.52-0.75), 0.94 (0.70-1.25), 0.83 (0.69-1.00), and 0.73 (0.63-0.83).

Supported By: Janssen Research & Development, LLC

5-LB

Sotagliflozin in Combination with Optimized Insulin Therapy Reduced HbA1c Levels with a Decreased Daily Insulin Requirement after 52 Weeks in Adults with T1D

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In most patients with T1D, adequate glycemic control is not achieved with insulin therapy alone, and intensifying insulin therapy can increase the risk of hypoglycemia. Sotagliflozin (SOTA) is a dual SGLT1 and SGLT2 inhibitor, which blunts and delays postprandial hyperglycemia and reduces renal glucose reabsorption. In two 52 weeks phase 3 studies adults with T1D were randomized 1:1:1 to placebo + insulin (PBO), SOTA 200 mg + insulin or SOTA 400 mg + insulin, once daily, after 6 weeks of insulin therapy optimization. HbA1c change over 52 weeks, along with change of daily insulin dose and safety, were assessed using a pooled analysis. Significant HbA1c reductions were observed with SOTA 200 or 400 vs. PBO at week 24 and sustained to 52 weeks, with a concomitant decrease in total daily insulin dose, mainly due to reduction in bolus insulin (BI), as 70-80% of the total insulin reduction was from BI for both SOTA doses. At 52 weeks, patients in SOTA groups had a lower incidence of severe hypo (SH) but more genital mycotic infections, DKA and diarrhea than PBO.

In conclusion, SOTA demonstrated additional and sustained reduction of HbA1c on top of optimized insulin while reducing total daily insulin dose (mainly BI doses), with less incidence of SH. This may be an additional therapy for patients with T1D without good glycemic control despite optimized insulin therapy.

Table. Pooled Efficacy and Safety Results from Randomization to Week 52 on a Background of Optimized Insulin Therapy inTandem1 and 2 (inTandem1, NCT02384941 and inTandem2, NCT02421510).

	Placebo n=526	SOTA 200 mg n=524	SOTA 400 mg n=525
Baseline Characteristics			
Age (mean [s.d])	42.5 (13.3)	44.4 (13.7)	44.0 (13.4)
BMI mg/m^2 (mean [s.d.])	28.54 (5.28)	28.89 (5.56)	28.74 (5.18)
HbA1c (%) (mean [s.d.])	7.66 (0.81)	7.68 (0.77)	7.64 (0.78)
Total insulin dose (IU) (mean [s.d.])	64.4 (36.6)	62.7 (36.6)	62.8 (33.5)
Bolus insulin dose (IU) (mean [s.d.])	31.9 (23.4)	30.7 (20.8)	31.3 (21.1)
Basal insulin dose (IU) (mean [s.d.])	32.5 (17.5)	32.0 (20.5)	31.4 (16.9)
Efficacy: HbA1c change from Baseline			
Week 24 Treatment Comparison LS Mean (SE), [a] % (*p*-value)	N/A	-0.36 (*p*<0.001)	-0.38 (*p*<0.001)
Week 52 Treatment Comparison LS Mean (SE), [a] % (*p*-value)	N/A	-0.23 (*p*<0.001)	-0.32 (*p*<0.001)
Insulin Change from Baseline at Week 52			
Total insulin			
- Percent change (%) from Baseline			
LS Mean (SE), p-value	2.12 (0.959), p=0.028	-4.98 (0.955), p<0.001	-8.21 (0.958), p<0.001
Treatment Comparison vs. Placebo LS Mean (SE), p-value	N/A	-7.10 (1.301), p<0.001	-10.33 (1.303), p<0.001
- Absolute change (IU)			
LS Mean (SE), p-value	0.18 (0.657), p=0.78	-3.51 (0.654), p<0.001	-5.86 (0.656), p<0.001
Bolus insulin			
- Percent change (%) from Baseline			
LS Mean (SE), p-value	5.14 (2.338), p=0.028	-1.48 (2.332), p=0.52	-8.58 (2.338), p<0.001
Treatment Comparison vs. placebo LS Mean (SE), p-value	N/A	-6.63 (3.182), p=0.037	-13.73 (3.187), p<0.001
- Absolute change (IU)			
LS Mean (SE), p-value	-1.45 (0.511), p=0.004	-3.08 (0.508), p<0.001	-4.28 (0.510), p<0.001
- Proportion of insulin reduction attributable to bolus insulin[b]	N/A	82.8%	71.3%
Basal insulin			
- Percent change (%) from Baseline			
LS Mean (SE), p-value	4.75 (1.137), p<0.001	-2.36 (1.136), p=0.038	-4.50 (1.136), p<0.001
Treatment Comparison vs. PBO LS Mean (SE), p-value	N/A	-7.11 (1.554), p<0.001	-9.25 (1.554), p<0.001
- Absolute change (IU)			
LS Mean (SE), p-value	1.58 (0.337), p<0.001	-0.64 (0.336), p=0.055	-1.72 (0.336), p<0.001
- Proportion of insulin reduction attributable to basal insulin[b]	N/A	17.2%	28.7%
Patients with Safety Event through 52 Weeks			
Any TEAE, n (%)	374 (71.1)	393 (75.0)	390 (74.3)
DKA,[c,d] n (%)	1 (0.2)	15 (2.9)	20 (3.8)
Severe hypoglycemia,[c] n (%)	39 (7.4)	30 (5.7)	23 (4.4)
Diarrhea,[e] n (%)	27 (5.1)	34 (6.5)	46 (8.8)
Genital mycotic infection, n (%)	15 (2.9)	48 (9.2)	63 (12.0)

BMI, Body Mass Index; DKA, Diabetic Ketoacidosis; IU, International Units; LS (SE), Least Square Means and Standard Error; N/A, Not Applicable; TEAE, Treatment-Emergent Adverse Event. [a]Statistical comparisons of each SOTA arm to placebo were preplanned and performed using a generalized linear model with repeated measures statistics. [b]Proportion of insulin reduction attributable to bolus or basal insulin was calculated by LS Mean of absolute bolus or basal insulin dose change (IU) from BL over bolus + basal absolute dose change from baseline (IU), number of patients on which the raw means and LS means are not the same for each type of insulin. [c]Adjudicated event of special interest. [d]DKA cases were adjudicated as "yes with certainty," "yes, probably," "no, unlikely," "no with certainty," "unclassifiable," and "insufficient data." Positively adjudicated cases were classified as either "with certainty" or "probably." [e]Discontinuation of drug due to diarrhea was: 0.4% placebo, 0.4% SOTA 200 mg, and 0.8% SOTA 400 mg.

6-LB

Alirocumab and Cardiovascular Outcomes in Patients with Acute Coronary Syndrome (ACS) and Diabetes—Prespecified Analyses of ODYSSEY OUTCOMES

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Background: People with diabetes and recent ACS are at higher risk for ischemic CV events and derive greater benefit from intensive lipid-lowering therapy than those without diabetes. Effect of PCSK9 inhibition in patients with recent ACS and diabetes is unknown.

Methods: Alirocumab (ALI) is a fully human monoclonal antibody to PCSK9. In ODYSSEY OUTCOMES, 18,924 patients with recent ACS and LDL-C≥70mg/dL on a maximum-tolerated dose of atorvastatin or rosuvastatin were randomly assigned to ALI 75mg or placebo SC every 2 weeks. ALI blindly increased to 150mg or decreased to placebo to achieve an LDL-C of 25-50mg/dL. Primary efficacy endpoint was time to first MACE: CHD death, nonfatal MI, ischemic stroke or hospitalization for unstable angina. This prespecified analysis reports efficacy and safety by baseline glucometabolic status, including new-onset diabetes (NOD).

Results: Table reports incidence of MACE by assigned treatment and baseline glucometabolic status. Overall ALI reduced MACE, without evidence of effect modification by baseline glucometabolic status: a greater absolute risk reduction was observed with ALI in those with diabetes. NOD was not increased with ALI.

Conclusion: Patients with recent ACS and diabetes derived greater absolute benefit from ALI added to maximum-tolerated statin. No increase in NOD was seen with ALI (NCT01663402).

Table.

Category	N (% of cohort)	MACE cumulative incidence		ARR	Hazard ratio (95% CI)	$P_{interaction}$
		Alirocumab n/N (%)	Placebo n/N (%)			
All subjects	18,924 (100)	903/9462 (9.5)	1052/9462 (11.1)	1.6	0.85 (0.78, 0.93)	NA
Diabetes	5444 (28.8)	380/2693 (14.1)	452/2751 (16.4)	2.3	0.84 (0.74, 0.97)	0.98
Prediabetes	8246 (43.6)	331/4130 (8.0)	380/4116 (9.2)	1.2	0.86 (0.74, 1.00)	
Normoglycemia	5234 (27.7)	192/2639 (7.3)	220/2595 (8.5)	1.2	0.85 (0.70, 1.03)	

Median follow-up: 34 months. ARR, Absolute Risk Reduction; NA, Not Applicable.

Supported By: Sanofi; Regeneron Pharmaceuticals, Inc.

COMPLICATIONS—HYPOGLYCEMIA

7-LB

The Relationship between A1C and Hypoglycemia in the Diamond Study

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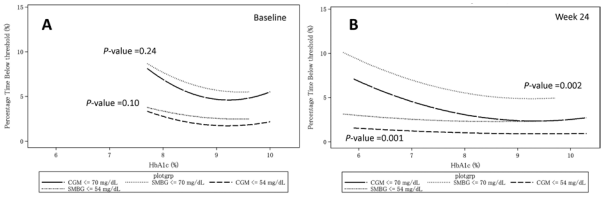
We revisited the well-known inverse relationship between A1C and hypoglycemia using data from phase 1 of the Diamond clinical trial that compared usual care to real-time continuous glucose monitoring (CGM) in subjects with type 1 diabetes using MDI and with A1C levels from 7.5% to 9.9%. Data from 157 subjects (104 and 53 in the CGM and control groups, respectively) were analyzed. The percentages of sensor glucose (SG) values ≤70 mg/dL (≤3.9 mmol/L) ("%≤70") and of those indicating clinically significant hypoglycemia (≤54 mg/dL [≤3.0 mmol/L]) ("%≤54") during the initial and final weeks of the 24-week study were calculated for each subject and compared to corresponding baseline and 24-week A1C values. At baseline, the percent ≤70 was similar for the two groups (p=0.24), as was the percent ≤54 (p=0.10). There was a trend toward more hypoglycemia for subjects near the minimum allowed A1C value of 7.5% (Figure A). At 24 weeks (Figure B), there were significant between-group differences in favor of CGM at both thresholds, and the association between decreasing A1C and increasing exposure to SG values ≤54 mg/dL was attenuated. Subjects in the CGM group averaged ~16 minutes/day with SG ≤54 mg/dL. These data suggest patients with access to CGM alerts and alarms take appropriate and timely measures to nearly eliminate exposure to clinically meaningful hypoglycemia. CGM allows safe intensification of MDI therapy and achievement of near-normal A1C levels.

Figures A-B.



8-LB

WITHDRAWN

9-LB

The Relationship between A1C and Hypoglycemia in the HypoDE Study

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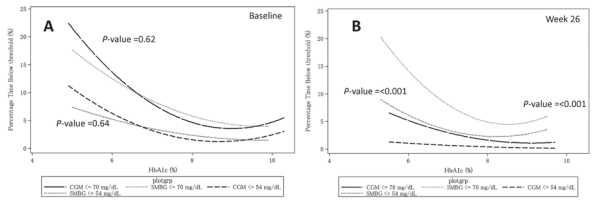
There is an inverse relationship between A1C and hypoglycemia which may be impacted by use of continuous glucose monitoring (CGM). Using data from the HypoDE clinical trial, we compared usual care to real-time CGM in subjects with type 1 diabetes using MDI and impaired hypoglycemia awareness or recent severe hypoglycemia. Data from 149 subjects (75 CGM/intervention and 74 SMBG/control) were analyzed. The percentages of sensor glucose (SG) values ≤70 mg/dL (≤3.9 mmol/L) ("%≤70") and of those indicating clinically significant hypoglycemia (≤54 mg/dL [≤3.0 mmol/L]) ("%≤54") during the blinded 4-week run-in and the final 4 weeks of the 26-week study were calculated for each subject and compared to corresponding baseline and 26-week A1C values. At baseline, the percent ≤70 and the percent ≤54 were similar for the two groups and there was a trend toward more hypoglycemia for subjects with lower A1C values (Figure A). At 26 weeks (Figure B), there were significant (p<0.01) between-group differences in favor of CGM at both thresholds, and the association between decreasing A1C and increasing exposure to SG values ≤54 mg/dL was attenuated. These data suggest patients at highest risk of hypoglycemia with access to CGM alerts and alarms take appropriate and timely measures to nearly eliminate exposure to clinically meaningful hypoglycemia. CGM allows safe intensification of MDI therapy and achievement of near-normal A1C levels in hypoglycemia-prone individuals.

Figures A-B.



10-LB

Opioid Receptor Blockade with Intranasal Naloxone Prevents the Development of Hypoglycemia-Associated Autonomic Failure

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Attainment of near-normal glycemic goals in type 1 diabetes (T1D) is limited by iatrogenic hypoglycemia. Repeated episodes of hypoglycemia lead to Hypoglycemia-Associated Autonomic Failure (HAAF), with blunted counterregulatory hormone responses. We previously reported that pharmacologic activation of opioid receptors experimentally recapitulates some features of HAAF (Diabetes 66:2764; 2017), and opioid antagonism with intravenous naloxone prevents experimentally induced HAAF in healthy subjects. We therefore hypothesized that intranasal naloxone would augment central blockade of opioid receptors by bypassing the blood-brain barrier, and would provide a feasible outpatient approach to prevent HAAF.

Using a randomized, double-blinded placebo-controlled study design, 7 healthy subjects (7M; age 43±3 year; BMI 25.9±0.9 kg/m^2) participated in paired two-day studies, 5 weeks apart. Day 1 consisted of two 120 minute hypoglycemic (~54 mg/dl) hyperinsulinemic clamps, with hourly intranasal administration of either saline (placebo) or naloxone (4 mg hourly). On day 2, subjects underwent one 120 minute hypoglycemic clamp (~54 mg/dl). As expected, HAAF was experimentally induced in the placebo studies, based on lower peak epinephrine levels (mean±SEM: first hypoglycemic episode=1375±182 vs. third episode=858±235, pg/ml, p=0.004). With intranasal naloxone, epinephrine levels did not differ from the first to the third hypoglycemic episode (first=942±190 vs. third episode=857±134 pg/ml, p=0.4). Naloxone did not alter the responses of plasma glucagon, cortisol or growth hormone, or hypoglycemic symptoms.

These findings suggest that HAAF can be prevented by acute blockade of opioid receptors during hypoglycemia, presumably by inhibiting opioid receptor activation by circulating endorphins. Thus, acute self-administration of intranasal naloxone could be an effective and feasible 'real-world' approach to ameliorate HAAF in T1D.

Supported By: National Institutes of Health

11-LB

Hypoglycemia Unawareness in T1DM Is Associated with Altered Brain Default Mode Network Connectivity

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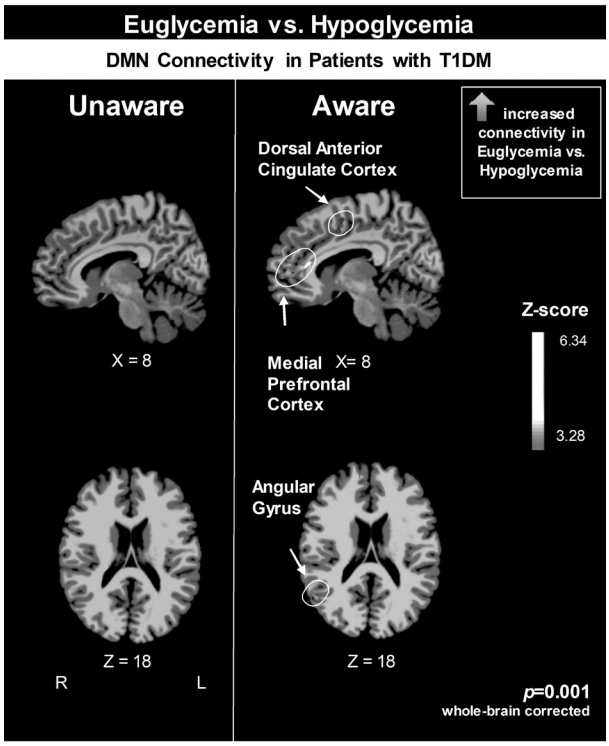
The impact of hypoglycemia awareness (HA) on brain resting state connectivity remains unclear. To examine the impact of HA on the default mode network (DMN), a functional network in the brain that is active during wakeful rest and associated with introspection, 12 T1DM individuals with hypo unawareness (T1DM-UW) (by Clarke score) (7F/5M, age 44±12 years, BMI 26.4±4.2 kg/m^2, HbA1c 7.1±0.7) and 15 T1DM-Aware (AW) (10F/5M, age 30±7, BMI 24.5±3.1, HbA1C 7.1±0.9) individuals underwent resting state BOLD fMRI scanning to assess the DMN during a two-step euglycemic (Eu)-hypoglycemic (Hypo) clamp (90-60 mg/dl). T1DM-AW individuals exhibited a hypoglycemia-induced decrease in DMN connectivity (P<0.001). In contrast, T1DM-UW individuals showed no difference in connectivity between conditions. Moreover, the degree of DMN inhibition correlated inversely with plasma cortisol (r=-0.432, p=0.031), norepinephrine (r=-0.40, p=0.038) and positively with hypoglycemia symptom scores (r=0.40, p=0.037). These findings suggest that, unlike T1DM-AW individuals, hypoglycemia fails to elicit changes in the DMN amongst T1DM-UA individuals. Furthermore, the change in DMN connectivity is associated with measures of physiological and interoceptive responses to stress. These findings highlight the need for future studies to investigate whether avoidance of hypoglycemia can restore brain connectivity patterns.

Figure.



Supported By: National Institutes of Health

12-LB

Novel Analysis of Bionic Pancreas Trial Data Emphasizing Benefit to Individuals Rather than the Group as a Whole

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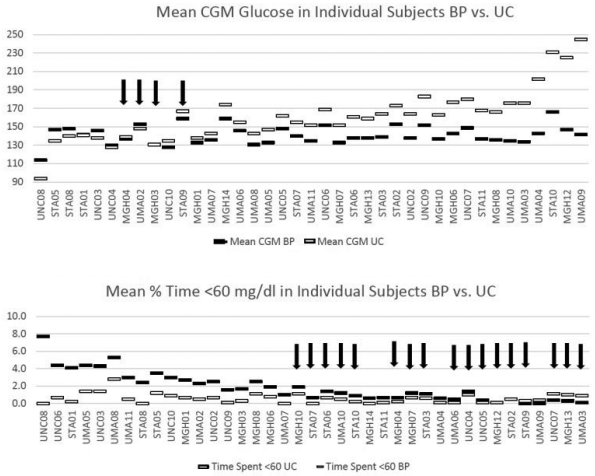
We previously showed in a multicenter, outpatient, random-order crossover trial (n=39, 11 days each arm) that the bionic pancreas (BP) reduced group mean CGM glucose (141±10 vs. 162±29 mg/dl, p<0.0001) and percent of time spent <60 mg/dl (0.6±0.6% vs. 1.9±1.7%, p<0.0001) relative to usual care (UC) with pump ± CGM (El-Khatib FH, et al. Lancet. 2017; 389:369-80). We applied a new statistical approach to these data to determine how many individuals saw benefit for each outcome. We compared the average CGM glucose and average time <60 mg/dl between the BP and UC arms for each patient using autoregressive time series models to determine significance of differences. We found that 72% of subjects had a statistically significant reduction in mean CGM glucose, 51% had significant reduction in time <60 mg/dl, 44% had a significant reduction in both, and 97% had a significant reduction in at least one outcome. For every subject with mean CGM glucose that was nominally higher in the BP arm, the mean glucose in the BP arm was <154 mg/dl (predicted A1c <7%) and the average time <60 mg/dl was less than in the UC arm (significantly less in 2/6 cases). These analyses provide a new prospective on the efficacy of the BP emphasizing the benefit to individuals rather than the group as a whole. Subjects least likely to benefit were those who had extremely tight glycemic control and minimal hypoglycemia under UC.

Figure 1: Comparison of mean CGM glucose and % time <60 BP vs. UC. Subjects are arranged on the X axis according to size of the difference between UC and BP. Arrows indicate comparisons for which the differences were NOT statistically significant. Only one subject had a statistically significant increase in hypoglycemia in the BP arm and the difference was small (0.4% vs. 0%, p<0.05).



COMPLICATIONS—MACROVASCULAR—ATHEROSCLEROTIC CARDIOVASCULAR DISEASE AND HUMAN DIABETES

13-LB

WITHDRAWN

14-LB

Enrichment of miR-126 Boosts the Therapeutic Effects of Endothelial Progenitor Cells Derived Exosomes on Ischemic Stroke in Diabetic Mice

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We have demonstrated that endothelial progenitor cell (EPCs) have therapeutic effects on ischemic stroke in diabetic mice and that microRNA (miR)-126 modulates the function of EPC through vascular endothelial growth factor receptor 2 (VEGFR2) pathway in cell culture studies. Here, we determined the effects of EPC-released exosomes (EPC-EXs) on ischemic stroke in diabetic mice and tested whether miR-126 enriched EPC-EXs (EPC-EXs^{miR126}) could have enhanced efficacy. Type 2 diabetic mice subjected to filament-induced focal ischemic stroke were intravenously administrated with vehicle, or PKH26 labelled EPC-EXs or EPC-EXs$^{miR-126}$. The neurological deficit score (NDS), cerebral blood flow (CBF), infarct volume, cerebral microvascular density (MVD), cell death, angiogenesis and neurogenesis, and levels of miR-126, VEGFR2 and cleaved caspase-3 were measured. We found: 1.) Injected EPC-EXs merged with brain endothelial cells, neurons and astrocytes dominantly in the peri-infarct area; 2.) EPC-EXs^{miR126} were more effective than EPC-EXs in decreasing NDS, ischemic damage and cell death, and increasing CBF and MVD on both day 2 and 14, and in promoting angiogenesis and neurogenesis on day 14; 3.) These effects were accompanied with down-regulated cleaved caspase-3 on day 2 and prolonged VEGFR2 up-regulation till day 14. The data suggest that transfusion of EPC-EXs^{miR126} has enhanced therapeutic efficacy on ischemic stroke in diabetic mice by attenuating acute injury and promoting neurological function recovery.

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

ADA-Supported Research

15-LB

Risk Factors for Cardiovascular Disease (CVD) in Adults with Type 1 Diabetes (T1D)

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The T1D Exchange (T1DX) Clinic Registry assessed CVD risk factors in a large, contemporary cohort of adults with T1D living in the U.S. To understand the incidence and CVD risk factors, we evaluated the association of CVD risk factors and 5-year risk of CVD in adults ≥18 years of age, without CVD at enrollment in the T1DX. CVD was defined as a composite outcome of clinic reported fatal or non-fatal events of ischemic heart disease and heart failure. Associations between diabetic specific and traditional CVD risk factors and incident CVD were examined by logistic regression adjusting for potential confounders. The study included 4,463 participants (55% female, 91% non-Hispanic white, mean age 41 years, T1D duration 21 years). At enrollment, mean HbA1c was 7.7%, 43% used statin, and 45% used blood pressure medication. Incident CVD was reported by 419 (9.4%) participants during the 5-year follow-up. Age, diabetes duration, elevated BMI, triglycerides (TG), and diabetic nephropathy were associated with greater odds of CVD [Table]. Sex, mean HbA1c, HbA1c variability, pulse pressure, and hypertension were not associated with CVD. Markers of insulin resistance (BMI and TG) and diabetic nephropathy are important risk factors for CVD. Longer follow-up is required to assess the impact of other CVD risk factors on CVD in adults with T1D.

Table: Association of diabetes related and traditional risk factors with CVD in adults with T1D over 5-year follow-up[1]

Variables	Incident CVD		
	Yes (n=419)	No (n=4,044)	Odds Ratio (95% CI)[2]
Diabetes related risk factors			
Diabetes duration at baseline	34 (21)	18 (18)	**1.36 (1.25-1.49)**
Mean HbA1c (%)	7.7 (1.2)	7.5 (1.3)	0.97 (0.87-1.08)
SD HbA1c (%)	0.5 (0.3)	0.5 (0.4)	0.95 (0.67-1.33)
Microalbuminuria	132 (33%)	581 (14%)	**1.89 (1.47-2.43)**
Macroalbuminuria	41 (10%)	114 (3%)	**2.29 (1.52-3.44)**
Mean e-GFR (mL/min)	69.8 ± 25.3	93.9 ± 21.9	**1.29 (1.22-1.36)**
Traditional CVD risk factors			
BMI	28.6 (7.1)	26.7 (6.4)	**1.02 (1.00-1.03)**
Age at baseline	57 (16)	39 (24)	**1.59 (1.44-1.74)**
Male sex	219 (52%)	1790(44%)	**1.30 (1.04-1.62)**
Dyslipidemia[3]	386 (92%)	3355 (83%)	1.02(0.65-1.60)
Mean Total Cholesterol (mg/dL)	158 (38)	171 (39)	**0.91 (0.88-0.95)**
Mean LDL (mg/dL)	79 (23)	91 (29)	**0.99 (0.99-1.00)**
Mean HDL (mg/dL)	57 (26)	62 (23)	**0.83 (0.77-0.90)**
Mean Triglycerides (md/dL)	87 (50)	78 (47)	**1.03 (1.01-1.05)**
Hypertension[4]	386 (92%)	2326 (58%)	1.16 (0.66-2.02)
Mean Pulse Pressure	57.4 ±10.5	49.5 ± 9.3	1.03 (0.91-1.17)

[1]Data presented as median (IQR), mean ± SD, or n (%). Bold in font represents statistical significance.
[2]Adjusted OR calculated for 10 units decrease of mean eGFR, 10 units increase of age, diabetes duration, mean LDL, mean HDL, mean Triglyceride, mean total cholesterol and mean pulse pressure, 5 units increase in mean BMI and 1 unit increase of mean HbA1c and SD-HbA1c.
[3]Dyslipidemia defined (using mg/dL) as if LDL ≥100, HDL ≤40, triglycerides ≥150, total cholesterol ≥200, and/or statin use.
[4]Hypertension defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg and/or BP medication use.

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

16-LB

The Effect of Liraglutide on 24-Hour Ambulatory Blood Pressure in Patients with T2DM—A Pilot Study

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The GLP-1 receptor agonists have been shown to decrease blood pressure (BP) in clinical trials using office BP measurements. However, the effect of GLP-1 agonist liraglutide on 24-hour ambulatory blood pressure and on the nocturnal BP decrease (dipping) have not been adequately assessed in large trials. To better characterize the effect of GLP-1 agonists on 24-hour ambulatory BP in subjects with T2DM we conducted a randomized controlled trial comparing the effects of liraglutide to placebo. Eleven subjects with T2DM (mean age 58.6±7.4 years, female 63.7%, African-American 72.7%) were randomized to 8 weeks of treatment with liraglutide (n=6) or placebo (n=5). ABPM and EndoPAT (Peripheral Arterial Tone) for assessment of endothelial dysfunction were done at baseline, 4 weeks and 8 weeks of therapy. Mixed models with repeated measures was used to estimate the treatment effect over time. Treatment with liraglutide was found to increase the nighttime SBP (LSM±SE): 135.3±4.3 vs. 102.1±4.5 (mmHg), p=0.0015), diastolic BP (DBP) (74.7±6.1 vs. 57.5±5.6 (mmHg), p=0.047) and increase daytime heart rate (109.5±9.2 vs. 77.1±7.9 (mmHg), p=0.021) after adjusting for age, race, history of hypertension, current use of ACE-I/ARBs and Reactive Hyperemia Index (RHI). There was no significant change in BMI between baseline and 8 weeks (1.5±2.4 vs. 1.0±2.5 (kg/m^2), p=0.65). After adjustment for treatment and other covariates, abnormal RHI (≤ 1.67) was associated with decreased nighttime SBP (110.6±3.4 vs. 126.8±3.4 (mmHg), p=0.0003), and increased nighttime DBP (69.1±5.0 vs. 63.2±5.1 (mmHg), p=0.16) although lack of power to detect the statistical significance.

In conclusion, our study showed that treatment with liraglutide over 8 weeks was unable to correct the abnormal elevation in nocturnal BP known to occur in patients with T2DM. ABPM also confirmed the known side effect of increase in heart rate previously seen in other liraglutide trials. Abnormal RHI tended to be associated with all patients with high DBP.

Supported By: Eunice Kennedy Shriver National Institute of Child Health and Human Development (K12HD043451); Building Interdisciplinary Research Careers in Women's Health; National Institutes of Health (U54GM104940)

17-LB

What Mediated Pioglitazone's Cardiovascular (CV) Benefit in the IRIS Trial?

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In the Insulin Resistance Intervention after Stroke (IRIS) trial, pioglitazone (PIO) reduced the risk of fatal/nonfatal stroke/MI by 24% vs. placebo (PLA) in 3876 nondiabetic patients with insulin resistance (IR) and recent stroke or transient ischemic attack (TIA). We sought to determine which factor(s) modified by PIO were associated with its CV benefit.

The effect of PIO was quantified using Cox models. Starting with a bivariate model, change from baseline at year 1 in a single factor (Table) was included as a covariate for stroke/MI events beyond year 1. The resulting percent change in log HR for PIO towards the null was defined as the percent mediation of PIO's effect by that factor. The combined effect was assessed in a model using all factors identified in bivariate models as potential mediators.

The factor with the largest impact (26%) was HDL-C, with smaller mediating effects (<15%) from CRP, TG, BP and glucose. Together, these factors accounted for 43% of the treatment benefit. We could not confirm any mediating effect from the reduction in measures of IR. Findings were similar in several sensitivity analyses.

In summary, no single factor explained the majority of PIO's CV benefit in IRIS. PIO's favorable effects in patients with IR and stroke/TIA is likely mediated through multiple and combined benefits on lipids, BP, glucose, and inflammation.

Table. Change in Log HR (Percent Mediation) after Controlling for Individual Factors and Their Combination.

Factor	Mean (SE) for Factor			Treatment Effect, Adjusted for Factor		%Δ log(HR)
	Baseline	Δ at Year 1				
	ALL	PLA	PIO	HR	95% CI	
None		—	—	0.779	(0.59, 1.02)	—
HDL-C (mg/dL)	46.8 (0.2)	2.3 (0.2)	5.5 (0.3)	0.831	(0.63, 1.09)	25.9%
CRP (mg/L)*	4.6 (0.2)	-0.3 (0.3)	-1.2 (0.3)	0.805	(0.61, 1.06)	13.1%
TG (mg/dL)*	137.5 (1.1)	-1.7 (1.3)	-16.2 (1.2)	0.799	(0.61, 1.05)	10.2%
Glucose (mg/dL)	98.1 (0.2)	1.3 (0.4)	-2.9 (0.3)	0.792	(0.60, 1.04)	6.6%
SBP (mm Hg)	133.0 (0.3)	-0.8 (0.5)	-2.1 (0.5)	0.792	(0.60, 1.04)	6.6%
DBP (mm Hg)	79.1 (0.2)	-1.0 (0.3)	-3.0 (0.3)	0.781	(0.59, 1.03)	1.0%
LDL-C (mg/dL)	87.5 (0.6)	2.3 (0.7)	3.2 (0.8)	0.772	(0.59, 1.01)	-3.6%
HOMA-IR*	5.4 (0.1)	0.3 (0.1)	-1.3 (0.1)	0.709	(0.53, 0.94)	-37.7%
Insulin (μU/mL)*	22.1 (0.2)	0.4 (0.4)	-5.1 (0.3)	0.707	(0.53, 0.94)	-38.8%
Combined model (HDL-C, CRP, glucose, SBP, DBP)				0.868	(0.66, 1.15)	43.3%

*Skewed distributions; values were log transformed before analysis. HDL-C= High Density Lipoprotein Cholesterol; CRP=High-Sensitivity C-Reactive Protein; TG=Triglycerides; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; LDL-C=Low Density Lipoprotein Cholesterol; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance.

Supported By: National Institute of Neurological Disorders and Stroke (U01NS044876)

18-LB

Gemigliptin, a Dipeptidyl Peptidase-4 Inhibitor, Protects against Cardiovascular System in Cardiac I/R Injury and Hypertensive Rats

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Cardiovascular disease (CVD) is implicated in the high morbidity and mortality in diabetic patients. Improvement in cardiovascular complications with maintaining glucose level and managing cardiovascular risk factors is important role. Currently, the impact of hypoglycemic medications on CVD is of increasing importance. Although dipeptidyl peptidase-4 inhibitors (DPP-4), a class of antidiabetic drugs, have pleiotropic protective effects on CVD in experimental studies, it remains undetermined whether gemigliptin has a beneficial effect on ischemia reperfusion (I/R)-induced myocardial injury and hypertension. Therefore, this study was performed to evaluate the effects of gemigliptin in the rat model of myocardial I/R injury and spontaneously hypertensive rats (SHR). Gemigliptin (20 and 100 mg/kg/day) was administered per oral to Sprague-Dawley rats for four weeks before I/R operation. Gemigliptin pretreatment improved hemodynamic function and limited infarction size against I/R injury. Additionally, gemigliptin (0.03% and 0.15%) was mixed into the powdered feed and fed to SHR. Gemigliptin treatment with SHR reversed hypertrophy and improved diastolic function. These results suggest that gemigliptin exerts beneficial effect not only on blood glucose but also on cardiovascular system in cardiac I/R injury and hypertensive rats.

Supported By: LG Chem

19-LB

WITHDRAWN

20-LB

WITHDRAWN

COMPLICATIONS—MACROVASCULAR—CELLULAR MECHANISMS OF ATHEROGENESIS IN DIABETES

21-LB

Melatonin Improves Neovascularization after Hind-Limb Ischemia Surgery in Streptozocin-Induced Diabetic Mice by Enhancing Endothelial Progenitor Cells Functions

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Objective: Diabetic patients show poor endothelial progenitor cell (EPC) functions and are prone to ischemic micro-vascular or macro-vascular complications. Melatonin has been shown to have protective effects in ischemic injury, possibly in part by modulating the functioning of EBCs. We investigated whether pretreatment with melatonin can restore the impaired functions of EPCs in diabetes.

Methods: Human EPC were isolated and cultured in a high-glucose medium for functional testing. Cell proliferation, nitric oxide (NO) production, and apoptosis assay were examined. A streptozocin (STZ)-induced diabetic mouse model was established to evaluate the actions of chronic hyperglycemia on ischemia-induced blood flow recovery. The circulating EPC number in the peripheral blood was determined by flow cytometry (Sca-1+/Flk-1+).

Results: Incubation with a high-glucose medium (25 mM) significantly suppressed EPC proliferation, reduced NO production, and lessened phosphorylations of Akt and eNOS. Moreover, EPC treated with high-glucose medium increased reactive oxygen species production, promoted cellular apoptosis and senescence, and also inhibited EPC tube formation. Treatment of melatonin could recover these harmful effects. Four weeks after hindlimb ischemia surgery, the STZ-induced diabetic mice had significantly reduced tissue reperfusion, EPC mobilization, and impaired neovascularization in the ischemic hindlimbs compared with the nondiabetic mice. In STZ-induced diabetic mice, the melatonin group showed significantly increased ischemic/non-ischemic limb blood perfusion ratios, higher capillary densities, and improved EPC mobilization.

Conclusion: Chronic hyperglycemia impaired blood flow recovery and EPC mobilization in response to tissue ischemia, and pretreatment of melatonin could reduce these effects.

Supported By: Ministry of Science and Technology of Taiwan (104-2314-B-075-047, 106-2314-B-010-033-MY3, 106-2314-B-075-078-MY3)

22-LB

Inhibition of Myeloperoxidase and MPO Reverses Microvascular Insulin Resistance in High-Fat Diet (HFD)-Fed Rats

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Chronic, low-level inflammation underlies much of the vascular and metabolic insulin resistance associated with HFD. Release of MPO by leukocytes may be an early contributor to the inflammatory process and endothelial dysfunction that accompanies HFD feeding. Plasma MPO concentrations are increased in both human obesity and diabetes and HFD-fed rats. However, the impact of MPO on microangiopathy and its relation to insulin resistance is unclear. We tested whether AZD5904 (a potent, irreversible inhibitor of MPO, AstraZeneca) improves endothelial function and vascular insulin responses in insulin resistant, adult male SD rats fed a HFD (60% calories from fat) for 2 weeks. HFD fed rats received vehicle (n=8) or AZD5904 (75 µmol/kg/day, n=10) via an Alzet Mini pump for 2 weeks. A 3rd group of rats (n=8, vehicle alone) were fed a chow diet for 2 weeks. After 2 weeks of HFD or control diet, rats were fasted overnight and received a 2-hour euglycemic insulin clamp (3 mU/kg/minutes). Hindleg muscle microvascular perfusion was assessed using contrast-enhanced ultrasound and insulin-stimulated steady-state whole body glucose disposal was determined. Insulin infusion increased muscle microvascular perfusion by 2-3 fold in chow fed rats ($p<0.05$). HFD feeding abolished insulin-induced microvascular recruitment in muscle, and decreased insulin-mediated glucose disposal by ~45% ($p<0.01$). Simultaneous treatment with AZD5904 fully restored insulin-mediated muscle microvascular perfusion ($p<0.05$) in HFD rats, but did not improve insulin-stimulated glucose disposal in HFD-fed rats. We conclude that inhibition of MPO with AZD5904specifically reverses muscle microvascular insulin resistance in HFD rats. This implicates MPO as a significant contributor to HFD-induced endothelial inflammation and suggests a role for MPO inhibition to improve microvascular complications in patients with vascular insulin resistance.

Supported By: AstraZeneca

23-LB

Novel Risk Panel for CAD and All-Cause Mortality in Type 1 Diabetes

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Coronary artery disease (CAD) prevalence is increased and life expectancy is reduced by more than a decade in people with type 1 diabetes (T1D) compared to nondiabetics (non-DM), but traditional risk factors do not explain all of the increased risk. We examined whether three novel risk markers, high-sensitive cardiac troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and growth differentiation factor 15 (GDF-15), are elevated in T1D and predict CAD and mortality.

1,416 adults age 19-56 (652 T1D, 754 non-DM) were enrolled in the Coronary Artery Calcification in type 1 diabetes (CACTI) study from 2000-2002. We assessed CAD events (fatal or non-fatal myocardial infarction, coronary artery bypass graft, or angioplasty) with annual follow-up questionnaires. In-person visits occurred at 3, 6, and 12 years after baseline. Serum samples from the visit prior to a CAD event or death or from the last in-person visit were available for 1,389 participants and were assayed for hs-cTnT, NT-proBNP, and GDF-15 at the University of Maryland. Elevated marker levels were defined as those above the 95th percentile among non-DM participants. Biomarker levels were compared by T1D status in linear regression, and logistic regression was used to examine associations with CAD and all-cause mortality.

Age- and sex-adjusted LSmeans ± SE for log hs-cTnT (2.0±0.02 vs. 1.6±0.02, $p<0.0001$), log NT-proBNP (3.8±0.04 vs. 3.5±0.03, $p<0.0001$), and log GDF-15 (6.5±0.02 vs. 6.2±0.02, $p<0.0001$) were significantly higher in T1D than non-DM participants. Over the follow-up period, there were 72 CAD events (53 T1D, 19 non-DM) and 76 deaths (58 T1D, 18 non-DM). Having elevated levels of all 3 vs. none of the markers was a significant predictor of both CAD (OR [95% CI] 6.4 [2.0-20.7]) and all-cause mortality (OR [95% CI] 10.7 [3.3-35.4]), independent of age, sex, renal function and T1D status.

A panel of novel markers, hs-cTnT, NT-proBNP, and GDF-15, are elevated in T1D and may help identify those at risk for CAD events and mortality.

Supported By: American Diabetes Association (7-13-CD-10 to J.K.S-B.); National Institutes of Health

ADA-Supported Research

24-LB

Metabolomic Profiling of Nonproteinogenic Amino Acids in Patients with Type 2 Diabetes and Hypertension

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Introduction: Identifying the amino acid signature of increased blood pressure might help us understand hypertension pathophysiology. We aimed to investigate the relationship of non-proteinogenic amino acids with ambulatory blood pressure mean and variability in type 2 diabetes patients.

Methods: Serum non-proteinogenic amino acids' profiling was performed by high performance liquid chromatography coupled with mass spectroscopy analysis. Blood pressure variability was calculated as standard deviation of mean systolic and diastolic blood pressure evaluated over 24-hour ambulatory monitoring.

Results: The study population consisted of type 2 diabetes hypertensive patients (n=80), 58% women, aged 59.8±7.7 years old with diabetes duration 9.0±8.7 years. Serum non-proteinogenic amino acids levels (nmol/mL) were: gamma-aminobutyric acid 0.2±0.1, aminoisobutyric acid 22.6±7.9, beta-aminoisobutyric acid 1.2±0.7, 4-hydroxyproline 12.2±9.9, 3-methylhistidine 4.7±2.8, alpha-aminoadipic acid 1.0±0.5, sarcosine 11.3±5.6. In linear regression analysis, aminoisobutyric acid was significantly associated with 24-hour systolic blood pressure variability (r=0.23; p=0.044), sarcosine was significantly associated with nighttime systolic blood pressure variability (r=0.27; p=0.017), while beta-aminoisobutyric acid was significantly associated with mean daytime (r=-0.25; p=0.024) and 24-hour (r=-0.24; p=0.032) diastolic blood pressure.

Conclusion: Serum metabolomes aminoisobutyric acid and sarcosine directly associated with ambulatory systolic blood pressure variability, while beta-aminoisobutyric acid inversely associated with mean diastolic blood pressure. Our results indicate changes in serum non-proteinogenic amino acids as consequences of increased blood pressure that should be further evaluated in connection to cardiovascular disease, particularly in the presence of type 2 diabetes.

Supported By: University of Medicine and Pharmacy, Cluj-Napoca, Romania (4994/3/08.03.2016)

COMPLICATIONS—NEPHROPATHY—CLINICAL AND TRANSLATIONAL RESEARCH

25-LB

Risk Factors for Adverse Kidney Disease Outcomes in Type 1 Diabetes (T1D)

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Diabetic kidney disease (DKD) is a major complication of T1D. To better understand the risks of developing DKD, we evaluated risk factors in participants from the T1D Exchange registry who completed 5-year follow-up. Participants had at least two eGFR and albuminuria measurements recorded during the 5 year period; also T1D duration ≥1 year, age ≥10 years, eGFR ≥60 ml/minute and no documented albuminuria at enrollment. Adverse kidney outcomes were defined as eGFR <60 ml/minute and/or micro/macroalbuminuria (micro/macroALB) at any follow-up visit. Univariate chi-square tests, Wilcoxon tests and multivariate logistic regression were used to determine associations between adverse kidney outcomes and risk factors. Among 3,296 participants (mean age 41 ± 15 years, T1D duration 21± 13 years, mean HbA1c 7.6 ± 1.2%, 91% white non-Hispanic,56% female at enrollment) with valid data, 547 (16.6%) experienced an adverse kidney outcome during 5-year follow-up: 224 (6.8%) experienced micro/macroALB while eGFR remained ≥60 ml/minute, 274 (8.3%) had a decline in eGFR to <60 ml/minute without micro/macroALB, and 49 (1.5%) experienced eGFR <60 ml/minute with micro/macroALB. Higher HbA1c, higher SBP, lower DBP as well as older age and lower education level were the significant risk factors for the development of an adverse kidney outcome over 5 years (Table). Control of risk factors and better glycemic control may minimize future DKD.

Table: Demographic and clinical characteristics among T1D participants with/without adverse renal outcome

	No Adverse Renal Outcome	Adverse Renal Outcome				
Participants Characteristics [1]	1.Never experienced e-GFR < 60 or micro/macroALB (n=2749)	2. Experienced only micro/macroALB (n=224)	3. Experienced only e-GFR <60 (n=274)	4. Experienced both e-GFR <60 and micro/macroALB (n=49)	Unadjusted P-value[2]	Adjusted P-value[3]
Age at enrollment	40 (21)	39 (22)	52 (32)	54 (20)	<0.001	0.021
Race/Ethnicity						
White Non-Hispanic	2521(92%)	196 (88%)	253 (92 %)	44 (90%)	0.44	NA
Black Non-Hispanic	71 (3%)	14 (6%)	4 (1%)	2 (4%)		
Hispanic or Latino	83 (3%)	5 (2%)	9 (3%)	2 (4%)		
Other race/ethnicity	73 (3%)	9 (4%)	8 (3%)	1 (2%)		
Female	1517 (55%)	130 (58%)	161 (59%)	28 (57%)	0.18	NA
Highest Annual household income						
<$25,000	120 (5%)	16 (8%)	21 (9%)	4 (10%)	<0.001	NA
$25,000 - $35,000	110 (4%)	16 (8%)	15 (6%)	4 (10%)		
$35,000 – <$50,000	201 (8%)	21 (10%)	20 (8%)	6 (15%)		
$50,000 – <$75,000	386 (16%)	36 (18%)	47 (20%)	7 (17%)		
$75,000 – <$100,000	448 (18%)	39 (19%)	47 (20%)	4 (10%)		
≥$100,000	1196 (49%)	77 (38%)	86 (36%)	16 (39%)		
Education Level						
<High School/GED	28 (1%)	5 (2%)	14 (5%)	3 (7%)	<0.001	0.026
High school/GED	695 (26%)	83 (38%)	86 (33%)	14 (32%)		
Associate degree	236 (9%)	18 (8%)	31 (12%)	5 (11%)		
Bachelor degree	1011 (38%)	75 (35%)	64 (24%)	12 (27%)		
Master degree	489 (18%)	28 (13%)	55 (21%)	7 (16%)		
Professional or Doctorate degree	199 (7%)	7 (3%)	14 (5%)	3 (7%)		
Ever used pump	1999 (73%)	161 (72%)	198 (72%)	37 (76%)	0.88	NA
Ever used CGM	1546 (56%)	108 (48%)	131 (48%)	21 (43%)	<0.001	NA
Age at T1D onset						
Childhood onset (<19 yrs)	1487 (54%)	153 (68%)	150 (55%)	25 (51%)	0.01	<0.001
Adult onset (≥19 yrs)	1262 (46%)	71 (52%)	124 (45%)	24 (49%)		
T1D duration at enrollment	19 (18)	22 (19)	20 (29)	33 (27)	<0.001	NA
Mean HbA1c	7.6 ± 1.0 %	8.1 ± 1.3 %	7.9 ± 1.3%	8.3 ± 1.3%	<0.001	<0.001
Mean systolic blood pressure (SBP)	121.7 ± 10.1	124.6 ± 11.1	122.6 ± 9.9	127.2 ± 11.0	<0.001	<0.001
Mean diastolic blood pressure (DBP)	72.7 ± 6.6	73.1 ± 7.2	69.4 ± 6.8	69.4± 8.1	<0.001	<0.001

[1] Data were presented as median (IQR), mean ± SD, and n (%)
[2]P-values indicating association between binary adverse renal outcome (Yes/No) and risk factors testing by chi-square tests and Wilcoxon tests.
[3]Significant variables in univariate analysis were included in logistic regression model testing association of binary adverse renal outcome and risk factors. Final model from stepwise model selection included age at enrollment, education level, age at T1D onset, mean systolic blood pressure, and mean diastolic blood pressure.

26-LB

Increased HbA1c Variability May Shorten Time to Microalbuminuria Development in Type 1 Diabetes (T1D)

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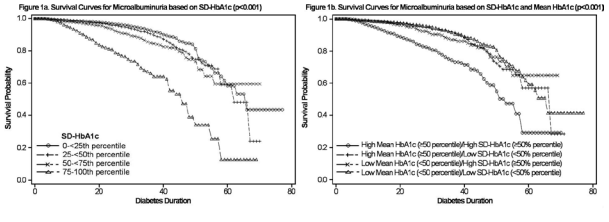
We aim to understand the impact of HbA1c variability, as measured by SD-HbA1c, on risk of microalbuminuria in T1D population. An analysis was performed utilizing data of 8,680 participants in the T1D Exchange Clinic Registry (50% female, 86% non-Hispanic white, mean age 34 years, mean diabetes duration 14 years at enrollment) who met the following criteria: ≥2 clinic visit records, T1D duration ≥1 year at enrollment, age of diagnosis ≥10 years old and no known renal disease (including no microalbuminuria) at the time of registry enrollment. Median number of albuminuria and HbA1c measures were 4 and 21 per participant, respectively. Microalbuminuria was present during follow-up in 562 (6.5%) participants. Median intrapersonal mean HbA1c and SD-HbA1c were 7.8% and 0.6% respectively. Participants with high HbA1c variability had shorter time to first microalbuminuria ($p<0.001$, Figure 1a.) Those with high (≥50th percentile) mean HbA1c and high SD-HbA1c also had shorter diabetes duration prior to first reported microalbuminuria compared to high mean-HbA1c but low SD-HbA1c ($p<0.001$, Figure 1b). HbA1c variability relates to risk of microalbuminuria in T1D; its relationship to other outcomes should be studied.



Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

27-LB

Serum Anti-Phospholipidase A2 Receptor Antibody Differentiating Membranous Nephropathy from Diabetes Kidney Disease in a Large Population of Type 2 Diabetes Mellitus Patients

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Background: With the increase of diabetes, diabetes kidney disease (DKD) was increasing year by year. The pathological types of DKD were various, among which, membranous nephropathy (MN) accounts for a large proportion of nondiabetic renal diseases (NDRD). Recently, serum anti-phospholipidase A2 receptor antibody(sPLA2R-Ab) was used for the diagnosis of MN, the diagnostic efficacy of sPLA2R-Ab for MN in DKD population need to be further verified.

Methods: Screened on patients with type 2 diabetes mellitus (T2DM) who underwent a renal biopsy and have a valid sPLA2R-Ab test results, hospitalized in the general hospital of the people's liberation army of China between May 1st, 2016 and January 30th, 2018. Eligible patients were divided into two groups according to the pathological results: MN group and non-MN group. Patients' clinical and laboratory datas were collected. Statistical analysis was performed with SPSS20.0, and $P<0.05$ was considered statistically significant.

Results: The study included 252 patients: 59 (23.4%) in the MN group and 193 (76.6%) in the non-MN group. MN accounts for 38% of NDRD. The sPLA2R-Ab test results of 35 patients were positive, all of them belonged to MN group. The positive rate of sPLA2R-Ab was 59.3% in MN group and 0 in non-MN group. Patients in the MN group had a higher fasting plasma glucose, age and lower estimated glomerular filtration rate, creatinine and blood pressure as well as a shorter duration of DM than patients in the non-MN group. sPLA2R-Ab achieved a good diagnostic efficiency with a sensitivity of 59.3%, specificity of 100%, negative predictive value of 88.9% and accuracy of 90.5% for MN in DKD.

Conclusion: If the sPLA2R-Ab result of DKD patients is positive, the patient must be MN, and if the result is negative, further renal biopsy should be done. The high accuracy of sPLA2R-Ab may be substituted for renal biopsy partially in the diagnosis of MN in DKD population.

Supported By: Chinese People's Liberation Army General Hospital

28-LB

WITHDRAWN

COMPLICATIONS—NEUROPATHY

29-LB

Effects of the Diabetes-Induced MicroRNA-155 on Wound Healing and Fibroblast Growth Factor 7 Expression

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Impaired wound healing is a serious late-diabetic complication resulting in significant morbidity. MicroRNAs (miRNAs), post-transcriptional gene-regulators, are differentially expressed in several conditions, such as diabetes. To assess the mechanistic action of miRNAs in diabetic wound healing streptozotocin (STZ)-induced diabetic and control mice (n=6/group, 6 weeks of diabetes) were subjected to 6-mm full-thickness excisional wounds. Biopsies were obtained at days 3 and 10 post-wounding. Wound healing was delayed in diabetic mice ($p<0.05$). The skin miRNA profile was determined for up to 561 unique miRNAs using Taqman MicroRNA array cards. We identified 288 different robustly expressed miRNA in skin. While half of them were decreased more than 1.5 fold, 41 were increased more than 1.5 fold, during wound healing. MiR-155-5p was increased in diabetic skin (15.8 fold (95% CI: 3.5-28.1), however, it was 9.7 fold (95% CI: 4.2-15.2) decreased at day 10 post wounding, as compared to nondiabetic mouse skin. Scratch assays in HaCaT cells showed increased scratch closure after 24 hours, when miR-155 was inhibited (Ctrl: 31%, miR-155 inhibitor: 8.1% of scratch remaining, $P<0.001$). In vivo, topical treatment of diabetic mouse wounds with miR-155 inhibitor dose-dependently accelerated wound closure with maximal effect at 2.5pmol ($P<0.03$). Interestingly, reporter-gene analysis identified fibroblast growth factor (FGF) 7 mRNA as a target of miR-155-5p. Moreover, miR-155 inhibitor treated mouse wounds showed significant increase in FGF7 protein expression by immunofluorescence. We present evidence that miR-155-5p expression is altered in diabetic mouse skin and its suppression significantly improves wound healing under diabetic conditions, indicating its potential as a novel chronic diabetic foot ulcer treatment.

Supported By: European Foundation for the Study of Diabetes; HealthyAging2020 (CENTRO-01-0145-FEDER-000012-N2323); Claude D. Pepper Older American Independence Centers (P30AG028718); Novo Nordisk Foundation

30-LB

NOX, NOX, Are You Here? The Emerging Role of NOX5 in Diabetic Neuropathy

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Diabetic neuropathy (DN) is one of the most common complications of diabetes worldwide, affecting up to 60% of all diabetic patients. Although the pathogenesis of DN is poorly understood, it is widely accepted that reactive oxygen species (ROS) mediate in part the cellular and molecular injury observed in DN. NADPH oxidase (Nox) enzymes generate ROS and of the 7 isoforms, NOX5 is present only in man. In this study, we aimed to investigate a role for NOX5 in DN by identifying the cellular localization, methylation status and expression levels of NOX5 in cutaneous nerve fibers and sural nerve biopsies of diabetic patients. Cellular localization of NOX5, myelin basic protein (MBP) and protein gene product (PGP) 9.5 were determined in cutaneous nerve fibers of controls and subjects with DN. NOX5 methylation status and protein levels were assessed in subjects with DN that were divided into two groups based on changes in sural nerve myelinated fiber density: regenerators (showing significant nerve regeneration) and degenerators (showing significant nerve degeneration). NOX5 expression was present in deep myelinated cutaneous fibers. Bisulfite sequencing revealed that the NOX5 promoter, enriched with CpG sites, is hypomethylated in sural nerve biopsies of the degenerator cohort compared to the regenerator. The increase in NOX5 expression in degenerator sural nerves was accompanied with a decrease in MBP levels relative to the regenerator group. Our results highlight that in subjects with DN with sural nerve degeneration, there is hypomethylation of the NOX5 promoter associated with an increase in its protein expression, suggesting a potential epigenetic and mechanistic role of NOX5 in DN.

31-LB

Saturated Fatty Acids Impair Organellar Trafficking in Dorsal Root Ganglion (DRG) Sensory Neurons

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Diabetic neuropathy (DN) is a highly prevalent complication of type 2 diabetes that is associated with dyslipidemia and causes length-dependent sensory nerve damage in the lower extremities. The primary sensory neurons, dorsal root ganglion (DRG) neurons, extend bundles of axons into the peripheral nerves and transmit sensory information from the limbs. These neurons require a constant supply of mitochondrial derived energy maintained by trafficking of the mitochondria throughout the length of the DRG axon. We have shown that dyslipidemia-associated saturated fatty acid (FA) palmitate impairs mitochondrial trafficking whereas unsaturated FA oleate prevents this impairment. In the current study, we assessed whether FAs alter trafficking of synaptic vesicles in DRG axons to determine whether palmitate impairs mitochondrial trafficking specifically or global organellar transport. Primary DRG neurons were treated with physiological concentrations of FAs ranging from 31.25-250 μM saturated FA palmitate, unsaturated FA oleate, and oleate/palmitate mixtures. Mitochondria and synaptic vesicles showed a significant dose-dependent reduction in motility with increasing concentrations of saturated FA palmitate. However, mitochondria and synaptic vesicles retained motility with treatments of unsaturated FA oleate compared to the controls. Similarly, palmitate induced a trending decrease in velocity of bi-directional motile mitochondria and synaptic vesicles, whereas oleate treatments did not alter mitochondrial and synaptic vesicle velocity. Finally, co-incubation of oleate prevents palmitate-induced inhibition of mitochondrial and synaptic vesicle trafficking. These results suggest that high concentrations of saturated FAs lead to the dysfunction of global organellar transport throughout the DRG axon associated with the development and progression of DN.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive Kidney Diseases (R24DK082841, R01DK107956, 1T32DK101357-01, F32DK112642-01A1, P60DK020572, DK076169); University of Michigan; Novo Nordisk Foundation (NNF14SA0006), Program for Neurology Research and Discovery; A. Alfred Taubman Medical Research Institute

32-LB

Toll-Like Receptors 2/4 and Diabetic Peripheral Neuropathy

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Peripheral neuropathy (PN) is a common, morbid complication of diabetes and prediabetes. Dysfunction of toll like receptors (TLR) 2 and 4 has been implicated in PN pathogenesis, and blocking TLR4 is proposed as a treatment for neuropathic pain.

WT and TLR 2/4 global KO (TLR2/4$^{-/-}$; n=5) mice were placed on a 60% high fat diet (HFD, n=5), with 5 WT controls provided a standard diet (CON, n=5). Mice underwent metabolic, neuropathic, and immunological phenotyping (Table 1) at early and late disease time points.

TLR2/4$^{-/-}$ mice weighed more ($P \leq 0.023$) but did not have increased fasting blood glucose levels. They had reduced hind paw withdrawal latencies (HPL) compared to HFD mice ($P \leq 0.01$) and were similar to CON in early disease, but worsened in later disease. TLR2/4$^{-/-}$ mice consistently had lower sural nerve conduction velocities than CON and worsened as disease progressed ($P \leq 0.048$). Immunophenotyping during late disease showed differences in the number of peripheral blood Ly6C- myeloid cells ($P \leq 0.05$) and F4/80+ expression ($P \leq 0.0001$). Inflammatory profiles of the sural nerve indicated a lower gene expression of the chemoattractant CCL-12 chemokine in TLR2/4$^{-/-}$ compared to CON mice.

These results suggest that TLR2/4 KO may be initially protective against HFD induced neuropathy, but as PN progresses this effect is lost. Differences in circulating immune cells and CCL-12 gene expression may indicate an anti-inflammatory phenotype in TLR2/4$^{-/-}$ mice.

Table 1. Metabolic, Neuropathic and Immunological Phenotyping.

Phenotypic Metric	CON (n=5)	HFD (n=5)	TLR2/4$^{-/-}$(n=5)
Late stage weight (g)	26 ± 3	39 ± 3	51 ± 3
Late stage fasting blood glucose (mg/dL)	150 ± 22	190 ± 22	172 ± 22
HPL (sec)	Early: 3.6 ± 0.3 Late: 3.5 ± 0.4	Early: 5.7 ± 0.3 Late: 5.5 ± 0.4	Early: 4.4 ± 0.3 Late: 6.1 ± 0.4
Sural NCV (m/s)	Early: 22.0 ± 0.7 Late: 23.9 ± 0.7	Early: 18.5 ± 0.7 Late: 17.9 ± 0.7	Early: 20.0 ± 0.7 Late: 17.2 ± 0.9
Late stage Ly6C- circulating myeloid cells (10^4 cells/mL)	7.8 ± 2.6	14.0 ± 2.7	4.8 ± 2.7
Late stage circulating myeloid F4/80 expression (mean florescent intensity)	978 ± 961	1383 ± 1019	9967 ± 1019
Late stage CCL-12 sural nerve gene expression (relative quantity)	1.16 ± 0.24	0.59 ± 0.28	0.32 ± 0.24

COMPLICATIONS—RETINOPATHY

33-LB

Recombinant Probiotics Expressing Angiotensin-(1-7) Improves Glucose Metabolism and Diabetes-Induced Renal and Retinal Injury

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Purpose: Multitude of animal studies substantiate the beneficial effects of Ang-(1-7) in diabetes and associated complications. However, the biggest impediment to translate this into clinical application is large-scale production of high quality Ang-(1-7) with enhanced tissue bioavailability. As emerging evidence also implicates the beneficial effects of probiotics in managing diabetes, this study aimed to test the hypothesis that oral delivery of recombinant probiotics expressing Ang-(1-7) will improve glucose metabolism and diabetes-induced tissue damage in animal models.

Method: Ang-(1-7) was expressed as a secreted fusion protein with a transepithelial carrier in Lactobacillus paracasei (LP) to allow uptake into circulation and target tissues. Adult diabetic eNOS$^{-/-}$ mice were orally gavaged daily with $1x10^9$ CFU of LP secreting Ang-(1-7) (LP-A), or LP alone for eight weeks. Glucose metabolism and tissues were assessed using standard assays and histochemical techniques.

Result: Oral feeding of LP-A significantly lowered fasted-state blood glucose (P=0.042); improved the intraperitoneal glucose tolerance test (P=0.034) than control mice. LP-A-treated mice showed higher plasma insulin level (P=0.028) and insulin expression in islets β cells compared to control mice. LP-A treatment significantly reduced apoptotic cell death in kidney, improved diabetes-induced collagen deposits in the glomerular tuft and the tubular epithelia in diabetic mice. LP-A treatment also significantly reduced retinal gliosis, inflammation, neuronal cell death and loss of retinal vascular capillaries.

Conclusion: Oral administration of recombinant probiotics secreting Ang-(1-7) improved glucose tolerance by enhancing insulin level, and reduced diabetes-induced damage in kidney and retina. Thus, recombinant probiotics-based delivery of Ang-(1-7) may hold promising therapeutic potential for diabetes and associated complications.

Supported By: American Diabetes Association (1-15-BS-115 to Q.L.); National Institutes of Health (EY021752, EY024564); BrightFocus Foundation; National Eye Institute (P30EY02172); Research to Prevent Blindness

34-LB

Deletion of 12/15-Lipoxygenase Preserves Retinal Neuronal Function in Diabetic Retinopathy

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Purpose: Diabetic retinopathy (DR) is a neurovascular complication of diabetes with critical limitations in current treatment due to a lack of neuroprotection. These limitations mandate the necessity for new therapy that considers the neuronal component of DR. The goal of this study is to explore the role of 12/15-lipoxygenase (LO) in diabetes-induced retinal neuronal dysfunction.

Methods: 12/15-LO deficient (12/15-LO$^{-/-}$) mice were crossbred with Ins2$^{Akita/+}$ (Akita) mice, a classical model of DR, to generate a new mouse model with a double knockout (12/15-LO$^{-/-}$/Akita). The generated mice were subjected to comprehensive electroretinogram (ERG) analyses after 6 months of diabetes.

Results: Profound effects of knocking 12/15-LO out on diabetes-induced reduction in visual system's functionality were observed. First, Scotopic Threshold Response (pSTR) peak heights, which measure the functionality of ganglion cells (GCs), are consistently lower in Akita than in wild type (WT) mice. Knocking 12/15-LO out significantly improved the overall pSTR and significantly restored the loss of the GC marker (Brn3) as compared with Akita mice. Second, diabetes reduced the functionality of cone-bipolar cells by 32%, as assessed by photopic B-Wave (pBW) amplitudes, however, this reduction was significantly improved in 12/15-LO$^{-/-}$/Akita mice compared with Akita mice ($p<0.05$, n=9). Lastly, diabetes caused a significant reduction (22%) in cone photoreceptor functionality as indicated by a lower response to natural noise stimuli (NNS) in Akita compared to WT mice ($p<0.05$, n=8) and this reduction was completely recovered in 12/15-LO$^{-/-}$/Akita mice ($p<0.05$, n=9).

Conclusion: To our knowledge, this is the first report that elimination of 12/15-LO protects against diabetes-induced visual system dysfunction. The findings may lead to new therapeutic approaches in prevention and treatment of DR.

Supported By: National Institutes of Health (5R01EY023315)

35-LB

Deep Phenotyping of a Spontaneous Nonhuman Primate Model of Diabetic Macular Edema

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Diabetic retinopathy (DR) is a diabetic complication involving damages to blood vessels in the retina that, if left untreated, can lead to blindness. It is estimated that over 93 million people suffer from DR worldwide and in fact the disease accounts for 12% of all new cases of blindness each year in the United States. Diabetic macular edema (DME) is one of the manifestations of DR, in which fluids leak from the blood vessels into the centre of the macula, causing pain, swelling, and blurred vision. However, the underlying pathogenesis of DR/DME is complex and not well understood, thus impeding the development of effective treatment. Consequently, the use of animal models of DR is of critical importance for better understanding of the underlying pathogenesis of DME, as well as developing new drugs. Non-human primate (NHP) models of diabetes are known to be the most clinically translatable animal models, where the animals develop major clinical phenotypes along the disease progression, including DR. As such, in this study we phenotyped a cohort of type 2 prediabetes/diabetes NHPs (n=123, weight: 11.5±2.0kg, age: 15.5±2.9 years) using clinically relevant circulating and imaging biomarkers. Specifically, spectral domain optical coherence tomography (OCT) was first used to identify a subgroup of the animals with significantly thickened retina (329 ± 6.77μm) with an accumulation of hard exudates and inter-retinal cysts (n= 59). Fundus fluorescein angiography (FA) imaging further confirmed the presence of retinal vascular leakage into the cystoid spaces during the late-phase FA. Levels of vascular endothelial growth factor (VEGF) in both plasma and vitreous fluid were also measured and the results appear to correlate with retina thickness (vs. aged-matched controls). Taken together, our findings demonstrate a clinically translatable NHP model for DR/DME that allows characterization of disease progression in vivo, investigation of co-morbidities, and evaluation of novel therapeutics.

36-LB

Subclinical Microvascular Lesions among Normoglycemic and Prediabetic Subjects—The PROP-ABC Study

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Background: We investigated the occurrence of microvascular lesions in nondiabetic offspring of parents with T2DM enrolled in the PROP-ABC (Pathobiology and Reversibility of Prediabetes in A Biracial Cohort)* study.

Design and Methods: We assessed albumin:creatinine ratio (MCR), vibration perception threshold (Vibratron II, Physitemp Instruments Inc, Clifton, NJ) and nonmydriatric retinal images (Zeiss digital camera, Carl Zeiss Meditec AG, Jena, Germany).

Results: There were 223 subjects (117 black, 106 white; 70% female), of whom 122 had prediabetes (impaired fasting glucose or impaired glucose tolerance) and 101 had normal glucose regulation (NGR; FPG <100 mg/dl and 2hrPG<140 mg/dl). The mean (± SD) age was 53.3 ± 9.1 years. Retinal lesions were found in 24 subjects (10.8% of the cohort), comprising macular changes (n=9), optic disc changes (n=8), epiretinal membrane (n=6), diabetic retinopathy (n=4), and vitreous opacities (n=2). The frequency of any retinal lesion was 12.3% vs. 8.9% among prediabetic vs. NGR subjects. The mean MCR was 9.95±2.1 ug/g among subjects with normal retina vs. 16.6 ±9.89ug/g among those with retinal lesions. There was a strong correlation between albuminuria and presence of retinal lesions (r=0.42, P<0.0001). The index finger vibration amplitude was 0.56 ±0.31 microns in prediabetic subjects vs. 0.43±0.25 microns in NGT subjects (P=0.013).

Conclusions: We here demonstrate a significant association between albuminuria and diverse retinal lesions in a biracial cohort of nondiabetic subjects, and further show relative impairment of vibration perception in prediabetic subjects (NCT02027571).

Supported By: National Institutes of Health (R01DK067269)

DIABETIC DYSLIPIDEMIA

37-LB

A Study of APOC3 Gene Polymorphism in Patients of Diabetes Mellitus with Hypertriglyceridemia

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Aims and Objectives: To find out the presence of Sst I polymorphism in APOC3 gene in patients of diabetes mellitus with Hypertriglyceridemia.

To find out the correlation between serum triglyceride levels and Sst I polymorphism.

To find out the correlation between serum levels of various lipoprotein fractions and Sst I polymorphism.

Methods: The present study is a hospital-based observational case-control study, carried out in 300 patients of diabetes mellitus. Of these 300 subjects, 150 were hypertriglyceridemic and served as cases, while the other 150 who were normotriglyceridemic served as controls. PCR for APOC3 gene was done in all subjects.

Result: In a total of 300 subjects, 26.33% (n=79) had shown presence of Sst I polymorphism in APOC3 gene. Polymorphic gene was present in 35.33% of cases while only in 17.33% of controls. The mean cholesterol level in the group with Sst I polymorphism was significantly higher than in group with S1 allele only. The mean triglyceride in the group with S1 allele only was 152.97±45.86 mg/dl and that in the group with Sst I polymorphism was 212.84±103.07 mg/dl, and this increased mean triglyceride level was statistically significant as determined by chi-square test. Mean HDL level was also significantly lower in the group with Sst I polymorphism as compared to that with S1 allele only. The odds ratio of developing hypertriglyceridemia was 2.6059 in those carrying the Sst I polymorphism as compared to those with only S1 allele. The association between increasing levels of triglyceride and the increasing percentage of Sst I polymorphism was also statistically significant.

Conclusion: This is the first study from North-East India to determine the Sst I polymorphism in APOC3 gene, and demonstrate a clear association between the polymorphism and serum levels of various lipoprotein fractions, including triglycerides. A prospective study comprising of a wide population group will help us in forming a definite conclusion.

Supported By: Tezpur University, India

38-LB

A Prospective, Multicentric Study to Evaluate the Effects of Saroglitazar on Non-HDL Cholesterol and Small Dense LDL Particles in Patients with Diabetic Dyslipidemia

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Saroglitazar, a dual PPAR α/γ agonist, is approved in India for the treatment of diabetic dyslipidemia (DD) not controlled with statins. DD is highly atherogenic as it is associated with high triglycerides (TG), high small dense LDL (sdLDL) and low HDL-C. In this, prospective multi-centric study conducted in patients with type 2 diabetes and triglycerides (TG) ≥200 mg/dL after lifestyle and stable statin therapy for at least 3 months, efficacy and safety of saroglitazar has been evaluated. Total 104 patients (78% male) with mean age of 59.1 ± 11.4 years were enrolled. All subjects were given saroglitazar 4mg once daily for 24 weeks. The effects of saroglitazar were evaluated at 24 weeks by using paired t-test. Six months follow-up data is available from 73 patients. At 24 weeks the primary end point showed a significant reduction in non-HDL-C (from 138 ± 51 mg/dL to 113 ± 44 mg/dL; p<0.001) and sdLDL (from 31.7 ± 11.8 mg/dL to 26.0 ± 11.9 mg/dL; p<0.001). Of the secondary end points the values of TG, HDL-C, total cholesterol and HbA1c were also significantly improved at 24 weeks (Table). No major adverse event reported during the study period. This is the first study evaluating the effect of saroglitazar on sdLDL in patients with DD. The results indicate that saroglitazar is safe and well tolerated and effectively reduces sdLDL particles along with non-HDL-C.

Table. Change in Laboratory Parameters at 24 Weeks Follow-Up (All Values are Mean±SD).

Laboratory parameters	Baseline	24 weeks follow-up	P-value
Non HDL-C (mg/dL)	138±51	113±44	<0.001
TG (mg/dL)	351±360	247±445	<0.001
LDL-C (mg/dL)	90±38	82±24	0.074
sdLDL (mg/dL)	31.7±11.8	26.0±11.9	<0.001
HDL-C (mg/dL)	35.6±7.5	40.6±8.0	<0.001
Total cholesterol (mg/dL)	172±52	154±43	<0.001
HbA1c (%)	7.98±1.66	6.95±0.71	<0.001

39-LB

Lipocalin-Type Prostaglandin D2 Synthase (L-PGDS) Knockout Mice Exhibits Hepatosteatosis Mediated by Enhanced Cd36 Hepatic Expression as a Result of Hyperinsulinemia

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Hepatosteatosis is strongly associated with hyperinsulinaemia and obesity. Previously, we demonstrated accelerated atherosclerosis and impaired glucose tolerance in L-PGDS knockout (KO) mice. Interestingly, L-PGDS KO mice also exhibit hyperinsulinemia on high fat diet in a time-dependent manner. In this study, we investigated the role of L-PGDS on liver pathophysiology using L-PGDS KO mice compared to control C57BL/6 mice) (n=6/group). Mice were kept on high fat diet (60% fat) for 14 weeks and all parameters were measured initially and at 4-, 8- and 14-weeks post high fat diet. Data were analyzed by unpaired t-test or one-way ANOVA where appropriate with p<0.05 deemed significant. Fasting insulin, blood glucose and calculated HOMA-IR were determined. KO mice showed significantly higher HOMA-RI 19.3± 4.62 and 19.7±4.74 at 8 and 14 weeks, respectively, compared to the C57BL/6 mice, which were 7.73±1.14 and 10.1±1.87 at 8 and 14 weeks, respectively. Hepatic Cd36 protein expression was significantly increased at 14 weeks in KO mice compared to the control. Liver steatosis directly correlated with elevated serum triglyceride levels, which significantly increased to 81.7±3.24 and 82.8±1.63 mg/dl at 8 and 14 weeks respectively, compared to the initial level of 64.1±5.66 mg/dl Control serum triglyceride levels were 61.1±3.49 and 73.6±3.2 mg/dl at 8 and 14 weeks, respectively. Furthermore, immunohistochemistry staining of lipid showed severely more liver steatosis in KO mice at all-time points when compared to control mice. Interestingly, KO mice always weighed less compared to the control mice at all-time points, which suggests that L-PGDS partially or fully contributes towards the development of hepatosteatosis independent of body weight. We conclude that L-PGDS is an essential component of hepatic metabolic substrate utilization and may play a significant role in diabetes-related steatosis.

Supported By: American Heart Association; George Link Foundation

FOOT CARE—LOWER EXTREMITIES

40-LB

Comparison of Peak Plantar Pressure and Peak Pressure Gradient among Patients with Prediabetes and Diabetes

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Background: Foot ulcers are a serious complication associated with diabetes peripheral neuropathy (DPN). Diabetes foot complications associated with increased ulcer risk include: 1.) decreases in plantar soft-tissue thickness, 2.) increases in plantar tissue stiffness, and 3.) increases in forefoot (FF) to rearfoot (RF) loading.

Aim: The purpose of this study was to determine whether patients with DPN demonstrate higher forefoot to rearfoot pressures during barefoot walking compared to diabetes patients without peripheral neuropathy (DWPN) and prediabetes patients without peripheral neuropathy (PWPN).

Methods: Eight PWPN, twenty-six DWPN and fourteen DPN patients participated in the study. Barefoot walking trials were performed while wearing Medilogic® pressure-measuring insoles. Peak plantar pressure (PPP) and peak pressure gradient (PPG) were measured on the right foot for the FF and RF regions. FF to RF PPP and PPG ratios were then calculated and normalized to body mass. Walking velocity was used as a co-variate for ANCOVAs. A priori statistical significance was set at α=0.05.

Results: No significant interactions were observed for Group*Region for PPP ($F(2, 89)=1.454$, $p=0.239$) and PPG ($F(2, 89)=0.579$, $p=0.563$). Main effects of region revealed significantly higher FF to RF loading in both PPP ($F(1, 89)=6.67$, $p=0.011$) and PPG ($F(1, 89)=4.02$, $p=0.048$) measures driven by DWPN and DPN patients. No significant differences were observed between groups for FF to RF PPP ($F(2, 44)=2.624$, $p=0.084$) or PPG ($F(2, 44)=1.331$, $p=0.275$) ratios.

Conclusion: Our findings suggest DWPN and DPN patients demonstrate a pattern of loading related to elevated foot ulcer risk. However, no significant difference was observed between groups for FF to RF PPP and PPG ratios. Inclusion of a more robust sample size will allow better testing of our hypothesis.

Supported By: National Institute of General Medical Sciences (GM103440)

41-LB

Temperature Regulating Shoes for Prevention of Diabetic Foot Ulcers

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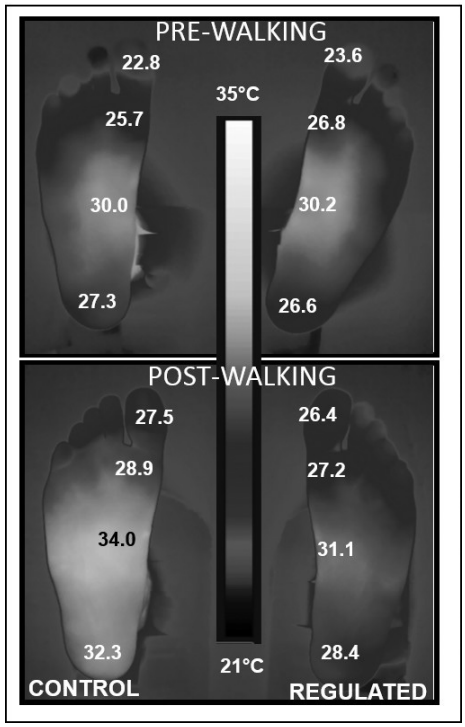
Diabetic foot ulcers (DFU) continue to burden Americans with over 100,000 amputations every year. We believe that better understanding of the etiology and a multi-factorial approach that combines in-shoe temperature regulation along with plantar stress reduction could dramatically improve this outcome. Previous research indicated that soft tissue is prone to ulceration at warmer temperatures. Likewise, animal studies indicate higher tissue resistance to break-down when cooled to 25 °C to 28 °C. Insulated diabetic footwear and load-bearing activity lead to high plantar tissue temperatures and increased risk of DFU. The purpose of this study was to design/develop a novel temperature regulating footwear and test cooling effectiveness. An extra-depth diabetic shoe was instrumented with temperature control apparatus set to cool to 28 °C. Three subjects wore this shoe and a non-cooling (control) shoe while walking for 10 minutes. Post-walking thermographs of the regulated foot revealed: forefoot temperatures below 28 °C; heel temperatures around 28 °C with a 3.9 °C bilateral cooling effect; midfoot regions 2.9 °C less than the control foot but still over 28 °C, perhaps due to poor contact with the cooling insole or a need for increased localized control of cooling. These results suggest feasibility of in-shoe temperature regulation. Further research is needed to improve our design and ultimately explore DFU prevention in a clinical trial.

Figure.



Supported By: National Institutes of Health

42-LB

Specific Deletion of PKC Delta in Endothelial Cells Restores VEGF Action in Diabetes

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Introduction: Ischemia due to narrowing of the femoral artery and distal vessels is also a major cause of peripheral arterial disease and morbidity affecting patients with diabetes. Our laboratory has previously shown that hyperglycemia reduced vascular endothelial growth factor receptor (VEGFR2) activity in ischemic muscle of diabetic mice, which was not observed in protein kinase C (PKC)-δ deficient mice. The objective of this study is to evaluate the impact of a specific deletion of PKC-δ in endothelial cells in diabetic mice.

Methods: Nondiabetic (NDM) and 3 months diabetic (DM) mice with deletion of PKC-δ specifically in endothelial cells ($Prckd^{EC-}$) were used. Ligation of the femoral artery was performed and blood flow reperfusion was measured by laser Doppler for 4 weeks. Primary lung endothelial cells (EC) isolated from each group of mice were exposed to normal (5.6mM; NG) or high glucose concentrations (25mM; HG) for 48 hours, in normoxia (20% oxygen) or hypoxia (1%) for the last 24 hour in presence of VEGF, a pro-angiogenic factor.

Results: Blood flow was recovered to 43% in DM mice compared to 78% in NDM mice. Specific EC deletion of PKC-δ enhanced reperfusion in NDM and DM mice up to 88% and 71%, respectively. Expression of VEGFR2 was decreased in ischemic muscle of DM mice, but not in DM-$Prkcd^{EC-}$ mice. In vitro, VEGF-induced Akt phosphorylation was reduced by 40% in EC isolated from DM mice compared to NDM mice, which was prevented in EC isolated from DM-$Prkcd^{EC-}$ exposed to HG+hypoxia.

Conclusion: Diabetes induced PKC-δ activity and caused inhibition of VEGF actions in EC, whereas the deletion of PKC-δ specifically in EC restored VEGF action, VEGFR2 expression and blood flow reperfusion in diabetic mice.

Supported By: Canadian Institutes of Health Research

43-LB

Multinational, Multicenter, Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy of Cyclical Topical Wound Oxygen Therapy (TWO2) in the Treatment of Chronic Diabetic Foot Ulcers

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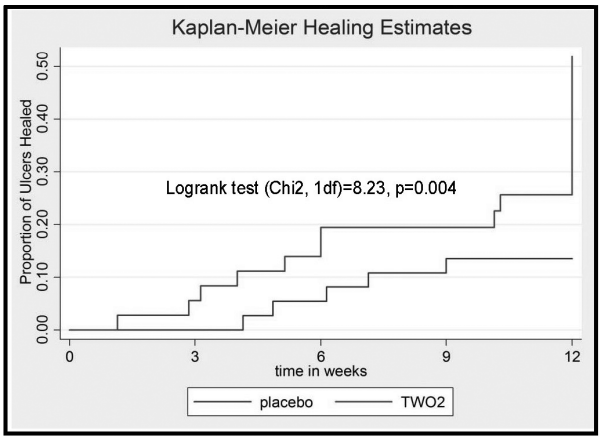
Non-healing DFUs lead to increased mortality, morbidity and health economic burden. Our RCT (NCT02326337) was undertaken to explore the efficacy of Topical Wound Oxygen (TWO2) homecare therapy in healing DFUs that had failed to heal with Standard of Care (SOC) alone. A Group Sequential Design was utilized with 2 interim analyses, requiring a significance of p<0.022 at each. All subjects meeting the incl/excl criteria were enrolled into a run-in of SOC that included gold-standard offloading and sharp debridement. Only DFUs not on a proven healing trajectory with SOC alone (<30% wound area reduction) were randomized into the active phase of the study, where they were assigned (double blind) to either active, or sham (placebo), TWO2 device treatment arms. The primary endpoint of the study was ulcers healed at 12 weeks. At the first interim analysis point of 73 subjects, the active TWO2 arm was shown to be significantly superior to the sham arm (Pearson Chi^2 =7.2707, P=0.007). Multivariable analysis using logistic regression and Cox proportional hazards modelling of the secondary outcome measure of time to heal showed no other covariates achieved significance. The active TWO2 arm showed nearly 4 times the likelihood to heal DFUs in 12 weeks compared to the sham arm HR 3.88 (95% CI 1.40 to 10.71), p=0.009.

Table 1. Results by Randomized Group using ITT Analysis

	Placebo	TWO2	Total
N	37	36	73
Gender			
Female	6 (16.2%)	4 (11.1%)	10 (13.7%)
Male	31 (83.8%)	32 (88.9%)	63 (86.3%)
UT Scale			
1A	29 (78.4%)	25 (69.4%)	54 (74.0%)
1B	2 (5.4%)	2 (5.6%)	4 (5.5%)
1C	1 (2.7%)	0 (0)	1 (1.4%)
2A	5 (13.5%)	8 (22.2%)	13 (17.8%)
2B	0 (0)	1 (2.8%)	1 (1.4%)
Neuropathic			
Yes	29 (78.4%)	28 (77.8%)	57 (78.1%)
No	8 (21.6%)	8 (22.2%)	16 (21.9%)
Infection			
Yes	3 (8.1%)	1 (2.8%)	4 (5.5%)
No	34 (91.9%)	35 (97.2%)	69 (94.5%)
Age (years)			
mean	61.9	64.6	63.3
sd	9.5	10.3	9.9
Wound area (cm^2)			
mean	3.22	3.02	37
sd	2.54	2.66	36
Duration (days)			
mean	174.6	157.9	166.4
sd	94	96.3	94.8
Hgba1c			
mean	8.07	8.43	8.25
sd	1.5	1.75	1.64
Ulcers Healed at 12 weeks	5 (13.5%)	15 (41.7%)	20 (27.4%)



44-LB

Cold Atmospheric Pressure Plasma as a Novel Treatment Modality in Diabetic Foot Ulcers—A Pilot Study

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Introduction: Antimicrobial resistance is a growing problem in the treatment of diabetic foot ulcers. Plasma devices generate an ionized gas with a cocktail of highly reactive species, electric fields and UV light. Cold atmospheric plasma (CAP) treatment has advantages over antiseptic or antimicrobial infection prevention and control; it disinfects efficiently, painlessly and instantly, without development of antimicrobial resistance. Concurrently, plasma can stimulate human cell proliferation and migration as well as microcirculation. We studied the safety of a novel CAP device, that is simple to use and in the future can be applied at a patient's home.

Method: We included subjects with diabetic foot ulcers (maximum depth 5 millimeters) without clinical signs of infection or exposed bone or joint in the wound base. Subjects were treated with CAP on a daily basis for ten days in a two-week period. Primary endpoint of this study was the occurrence of serious adverse events (SAE) as a result of treatment. Safety was defined as ≤ 10% of subjects experiencing SAE related to treatment other than infection, and ≤ 60% of subjects developing infection within 30 days after treatment. Standard protocols for wound treatment were deployed, including weekly debridement and offloading.

Results: Twenty subjects were enrolled. Three SAEs (infections) occurred at the site of application within one month of treatment, of which one occurred during treatment. Three SAEs unrelated to treatment occurred: pneumonia, toe amputation on the contralateral foot and a soft tissue infection of the ipsilateral leg. Transient adverse events (AE grade 1) during one or more applications were reported by 53% of subjects.

Discussion: No SAE other than infection occurred as a result of treatment and ≤ 60% of subjects developed an infection. The AEs were low graded and transient. The results of our study demonstrate that the application of CAP in diabetic foot ulcers is safe.

Supported By: Dutch Diabetes Research Foundation

DIABETES EDUCATION

45-LB

Virtual Diabetes Prevention Program—Effects on Medicare Advantage Health Care Costs and Utilization

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This study evaluated the impact of a virtual version of the Diabetes Prevention Program (DPP) on healthcare utilization and costs in a Medicare Advantage population. The program was offered during 2015 to a random sample of 9,497 individuals who had metabolic syndrome or prediabetes. Program enrollees (n=501) received a 12-month virtual DPP including a wireless scale, pedometer, nutrition tracker, educational lessons, health coaching, and peer group support through an online platform. Participants with available administrative claims data during the 12 months before and 24 months following program start (n=495, mean age=69 years; 64% female;

85% white) were propensity-score matched on demographic, behavioral, and clinical factors in a ratio of 1:1 to a comparison group (n=495, selected from 6,490; mean age=69 years; 58% female; 87% white) who did not receive the DPP. In the 24 months following DPP enrollment, participants averaged 0.2 inpatient admissions, 0.3 emergency department visits, and 12.2 physician visits, compared to 0.2, 0.4, and 12.0 for controls. While the utilization values do not show a large change, a difference-in-differences regression analysis of total medical and pharmacy cost for 24 months following program start showed cost savings. The adjusted difference-in-differences effect on average cumulative cost difference was $1,110 per participant, or $46.25/month. Medical and pharmacy costs were consistently lower for participants in the post-program year. Pharmacy savings were statistically significant during the last 6 months, with a 24-month cumulative adjusted savings of $408. These cost estimates do not include the cost of the program. Results suggest that a virtual DPP can change the pattern of utilization and reduce costs in a Medicare population.

46-LB

A Machine-Learning Model Accurately Predicts Projected Blood Glucose

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Background: Clinical guidelines do not specify the frequency of self-monitoring of blood glucose (SMBG) for the ~85% of people with type 2 diabetes (T2D) not on intensive insulin therapy. For these individuals, insurance covers a limited amount of testing supplies, and blood glucose (BG) checks are infrequent. With limited BG data, people may not know how foods, activity, and other factors affect their BG levels. Other, non-SMBG-dependent, approaches are needed to illustrate how self-care choices affect BG.

Objectives: 1.) Use a large dataset to train a machine learning model 2.) Use the model and minimal data inputs to predict BG values at variable times 3.) Test the accuracy of the prediction.

Methods: The One Drop | Mobile app collected 1,923,416 BG measurements from 14,706 people with noninsulin treated T2D. Contextual information (CI), when available, included demographics, health metrics (e.g., weight, A1c), and self-care. Inputs to each BG prediction included a prior BG and available CI. The model did not distinguish whether BGs with similar CI were from the same or different users. Forecast horizons were set by the time since prior BG and varied from 10 minutes to several days. Machine learning algorithms to predict BG values were trained and vetted on BGs entered prior to Sept. 2017 (83% of all BGs). BGs (17%) entered from Sept.-Nov. 2017 were held out and predicted.

Results: Users were 59% male, with 80% from North America, 9% from Europe, and 11% from elsewhere; 50% were diagnosed with T2D in the past 3 years. The median and mean absolute error of holdout predictions were 14.2 and 21.3 mg/dL respectively, with 91% of predictions within +/-50 mg/dL.

Discussion: A machine learning model with minimal inputs accurately predicts future BG values in noninsulin treated people with T2D. Whether people modify their behavior (e.g., eating less carbohydrates) after knowing a planned behavior (e.g., a 60 carbohydrate gram meal) produces an undesirable BG (>140 mg/dL postprandial) is an empirical question worth investigating.

47-LB

Reducing Hypoglycemia through Increased Knowledge of an Evidence-Based Guideline

THAYER A. CLARK, LEIGH BAK, *New Haven, CT*

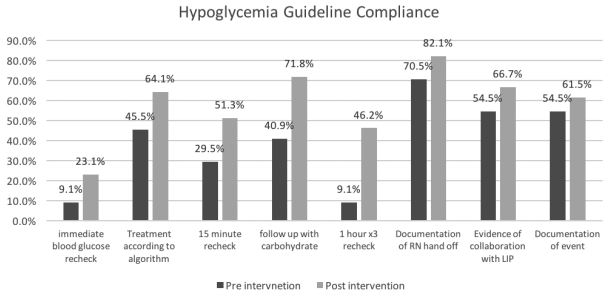
Purpose: The purpose of this project is to increase compliance with a hypoglycemia guideline to improve patient care of those experiencing hypoglycemia in the emergency department at a large academic medical center.

Methods: In order to gain an understanding of current compliance to the hypoglycemia guideline, for four weeks all hypoglycemia events were analyzed looking at eight measures (Figure) pre-intervention (n=43), and this step was repeated post intervention (n=39). The intervention period included one month dedicated to educating the staff about the guideline, implementing visual aids throughout the department, and having a staff member act as a glucose champion for all blood glucose related questions.

Results: Overall there was low compliance to the protocol initially, but after the intervention there was improvement in all eight areas analyzed. Areas that showed the most improvement included: immediate blood glucose recheck (9.1% to 23.1%), 15 minute recheck (29.5% to 51.3%), follow-up with a carbohydrate (40.9% to 71.8%), and hourly recheck x3.

Conclusion: Increasing awareness of the hypoglycemia guideline through education, and visual aids led to increased compliance. Anecdotally staff found having a glucose champion to be the most helpful in adhering to the guideline and delivering best care. Going forward having at least one assigned RN as a glucose champion is recommended.

Figure.



48-LB

Improving Quality of the Informed Consent Process—Developing an Easy-to-Read, Multimodal, Patient-Centered Format in Diabetes Research

KAREN LINDSLEY, *Atlanta, GA*

Objective: To develop a patient-centered informed consent and assessment written at a 6th grade-level that is multimodal, affordable, transportable, and readily modifiable for protocol updates.

Methods: This quality improvement initiative was performed in two phases on an actively-recruiting, familial study at a pediatric diabetes multi-site clinic. In phase I, 38 subjects completed the standard paper consent, a comprehension assessment and provided process feedback. Using feedback and the structure of the Plan-Do-Study-Act cycle a multimodal consent explanation and assessment were developed. In phase II, subjects were randomized to the standard (n=25) or the multimodal consent (n=25) and all completed the same comprehension assessment via touch-screen tablet. Primary outcomes were comparison of the individual and total comprehension assessment scores.

Results: Total comprehension scores were higher in the multimodal vs. the standard consent group ($p<0.001$) and on the elements of benefits ($p<0.001$), risks ($p<0.001$), volunteerism ($p<0.012$), results ($p<0.001$), confidentiality ($p<0.004$) and privacy ($p<0.001$).

Conclusion: A multimodal consent explanation and assessment presented sequentially on a touch-screen tablet were patient-centered enhancements to standard consent.

49-LB

Real-World Implementation of Hybrid Closed-Loop (HCL) Insulin Delivery

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Objective: Clinical trials demonstrate improved glycemic control with HCL insulin delivery systems, yet limited real-world data exists substantiating these findings. Data from the inaugural cohort of patients initiating a HCL system (Medtronic 670G) at a university medical center was used to examine real-world utilization, adherence, and glycemic control over the first 6-12 weeks of pump use.

Research Design and Methods: Data from 35 patients with type 1 diabetes (22-72 years of age) were obtained from insulin pump downloads at 4 time points: previous insulin pump, HCL start in manual-mode, 2-weeks after auto-mode transition, and between 6-12 weeks after HCL start. In person training by certified diabetes educators was performed for manual-mode, sensor initiation, and auto-mode with phone and electronic messaging following initiation of auto-mode.

Results: A total of 46 patients received HCL between June 1 and December 31 of 2017. Of these, 7 patients did not have sensors allowing them to initiate HCL, 3 did not have a 6-12 week download, and 1 never transitioned into auto-mode. Mean self-monitoring blood glucose (SMBG) per day increased from 5.15 baseline to 6.49 at 6-12 weeks ($p<0.05$) with 3.26 sensor calibrations per day. Time in auto-mode was 79.3% at 2 weeks, and 71.7% by 6-12 weeks with 82% of patients spending >50% of time in auto-mode. Over the 14-day final download there were 8.2 auto-mode exits. Time in target was 65.5% in manual-mode, 73.4% at 2-weeks ($p=0.09$), and 71.7% by 6-12 weeks ($p=0.06$). HbA_{1C} decreased 0.51% ($p=0.02$), total daily dose increased ($p=0.027$), while basal-to-bolus ratio did not change over the study period. Baseline mean SMBG and HbA_{1C}, but not basal:bolus ratio, bolus calculator use, or bolus frequency, were significant predictors of time in auto-mode and time-in-target at 6-12 weeks.

Conclusions: These data illustrate real-world implementation of HCL technology within a major medical center. Patients initiating HCL achieved acceptable time-in-auto mode and time-in-target range.

50-LB

On-Demand, App-Delivered Coaching to Enable Diabetes Self-Management in Adults with Type 2 Diabetes—A Feasibility Study

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Introduction: Diabetes self-management training (DSMT) is clinically effective but places a heavy burden on patients. Personalized coaching delivered via scalable mobile app platforms has the potential to provide much needed patient support.

Objectives: This study assessed feasibility and participant experience of a new mobile app-based platform for delivering DSMT to people with type 2 diabetes (T2D). The primary objective was to evaluate participant enrollment (recruitment into the study and completing first sign-in). Engagement with app features and health coach for the study duration was also evaluated.

Methods: Adults with T2D were enrolled into a 4-week prospective, single arm, observational study of the T2D App-based program. The T2D App provided medication reminders, meal logging, blood glucose (BG) tracking, and secure text messaging with a health coach. Participant engagement, satisfaction, participation in self-management behaviors, and finger stick BG results were also measured.

Results: Of 67 participants recruited 99% (66) were able to sign-in to the app and 64 of 67 (96%) completed the 4-week program. The majority of program participants used the T2D App daily (median 100% of days, mean 95% of days). Engagement rates in coach messaging and BG logging exceeded 95% of subjects and were sustained across the study duration. Average blood glucose (AG) in the study participants decreased from week 1 to week 4 (mean -7.8 mg/dL, sd 20.3, P=0.008). The subgroup of individuals with starting AG greater than 154 mg/dL (n=13) experienced the largest declines in AG (mean -29.6 mg/dL, sd 17.9, P<0.0001).

Conclusion: This initial feasibility study of a T2D App-based diabetes management program successfully enrolled participants and sustained their engagement. A decrease in AG was observed which, if sustained, would be clinically significant. Future studies with long term glycemic endpoints and an active control group are needed to validate this observation.

51-LB

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

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SMBG in a diabetes education program improves T2D outcomes. This study was done to evaluate if use of SMBG taught by clinical pharmacists or Certified diabetes educators improved A1C compared to diabetes classes and medication review in HRM. A pretest-posttest format was used. Subjects (n=807) were referred by providers from 5 federally qualified health centers and a practice group.

HEDIS measures collected included: A1C, BP, FPG, BMI, total cholesterol (TC), LDL-C, HDL-C, and TGs. Subjects received a validated knowledge test initially, 3 months after taking a diabetes class and at study end. A psychosocial inventory was collected initially and at study end. This multi-component model was a four-arm study comparing Diabetes Classes (DC), Pharmacist Medication Management (MTM), Pattern Management (PM) using a glucose meter data management system, and control subjects who did not participate (Ctl). Subjects had at least two interventions prior to assignment to PM. 258 subjects attended the diabetes classes, 71 in the MTM arm, 44 in the PM arm, and 138 Ctls. 296 were lost due to incomplete and/or lost data. Demographics revealed 77% in the 20-64 years old range, 21% in the >65 age group, and 16% in the <20 age group, with 65% female subjects. The mix was 86% non-Hispanic black and 13% non-Hispanic white. 60% of subjects were on Medicare/Medicaid, 30% employer-insured, and 16% uninsured. Mean A1C levels in the DC group decreased from 7.93 to 7.60, 8.06 to 7.32 in the MTM group, 7.70 to 7.28 in the PM group, while Ctls increased from 7.00 to 7.36. The PM group had the greatest mean changes in multiple measures including BMI, BP, FP, TC, and TG. The MTM group had the greatest improvement in A1C.

Conclusions: The PM group had the largest changes in overall measures of T2D control. There was increased diabetes knowledge and reduced ER visits. Thus, in HRM using PM from SMBG, the improvements suggested better monitoring of multiple metrics of relevance in T2D control.

Supported By: DC Department of Health

52-LB

Recreational Running Training Favourably Affects Antioxidants Gene Expression in Type 2 Diabetes Patients

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Increased levels of oxidative stress and inflammation have been linked to the progression of diabetes. To reduce oxidative stress and inflammation related to diabetes, diet and chronic exercise is often recommended. Data suggests high intensity interval training may be more beneficial than traditional aerobic exercise. However, appraisals of differing modes of exercise, along with explanations of mechanisms responsible for observed effects in humans, are lacking. This study assessed effects of twelve weeks of two models of high intensity intermittent training, recreational soccer (SO+D) or running (RU+D) training both combined with a caloric restricted diet vs. diet alone (D) in PBMC gene expression of type 2 diabetes patients. Training sessions were performed for 40 minutes, 3 times per week for 12 weeks. We examined PBMC mRNA expression of genes related to antioxidant enzyme activity (CASP9, SOD1, CAT, CASP3). Compared to the D group, only RU+D group resulted in increased mRNA expression of CASP9, SOD1 and CAT ($p<0.01$) whereas SO+D group mRNA expression did not alter after 12 weeks intervention. Compared to SO+D group, RU+D resulted in increased mRNA expression of CAT, CASP9, SOD1 and CASP3 ($p<0.01$) post-12 weeks treatment. The combined use of running training associated with dietary advice beneficially influenced expression of genes related to endogenous antioxidant enzyme activity and inflammation than soccer training and diet alone.

In conclusion, recreational running training was superior than soccer training and diet alone elicited lower oxidative stress and inflammation among type 2 diabetes patients.

Supported By: Fundação de Amparo a Pesquisa do Estado de São Paulo (2012/01400-0)

53-LB

Effects of Dietary Instructions Including Meal-Sequence for Prediabetes Subjects—Comparison with Conventional Approach

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Aims: In addition to total energy intake and nutritional balance, meal-sequence is an emerging focus in dietary instructions for individuals with diabetes. However, the effectiveness of dietary instructions including meal-sequence among prediabetes subjects awaits investigation.

Methods: The experiment was a multi-center, open label, cluster randomized trial. Prediabetes subjects received conventional dietary instructions (Group A) or dietary instructions including meal-sequence (Group B) after randomization and were monitored for their observance of the designated dietary instructions by public nurses through e-mail every month. Before and 6 months after dietary instructions, the subjects received physical and blood examinations as well as food frequency questionnaires.

Results: A total of 29 prediabetes subjects completed the study. Bodyweight was reduced in Group B, along with reduced total energy and fat intake 6 months after dietary instructions. Visceral fat was reduced in both groups, while FPG was reduced only in Group B. HbA1c and 1, 5-anhydroglucitol were largely unchanged in both groups.

Conclusion: The current findings show that dietary instructions including meal-sequence are more effective than conventional instructions in reducing bodyweight among prediabetes subjects.

Table. Changes of Selected Outcome Measures (*, $p<0.05$ vs. Group A; #, $p<0.05$ vs. 0 Month).

	Group A (n=11)			Group B (n=18)		
	0 month	6 month	Delta	0 month	6 month	Delta
BMI (kg/m^2)	25.6±0.39	25.9±0.50	0.32±0.16	26.1±0.59	26.0±0.74	-0.17±0.15*
Bodyweight (Kg)	75.7±1.5	76.6±1.6	0.90±0.48	79.7±2.2	79.2±2.1	-0.53±0.48*
Visceral fat area (cm^2)	153.5±5.5	140.9±9.0	-12.6±5.4#	159.2±7.0	149.5±5.8	-9.7±4.1#
Fasting plasma glucose (mg/dL)	111.0±4.9	107.4±5.5	-3.6±2.4	115.6±2.3	109.3±2.9	-6.3±1.9#
HbA1c (%)	6.00±0.17	6.07±0.15	0.07±0.07	5.94±0.08	5.99±0.08	0.05±0.04
1, 5-anhydroglucitol (μg/mL)	21.84±2.83	20.71±2.74	-1.13±0.52	20.59±2.20	20.42±2.29	-0.17±0.34

54-LB

Glycemic Index and Glycemic Load of the Diet in a Sample of Pregnant Women with Type 2 Diabetes Mellitus in Northwest Brazil

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During pregnancy, women with type 2 diabetes mellitus (DM2) needs specific dietary care to improve glycemic control and improve pregnancy outcomes. The recent updated researches points to dietary assessment and prescription based on glycemic index (GI) and glycemic load (GL) as possible strategies for achieving these goals. This study evaluated the GI and GL of the diet consumed by pregnant women with DM2. It is a quantitative-descriptive study, carried out in a diabetes treatment and care reference center in Brazil, with 20 DM2 pregnant women, randomly selected and interviewed during the outpatient routine visits follow-up. Dietary data were obtained in two 24-hour food recall (one weekday and one on weekend), one of that was collected by phone. These data were taken at home measurements and converted into grams/milliliters for subsequent determination of the GI and GL of the diets (protocol: FAO/WHO,1998) and classified according to Brand-Miller; Foster-Powell and Colagiuri (2003) and Burani (2006). Statistical analysis used the program S.P.S.S version 17, with the chi-square statistical test ($p < 0.05$). The diet of the pregnant women had a low GI (46.27 ± 7.18) and a low GL (64.15 ± 22.79). There was a positive relationship between schooling and GI, and the pregnant DM2 with a lower level of education consumed a moderate GI diet. Few studies have evaluated GI and GL in pregnancy and there are no studies with DM2 pregnant women. Similar studies point to the benefits of low GI and GL diets for glycemic control during gestation to decreased maternal-fetal comorbidities. The study population's diet had adequate GI and CG, which promotes glycemic control and reduce adverse outcomes. However, it is suggested that larger dietary assessments be performed to further deepen the relationship between diet, metabolic control and pregnancy outcomes of woman with DM2.

55-LB

Effect of Carnosine Supplementation on Cardiometabolic Risk Factors in Obesity, Prediabetes, and Diabetes—A Meta-analysis of Randomized Controlled Trials

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The burden of diabetes is rapidly increasing in line with the growing obesity epidemic. Identification of simple and easily scalable interventions is therefore urgently needed. Carnosine (beta-alanyl-L-histidine), a dipeptide with anti-inflammatory, anti-oxidative, and anti-glycating properties, has been proposed as a potential strategy for the prevention of diabetes. However, previous studies examining the effects of carnosine on cardiometabolic risk factors have produced inconsistent results. Here, we present the first systematic review and meta-analysis examining the effects of carnosine supplementation on cardiometabolic risk factors. Electronic databases including Medline, CINAHL, EMBASE and EBM Reviews were searched to identify all randomized controlled trials (RCTs) comparing supplementation with carnosine vs. placebo, usual care or other interventions. In meta-analyses of five trials with 309 participants, carnosine-supplemented groups had lower HbA1c (mean difference (MD) [95% CI]= -0.5% [-0.4,-0.6], $p<0.001$); fasting glucose (MD [95% CI]= -0.6 mmol/L [-1.1, -0.1], $p=0.03$); postprandial glucose (MD [95% CI]= -1.0 mmol/L [-1.4, -0.6], $p<0.001$); triglycerides (MD [95% CI]= -0.4 mmol/L [-0.6, -0.3], $p=0.005$); and high-sensitivity C-reactive protein (MD [95% CI]= -0.4 mg/L [-0.6, -0.2], $p<0.001$) compared with placebo. Low statistical heterogeneity was observed for all outcomes (I^2=0-1%) except fasting glucose (I^2=84%). However, heterogeneity in study design was an important limitation, including the different populations studied, and the use of varying doses of carnosine and mixed supplementation. Nevertheless, our findings suggest that carnosine may improve cardiometabolic risk factors and further well designed randomized controlled trials are needed to confirm these findings.

56-LB

Alcohol Consumption and Risk of Type 2 Diabetes Mellitus—A Nationwide Cohort Study

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Background and Aims: Alcohol consumption correlates with type 2 diabetes through its effects on insulin resistance, changes in alcohol metabolite levels, and anti-inflammatory effects. We aim to clarify association between alcohol consumption and risk of diabetes in Taiwanese population.

Methods: The National Health Interview Survey (NHIS) in 2001, 2005, and 2009 selected a representative sample of Taiwan population using a multistage sampling design. Information was collected by standardized face to face interview. Study subjects were connected to the Taiwan National Health Insurance claims dataset and National Register of Deaths Dataset from 2000 to 2013. Kaplan-Meier curve with log rank test was employed to assess the influence of alcohol drinking on incidence of diabetes. Univariate and multivariate Cox proportional regression were used to recognize risk factors of diabetes.

Results: A total of 43,000 participants were included (49.65% male; mean age, 41.79±16.31 years). During the 9-year follow-up period, 3,650 incident diabetes cases were recognized. Kaplan-Meier curves comparing the four groups of alcohol consumption showed significant differences ($p<0.01$). After adjustment for potentially confounding variables, compared to social drinkers, the risks of diabetes were significantly higher for non-drinkers (adjusted hazard ratio [AHR]=1.21; 95% confidence interval [CI], 1.09-1.34; $p<0.01$), regular drinkers (AHR=1.19; 95% CI, 1.06-1.35; $p<0.01$), and heavy drinkers (AHR=2.21, 95% CI, 1.56-3.13, $p<0.01$).

Conclusions: Social drinkers have a significantly decreased risk of new-onset diabetes compared with non-, regular, and heavy drinkers.

Supported By: Taipei City Government, Taiwan

57-LB

OPTIFAST® Medical Weight Loss Program—Outcomes in the Endocrinology Clinics at UPMC

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Background: The OPTIFAST® program at UPMC is a medically supervised program using very low calorie diet from Nestle products. It focuses on nutrition and lifestyle counseling, and transitioning to a low glycemic load diet to sustain glycemic benefits of weight loss. We evaluated the impact of our program on weight reduction in a 3-year period at UPMC clinics, and secondary parameters defining cardiovascular risk factors.

Methods: Patients were divided into Completer (C) and Non-Completer (NC) cohorts. For the C-group, HBA1C for diabetics, lipid profiles and systolic blood pressure (SBP) were compared at baseline and at >5 months. Adjusting for weight loss, effect of DM, BP and lipid-lowering drugs on HBA1C, SBP and lipid profile, respectively, was also evaluated.

Results: A total of 215 patients (mean age=49.63, 69% female) had mean baseline and end weights of 263.7 and 222.8 pounds respectively, with mean 14.04% weight loss ($p<0.0001$). 59% completed the program with mean 19.52% weight loss ($p<0.0001$). For the NC-group, weight difference from baseline was not significant.

Among diabetics, there was decrease in HBA1C (7.8% to 6%, $p<0.0001$), with a decrease in the no. of insulin units/day (71.4 to 34.6 units, $p=0.015$), but no significant decrease in the no. of noninsulin drugs from baseline to >5 months. There was a decrease in mean baseline to end SBP (139.3 to 122.5 mmHg, $p=0.0325$), and no. of BP meds (1.9 to 1.2, $p<0.0001$). There was a decrease in mean baseline to end values of: total cholesterol (TC) (192.4 to 140.7 mg/dl, $p<0.0001$), LDL (104.3 to 84.59 mg/dl, $p=0.02$) and triglycerides (TG) (209.2 to 111.9 mg/dl, $p<0.0001$). The increase in baseline to end HDL and difference in lipid lowering drugs were not significant. Adjusting for weight loss, medications had no significant association on trends of HBA1C, SBP and lipid profile.

Conclusions: Among completers, the medically supervised VLCD program at UPMC promotes significant weight loss, glycemic and SBP improvement, and lowering of TC, LDL and TG for over >5 months.

58-LB

Low Copy Number of the Salivary Amylase Gene (AMY1) Is Associated with Obesity, Dyslipidemia, and Chronic Low-Grade Inflammation but Not Insulin Sensitivity and Secretion

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Low salivary amylase gene (AMY1) copy number variations (CNVs) are associated with low serum amylase concentrations which have been shown to correlate with obesity, metabolic syndrome and predict type 2 diabetes. Recently, AMY1 CNV below 4 has been associated higher risk of obesity. Only one study has shown an association between AMY1 CNV and insulin resistance (HOMA). We assessed the relationship between AMY1 CNVs and adiposity (body mass index and dual X-ray absorptiometry), fasting and 2 hour glucose (75g OGTT), insulin sensitivity (hyperinsulinemic euglycemic clamp) and total, first and second phase insulin secretion (intravenous glucose tolerance test), inflammatory markers and adipokines (multiplex assays, Biolegend, CA) in 58 overweight and obese but otherwise healthy individuals (age 31±9 years, BMI 31±4 kg/m^2). Participants were non-smokers and had modest alcohol consumption. The participants were divided into two groups according to a median of 4 AMY1 CNVs. Individuals with less than 4 AMY1 CNVs had higher BMI (33±4 vs. 30±3 kg/m^2, p=0.04), fat mass (41±12 vs. 34±8kg, p=0.01), LDL cholesterol (3.3 ± 0.8 vs. 2.8±0.7mmol/l, p= 0.02), plasma interleukin 6 (53±56 vs. 24±22 pg/ml, p= 0.02) and leptin concentrations (0.83±0.56 vs. 0.50±0.46 ng/ml, p=0.02) compared to individuals with more than 4 AMY1 CNVs. There was no relationship between AMY1 CNVs and insulin sensitivity, insulin secretion, plasma fasting and 2 hour glucose, high sensitivity C-reactive protein, adiponectin, resistin and adipsin levels (all p>0.1). Our data indicated that AMY1 CNVs are associated with obesity, dyslipidemia and chronic low-grade inflammation but not glucose metabolism. Further larger studies are needed to confirm whether AMY1 CNVs could be a genetic biomarker for metabolic syndrome and type 2 diabetes.

Supported By: National Health and Medical Research Council of Australia (APP1047897)

59-LB

Dapagliflozin Doesn't Increase Dietary Intake in Japanese

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Purpose: We randomly allocate to dapagliflozin (DAPA) administered group (group A) and the group continuing current treatment (group B) for type 2 diabetic patients with stable glycemic control and investigate whether changes in eating behavior are observed or not.

Method: Group A orally administer 5 mg of DAPA once daily for 12 weeks in addition to current diet therapy · exercise therapy and diabetes drugs. In the group B, the current diet therapy/exercise therapy and diabetes drugs are continued for 12 weeks. Blood test and urinalysis were conducted 0 weeks, 4 weeks, 12 weeks after. The main endpoint was the comparison between the two groups of total calorie intake change using brief-type self-administered diet history questionnaire (BDHQ) at 12 weeks. And the secondary endpoints were comparison between two groups of the following items before and after treatment. 1.) nutritional status based on BDHQ, 2.) body weight, abdominal girth, blood pressure, grip strength, 3.) blood glucose profile, 4.) lipid profile.

Subject: There were 76 cases of consent to participation in this study, but since there were three dropout cases, the analysis subjects were 35 patients in group A, 38 patients in group B.

Result: In the group A, HbA1c (7.47±0.67 vs. 7.09±0.56 p<0.0001) and body weight (70.20±11.79 vs. 69.15±12.13 p<0.0002) decreased significantly, but no change in total caloric intake by BDHQ (1675.23±580.67 vs. 1636.92±625.32) was observed. On the other hand, in the group B, no changes in total calorie intake by BDHQ, HbA1c, body weight, were observed.

Discussion: This study indicated that no increase in dietary intake was observed upon weight loss by DAPA. It has already been reported that weight loss due to DAPA improves patients' QoL. Improvement of this QoL may be expected to have a positive influence on improvement of treatment motivation and diet therapy/exercise therapy which is the basis of diabetes treatment. This study suggests that in humans, unlike animal experiments, calorie loss by DAPA may have a positive effect on dietary behavior.

60-LB

A Whole-Grain Diet Confers Metabolic Advantages in Glucose Metabolism Compared to a Macronutrient-Matched, Refined-Grain Diet

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Observational studies suggest diets high in whole grains (WG) may confer metabolic benefits over diets based on refined grains (RG) for overweight/obese individuals, thus preventing the development of type 2 diabetes (T2D). However clinical data have been inconclusive, in part due to metabolic heterogeneity. Therefore, we investigated a WG and RG diet in individuals at high risk (HR) or low risk (LR) of developing T2D based on 1 hour glycemic level during an OGTT (oral glucose tolerance test). We conducted a double-blind randomized crossover trial in 15 overweight/obese adults. Participants were administered a 4 hour, 75g OGTT and stratified as HR or LR of developing T2D (HR: 1 hour OGTT glucose (GLU) ≥155 mg/dl; LR: 1 hour OGTT GLU <155 mg/dl). Isocaloric WG and RG diets were provided for two 8 week periods with 10 week washout. Macronutrients were matched except for WG or RG (50g/1000 kcal). Fifteen subjects completed the trial, 10 HR (38±3 years, 33±2 kg/m^2, 1 hour OGTT GLU 201±8 mg/dl) and 5 LR (38±4 years, 35±2 kg/m^2, 1 hour OGTT GLU 126±5 mg/dl). Groups differed only by 1 hour OGTT (p<0.05). Weight loss was similar but only HR reached statistical significance (-2.1 kg, p<0.05). HR-WG improved insulin sensitivity (Matsuda Index, +21%, p<0.05). Further, HR-RG had a significant negative association between change in BMI and Matsuda Index vs. WG (r^2=0.41, p<0.01). LR-RG reduced GLU clearance (iAUC 180 minutes, +27%, p<0.05 vs. WG). In agreement, LR-RG increased OGTT insulin (iAUC p<0.05 at 120, 180 and 240 minutes) and c-peptide (iAUC p<0.05 at 60 and 120 minutes). Interestingly, 1 hour OGTT GLU predicted change in waist circumference in WG (n=15, r^2=0.36, p=0.02), suggesting those with more impaired GLU tolerance may acquire greater benefit from WG. We observed differential effects of a WG and RG diet in overweight/obese adults. These data suggest a WG diet may improve measures of glucose metabolism in individuals at high risk of developing T2D, whereas a RG diet may impair glucose metabolism in lower risk individuals.

Supported By: Nestlé (to J.P.K.); National Institutes of Health/National Center for Research Resources (UL1RR024989); National Institutes of Health (T32 DK007319 (to J.P.K.)

PSYCHOSOCIAL, BEHAVIORAL MEDICINE

61-LB

High Prevalence of Distress among Patients with Type 2 Diabetes (T2DM)—A Hospital-Based Cross-Sectional Study from South India

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Background: Diabetes distress (DD) refers to unique, often hidden emotional burdens and worries, distinct from clinical depression, that are part of the spectrum of patient experience when managing diabetes.

Aim: To assess DD and its association with various parameters in patients with T2DM.

Methodology: A cross sectional study was done on 262 out-patients with T2DM in a multispecialty hospital in South India. DD was measured by DDS-17, a 17-item self-reported DD scale used with subscales in 4 domains - Emotional burden (EB), Physician, Regimen and Interpersonal distress. Overall score <2.0 was little or no distress, 2.0-2.9 moderate, ≥3.0 was high distress. Data was analysed using SPSS version 11.5.

Results: Mean age of participants was 59.7 ± 9.1 years. Females constituted 71.8%. BMI was ≤ 25kg/m2 in 32.8%. Duration of diabetes was <10 years in 42%. Insulin was used by 45%. Mean HbA1c was 8.7±1.7%. Prevalence of DD was 27.9%, with moderate distress in 22.1% and high distress in 5.7%. Mean total DD score was 1.67± 0.59. Mean for EB, physician-related, regimen-related and interpersonal distress were (2.1 ± 1.02), (1.09 ± 0.33), (1.92 ± 0.89), (1.30± 0.76) respectively. Total DD had significant association with BMI (p=0.04), duration of T2DM (p=0.04), HbA1c (p=0.01), neuropathy (p=0.002) and nephropathy (p=0.008). EB, considered most important domain, was associated with duration of T2DM (p=0.02), insulin use (p=0.002), neuropathy (p<0.001), nephropathy (p=0.008), high HbA1c levels (p=0.001), ASCVD in females (p<0.001). Regimen related distress was more in those with high HbA1c (p=0.001) and smokers (p=0.04).

Discussion: The study, first of its kind from South India, identifies high prevalence of DD in this population. Assessment of DD should be integrated into patients' self-care plan. Patients become more involved in managing diabetes if their specific emotional distress are taken care of, and have a better sense of social care, health control and self-efficacy.

62-LB

Reduction of Diabetes and Cardiovascular Risk in a Workforce after Digital Behavioral Counseling

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Background: We asked whether the integration of digital behavioral counseling with employer-sponsored annual biometric screening could reduce the risk of obesity-related chronic disease in a U.S. workforce.

Methods: We evaluated a cohort (n=113) who participated in an employer-sponsored annual wellness program with year-end biometric screening and enrolled in a digital behavioral counseling program. Individuals were included in the analysis if they participated in the wellness program in 2015, had prediabetes (fasting glucose (FG) 100 to 125mg/dL or Hb1Ac 5.7 to 6.4%) and a BMI ≥25 kg/m^2 in 2016, and agreed to participate in a digital behavioral counseling program followed by year-end biometric screening in 2017.

Results: The participants were 75% women and 61% Caucasian, 28% African American. At the 2016 year-end biometric screening, which preceded digital behavioral counseling, the characteristics of the cohort (mean± sd) were age, 50.0±9.9 years; BMI, 37.1±8.6 kg/m^2; Hb1Ac, 6.1±0.6%; and FG, 106.9±24.2 mg/dL. Following behavioral counseling, 28% of the participants lost 5% or more of body weight. Hb1Ac and FG levels both fell below prediabetic thresholds for 32% of the participants. Other biometric outcome measures improved (Table).

Conclusions: Digital behavioral counseling was effective in reducing risk for both diabetes and cardiovascular disease in a workforce cohort.

Table. Change in Annual Biometric Screening Results.

	The year preceding counseling (2015 to 2016)	The year counseling received (2016 to 2017)	P value (paired t-Test)
BMI (kg/m^2)	+0.66	-1.18	<0.0001
Hb1Ac (%)	+0.06	-0.22	0.001
Fasting Glucose (mg/dL)	+5.85	-2.84	0.02
Triglycerides (mg/dL)	+12.0	-17.2	0.01
10-year ASCVD risk* (%)	+1.83	-0.48	0.01

*Atherosclerotic Cardiovascular Disease Risk (2013 ACC/AHA Cardiovascular Risk Guideline).

63-LB

The Validity and Reliability of Japanese Version of the Diabetes Distress Scale for Adult Patients with Type 2 Diabetes

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Diabetes related distress is common for patients with type 2 diabetes (T2D), which exacerbates glycemic control through negative effects on emotional and physical well-being and self-care behaviors. Diabetes Distress Scale (DDS) is a widely used instrument to measure diabetes related distress.

The aim of this study was to develop the Japanese version of the DDS (DDS-J) and examine its psychometric properties. DDS-J was developed conceptually equivalent to the original English version by forward and backward translations and adjustments of inappropriate terms. The investigation was conducted in 132 (mean age 64.5 years, 67.4% male, mean duration 14.2 years, mean HbA_{1c} 7.7%) T2D patients at outpatient department of 2 hospitals in Aichi, Japan from February to March 2017. Cronbach's α was used to assess reliability, and factor analysis to analyze validity. The 5-item World Health Organization Well-Being Index (WHO-5) and Patient Health Questionnaire-9 (PHQ-9) scale were adopted to evaluate the criteria-related validity. The scores of DDS-J, WHO-5 and PHQ-9 were calculated, then their relationship analyzed using Pearson correlation analysis. Four factors of regimen-related distress (RD), emotional burden (EB), physician-related distress (PD), and diabetes-related interpersonal distress (ID) were extracted by exploratory factor analysis. This factor structure was the same as the original. The overall Cronbach's α was 0.91, while ones for RD, EB, PD, and ID were 0.86, 0.87, 0.73 and 0.86, respectively. The total DDS-J score was 24.4±18.7, WHO-5 15.3±5.4 and PHQ-9 3.5±4.4. The total DDS-J score showed a weak but significant correlation with WHO-5 ($r=-0.376$, $p<0.01$) and PHQ-9 ($r=0.425$, $p<0.01$).

In conclusion, DDS-J have good validity and reliability, and can be used as an effective tool to assess diabetes related distress of Japanese adult T2D patients. Furthermore, diabetes related distress is associated with well-being and depression in the studied patients.

Supported By: Japan Society for the Promotion of Science

64-LB

Longitudinal Changes in Depression and Glycemia in Adults with Type 1 Diabetes

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To assess change in depression over ≥4 years in adults with type 1 diabetes (T1D) and the association between change in depression and glycemic outcomes, we examined PHQ-8 data in adults in the T1D Exchange Clinic Registry with T1D duration ≥ 1 year (N= 2547; 57% female, 92% non-Hispanic white, year 1 age 43±16 years). PHQ-8 score ≥10 defined "depressed." Linear regression was used to assess association of continuous outcomes and depression; logistic regression was used for categorical outcomes. At year 1/year 5, 9%/11% were depressed. In this sample, 126 (5%) had Persistent Depression (depressed at year 1 and year 5), 112 (4%) Resolved Depression (depressed at year 1, not at year 5), 148 (6%) New Year 5 Depression (not depressed at year 1, depressed at year 5), and 2161 (85%) Not Depressed at year 1/year 5. Of those depressed at year 1, 53% were depressed at year 5; of those not depressed at year 1, 6% were depressed at year 5. Participants with persistent depression/new year 5 depression had a significant increase (↑) in A1c [adj mean ↑ 0.5± 0.2/0.5± 0.2; adj mean 8.1±0.1 for both; adj P's=0.001]; those not depressed at year 1/year 5 showed a trend in ↑A1c [0.3±0.1; adj mean 7.8±0.1; adj P=0.04]. Those with resolved depression did not show change in A1c [0.2±0.2; adj mean 7.7±0.2; adj P=0.28]. Those with persistent depression/new year 5 depression were more likely to report new year 5 DKA (DKA year 5 ǀ no DKA year 1) than those not depressed at year 1/year 5 (adj P's=0.03/0.04). There were trends for those with persistent depression to be more likely to report new year 5 severe hypoglycemia (SH) than those not depressed (11.1% vs. 4.8%); and for those with resolved depression to be less likely to report new year 5 SH (3.6 vs. 4.8%, adj P's=0.09/0.11). Depression category was not associated with change in BMI (adj P=0.80). As a continuous variable, ↑in PHQ-8 was associated with ↑ in A1c (adj P<0.001), but not with new year 5 SH or BMI change (adj P>0.50). Depression (persistent or new year 5) has a negative impact on glycemic control over time. Adults with T1D should be screened and treated for depression.

65-LB

I Wanted Diabetes Out—Lived Experiences of Diabetes Burnout from Bloggers with Type 1 Diabetes

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Objective: To define and understand diabetes burnout through thematic analysis of narrative posts, written by adults with type 1 diabetes (T1D), published in publicly available blogs.

Research Design and Methods: A qualitative thematic analysis of 35 posts published in 21 blogs from the U.S., UK, and Ireland, written by adults with T1D, provided the basis for definition(s) of diabetes burnout. Data management (Nvivo 11 Pro) and analysis included three phases: immersion, reduction, and interpretation (kappa=.91).

Results: Findings included five main themes that described diabetes burnout: 1.) Burnout is a "detachment" from diabetes care; 2.) the "demanding life" of diabetes leads to burnout; 3.) struggling with "perfect" numbers adds to burnout; 4.) "life events" are catalysts to burnout; 5.) and overcoming burnout is like "climbing out of a difficult hole."

Conclusions: Analysis of blogs provided unique insights into the concept of diabetes burnout. Five themes were identified that ranged from detachment from diabetes care to difficulties in overcoming diabetes. These data provide a next step into understanding diabetes burnout and factors that may co-occur. Further research needed to advance science of diabetes burnout to improve quality of care and quality of life of individuals with diabetes.

66-LB

Insomnia Is Associated with an Increased Risk of Type 2 Diabetes in the Clinical Setting

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Aims: Determine association between insomnia and risk of type 2 diabetes (T2DM).

Methods: We conducted a retrospective panel cohort study to examine risk of developing T2DM among prediabetes patients with and without insomnia (physician identified or insomnia medication dispense). Participants with prediabetes (physician identified or by 2 laboratory tests) between 1/1/2007 and 12/31/2015 were followed until 12/31/2016. Patients were determined to have T2DM when two of the following occurred within 2 years: physician-entered outpatient T2DM diagnosis, dispensing of an anti-hyperglycemia agent, A1C ≥6.5%, or fasting plasma glucose >125 mg/dl. One hospital inpatient stay with an associated T2DM diagnosis was also sufficient for T2DM classification.

Results: Our cohort comprised 79,608 persons with prediabetes. Almost 30% (23,370) were classified as having insomnia during the observation period. After adjustment for traditional risk factors, those with insomnia were 28% more likely to develop T2DM than those without. This estimate was essentially unchanged after adjusting for baseline A1C level (Table).

Conclusions: The association of insomnia with increased T2DM risk is similar to that of traditional risk factors such as overweight and nonwhite race. This finding has the potential to be of great value as a modifiable factor in diabetes prevention efforts.

Table: Risk of developing T2DM according to insomnia and other potential risk factors

		Baseline model (N=79,608)	Model adjusted for baseline A1c (N=43,922)
Risk factor	Description of comparison	Hazard Ratio (95% Confidence Limits)	Hazard Ratio (95% Confidence Limits)
Insomnia	Yes vs No	1.28 (1.23, 1.33)	1.34 (1.27, 1.43)
Baseline AGE	Per 10 year increment	1.12 (1.11, 1.34)	1.05 (1.03, 1.07)
Baseline BMI	High risk obesity (BMI ≥40 kg/m^2) vs normal weight	3.54 (3.31, 3.78)	2.60 (2.36, 2.88)
	Low to moderate risk obesity (BMI 30-39.9 kg/m^2) vs normal weight	2.03 (1.92, 2.15)	1.60 (1.47, 1.75)
	Overweight (BMI 25- 29.9 kg/m^2) vs normal weight	1.24 (1.17, 1.32)	1.11 (1.01, 1.21)
Baseline A1C	Per 0.1% increment	NA	1.28 (1.26, 1.29)
Sex	Male vs Female	1.05 (1.01, 1.08)	1.17 (1.11, 1.23)
Race	Asian vs White	1.64 (1.51, 1.78)	1.15 (1.02, 1.30)
	Black vs White	1.33 (1.21, 1.45)	0.92 (0.80, 1.05)
	Other vs White	1.23 (1.16, 1.31)	1.05 (0.95, 1.16)
Hispanic	Yes vs No	1.09 (1.00, 1.19)	1.09 (0.96, 1.23)
History Congestive Heart Failure	Yes vs No	2.15 (1.94, 2.38)	2.16 (1.85, 2.53)
History of Myocardial infarction	Yes vs No	1.43 (1.21, 1.69)	1.70 (1.35, 2.15)

67-LB

Diabetes Distress—Provider Perspectives

ANN-MARIE JOHN, *Springfield, VA*

Purpose: Though many studies focus on patient perspectives of diabetes distress (DD), provider perceptions of DD require further investigation. Defined as the diabetes-specific distress related to the emotional and behavioral burden of living with type 2 diabetes (T2DM), DD is a major psychological challenge to self-management. The purpose of this qualitative study was to explore how primary care team members identify factors that contribute to DD future intervention.

Methods: Eighteen care providers from three rural nurse-managed interprofessional clinics located in Northern Virginia participated in the study. Using purposive sampling, providers were interviewed to obtain perspectives on DD in the management of T2DM. Face-to-face interviews were conducted, digitally recorded, and transcribed. Two researchers coded the transcripts into themes. Data collection and analysis occurred sequentially using a constructivist grounded approach.

Results: Provider narratives identified a lack of awareness of DD in their experiences with T2DM-related psychological and emotional challenges in a low-income, immigrant, underserved patient population. When asked about DD, most participants discussed the biomedical aspects of diabetes management, such as diet, exercise, medications, and blood glucose management. The key facilitator identified by the few participants who recognized DD was the interdisciplinary team practice model. Perceived barriers included: 1.) limited knowledge of DD by the healthcare team, 2.) under recognition of DD in reported practice, 3.) time constraints, and 4.) limited clinical experience with treating or referring patients with DD to appropriate mental health services.

Conclusions: The American Diabetes Association (ADA) Standards of Medical Care in Diabetes recommends ongoing assessment and monitoring of DD to prevent and delay its progression. Therefore, the challenge is to enhance provider understanding of DD and promote strategies and activities that help reduce DD and improve diabetes outcomes.

68-LB

Development and Content Validation of the Health Care Transition Outcomes Inventory

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Background: Much of the literature on the healthcare transition from pediatric to adult centered-care focuses on how to prepare adolescents and young adults with chronic illness for a successful healthcare transition, with much less emphasis on how to measure whether the healthcare transition was successful. Research on healthcare transition outcomes is fraught with methodological difficulties, making it difficult to generalize and compare findings across studies. To address these gaps, we began an integrative research agenda to develop a multidimensional, multi-informant (i.e., young adult, parent, and healthcare provider versions) measure of healthcare transition outcomes, the Healthcare Transition Outcomes Inventory (HCTOI). Our preliminary qualitative study defined six content domains for the measure. The current study describes the development and refinement of the HCTOI item pool.

Results: Using rigorous measurement development methods including mixed qualitative and quantitative methods, the researchers developed a pool of 88 items evaluating the extent to which a young adult with T1D is successful on each of the six domains of healthcare transition outcomes. Ten physician and psychologist experts provided content validity ratings and feedback and the item pool was reduced and refined to 69 items. Cognitive interviews were then conducted on every item with end users (young adults, parents, and healthcare providers) and the item pool was further reduced to 54-item young adult- and parent-versions and a 47-item healthcare provider version.

Conclusions: Each stage informed development and refinement of the item pool. The HCTOI represents the first multi-informant, rigorously developed item pool that comprehensively measures the multiple components of the transition from pediatric to adult specialty healthcare. Discussion includes clinical implications and next steps for validation, item reduction and refinement.

Supported By: Nemours Biomedical Research

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—GLUCOSE MONITORING AND SENSING

69-LB

Cost Calculation and Adherence to ADA Recommendations Based on a Flash Continuous Glucose Monitoring System for People with T1DM or T2DM Using MDI Therapy

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Background: A novel, factory-calibrated, flash continuous glucose monitoring system (flash CGM; FreeStyle Libre™ system) was approved by FDA in September 2017. The clinical benefit of flash CGM as a replacement for routine self-monitoring of blood glucose (SMBG) for people using MDI therapy has been assessed in RCTs in T1DM (Bolinder, 2016) and T2DM (Haak,2017). In both 6-month studies, people using flash CGM achieved a substantial reduction in hypoglycemia compared with those using SMBG, without increasing HbA1c or reducing the dose of insulin. A cost calculation based on ADA recommendations is presented, comparing the acquisition cost of flash CGM with routine SMBG.

Methods: The ADA Standards of Medical Care in Diabetes (2017) recommend between 6 to 10 glucose tests per day for people with diabetes who are using MDI therapy. List prices are $1.42 per strip and $36.00 per sensor. Sensor duration is up to 10 days. In the T1DM RCT, people using flash CGM also used 0.5 SMBG tests/day on average; in the T2DM RCT, people using flash CGM also used 0.3 SMBG tests/day. The calculation is based on a 30-day month.

Results: Monthly cost of 10 SMBG/day is $426.00 and of 6 SMBG/day is $255.60. This is compared with the monthly sensor cost of $108.00, to which should be added the monthly cost of occasional SMBG based on utilization in the RCTs: $21.30 per person per month (PPPM) for people with T1DM and $12.78 for people with T2DM. For those testing 6 times/day, flash CGM saves over $120 PPPM compared with SMBG and it saves over $290 PPPM for people testing 10 times/day. For people testing more than 3 times/day, flash CGM has a lower acquisition cost than SMBG.

Conclusion: For people with T1DM or T2DM who use MDI therapy, flash CGM has demonstrated improved adherence to the ADA recommendation as well as reduced acquisition cost when compared with routine SMBG.

Supported By: Abbott Diabetes Care

70-LB

Real-World Patterns of Daytime and Nocturnal Hypoglycemia during Flash Continuous Glucose Monitoring

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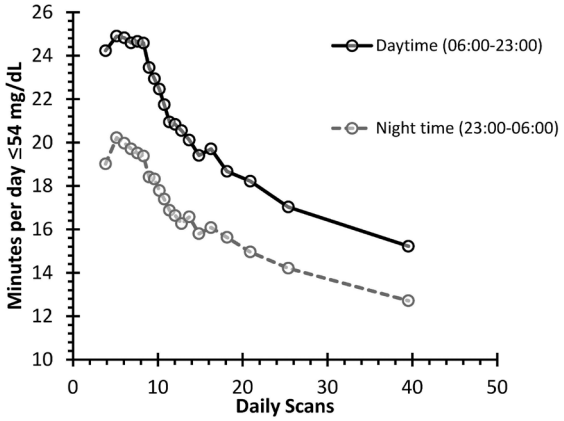
This study evaluated patterns of daytime and nocturnal hypoglycemia during flash continuous glucose monitoring using the FreeStyle Libre™ system. Users scan the sensor to collect the current glucose, trend, and up to 8 hours of glucose readings which are automatically stored every 15 minutes. The internet-connected PC-based software uploads the de-identified 90-day reader data to a database. De-identified data from September 2014 to September 2017 of all sensors with at least 120 hours of operation were analyzed from 237,747 readers and 1,569,588 sensors worldwide (88% from Europe). Readers were ranked by scan frequency and allocated to 20 equally sized groups. The association of significant hypoglycemia (≤54 mg/dL) and scan rate were analyzed. Users performed a mean (SD) of 13.2 (9.0) glucose scans per 24 hours, with 11.5 (8.1) during the day (06:00-23:00) and 1.7 (1.5) during the night (23:00-06:00). Time in significant hypoglycemia (≤54 mg/dL) decreased from 24.2 to 15.2 minutes/day comparing low with high frequency scanners during the 17-hour day period ($p<0.001$), with a similar pattern overnight (19.0 and 12.7 minutes/night, $p<0.001$). When expressed as a proportion of time, hypoglycemia accounted for 2.4 to 1.5% of daytime glucose (for low to high frequency scanners), prevalence of night time hypoglycemia was 4.5 to 3.0%. The benefits of scanning frequently during the day are evident at night time.

Figure.



71-LB

Glucose Variability and Flash Glucose Monitoring in the Real World

SUJIT JANGAM, YONGJIN XU, GARY HAYTER, TIMOTHY DUNN, *Alameda, CA, Oakland, CA*

High glucose variability is associated with increased hypoglycemia. Previous analyses of real-world data have shown that increased testing using flash glucose monitoring (FreeStyle Libre™ system) is associated with lower hypoglycemia and hyperglycemia. Here we studied: 1.) The relationship between glucose variability and hypoglycemia/hyperglycemia during flash glucose monitoring 2.) The relationship between increased glucose testing and glucose variability. De-identified glucose data is collected from individuals using the system when they upload data from their readers to the desktop software. Data from 237,747 individuals was analyzed. To understand the relationship between variability and hypoglycemia/hyperglycemia, individuals were divided into groups of high and low glucose variability using CV=36% as the threshold. Hypoglycemia (time below 70mg/dL) and hyperglycemia (time above 180mg/dL) metrics were then analyzed in the two groups. To understand the impact of testing frequency on glycemic variability, individuals were divided into 20 equal sized groups spanning the full range of daily testing frequency. Average CV was then calculated for each group. It was observed that individuals with high variability showed 35% more hyperglycemia (10.1±5.9 hours/day) compared to individuals with low variability (7.5±7.0 hours/day). Similarly, individuals with high variability showed 167% more hypoglycemia (144±281 minutes/day) compared to those with low variability (54±185 minutes/day). It was observed that increased testing with the system was associated with lower glucose variability. CV decreased from 40.6% to 34.5% from the lowest to highest testing frequency groups. High variability is associated with both increased hyperglycemia and hypoglycemia in a large sample population from the real world. Increased testing is associated with decreased glucose variability.

72-LB

A Meta-analysis of Real-World Observational Studies on the Impact of Flash Glucose Monitoring on Glycemic Control as Measured by HbA1c

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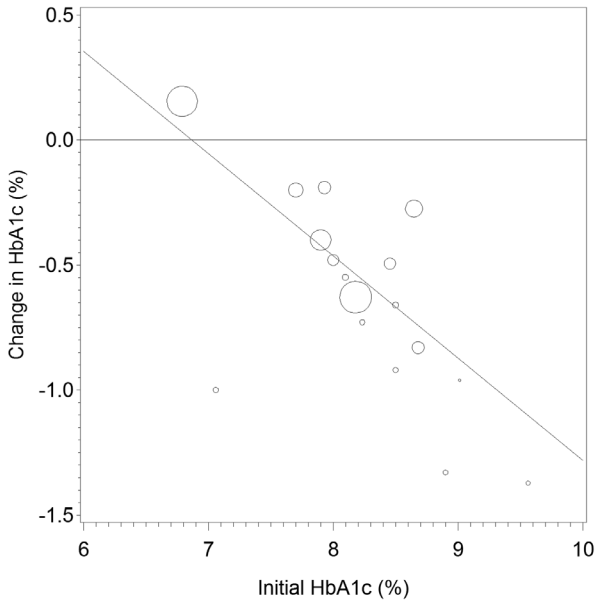
Flash glucose monitoring is proven in randomized clinical trials to reduce the amount of time that people with type 1 or type 2 diabetes spend in hypoglycemia, with glucose below 3.9 mmol/L (70 mg/dL). Here we report a meta-analysis of real world observational studies on the impact of flash glucose monitoring on glycemic control as measured by HbA1c. A series of 17 studies were identified as reporting longitudinal HbA1c data in a total 1338 participants with type 1 (n=1112) or type 2 diabetes (n=226) using the FreeStyle Libre flash glucose monitoring system. Data included observations on children, adolescents and adults. The studies were reported in peer-reviewed published manuscripts, congress poster presentations and in-press data.

Meta-analysis of change in HbA1c was performed using trial as a random effect and weighting with the inverse of the within trial variance. Overall mean change in HbA1c was -0.56, 95% CI (-0.76, -0.36), with substantial heterogeneity between trials (I^2=92.6%). Meta-regression was performed with the covariate initial HbA1c and treating trial as a random effect (Figure).

No significant differences were detected based on length of study, type of diabetes (type 1 vs. type 2) or children vs. adults.

Figure.



Supported By: Abbott Diabetes Care

73-LB

Comparing Patch vs. Pen Bolus Insulin Delivery in Type 2 Diabetes Using Continuous Glucose Monitoring Metrics and Profiles

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Patients with T2D (N=97, A1c ≥7.5% on basal insulin) used DexCom G4 CGM in a substudy of a large RCT (N=278) to evaluate bolus insulin delivery by patch (Calibra Medical) vs. pen (Novolog Flexpen®) using an SMBG-based titration algorithm.

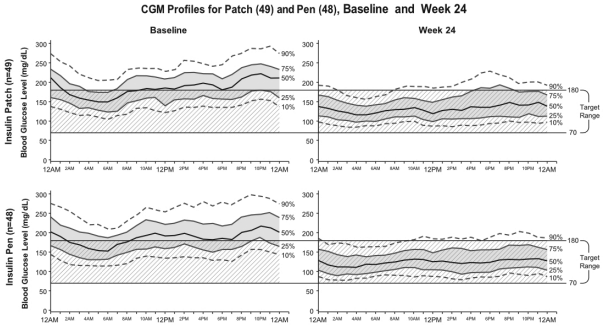
There was a significant improvement (p<0.0001) in A1c and all CGM metrics at week 24, but no difference between groups (Table). CGM profiles (Figure) demonstrate it is possible to optimize basal-bolus therapy, dramatically increasing time-in-target range (70-180 mg/dL) with minimal significant hypoglycemia (<54 mg/dL) while achieving a flat bedtime to AM glucose profile.

This is one of the first trials to clearly demonstrate how using CGM metrics and CGM profiles in T2D can provide a more clinically relevant comparison of different approaches to optimizing glucose management.

Table. CGM Metrics for Patch (49) and Pen (48), Baseline and Week 24.

	Patch Baseline	Patch Week 24	Pen Baseline	Pen Week 24
Central Lab A1c, % (± SD)	8.54 ± 0.90	6.82 ± 0.95	8.75 ± 1.03	6.70 ± 0.79
CGM Average Glucose, mg/dL (± SD)	188.9 ± 40.9	142.4 ± 31.4	200.3 ± 41.4	140.4 ± 28.3
CGM Glucose >250 mg/dL, % time (± SD)	18.3 ± 18.3	5.6 ± 9.7	23.4 ± 21.8	4.6 ± 8.3
CGM Glucose >180 mg/dL, % time (± SD)	50.4 ± 26.1	21.1 ± 19.9	56.7 ± 24.8	19.7 ± 17.5
CGM Glucose 70-180 mg/dL, % time (± SD)	48.4 ± 25.2	74.1 ± 18.7	42.4 ± 23.8	75.2 ± 16.1
CGM Glucose <70 mg/dL, % time (± SD)	1.2 ± 2.4	4.7 ± 5.2	0.9 ± 3.2	5.1 ± 5.8
CGM Glucose <54 mg/dL, % time (± SD)	0.2 ± 0.7	1.1 ± 2.0	0.2 ± 1.2	1.2 ± 2.0

Figure.



Supported By: Calibra Medical

74-LB

Real-World Improvement in Above-Target Estimated A1c with Sequential Use of Professional Flash Continuous Glucose Monitoring for Individuals with Diabetes

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Professional flash continuous glucose monitoring using the FreeStyle Libre ProTM system is recently available in the U.S. This is one of the first real-world studies evaluating glucose metrics of sequential monitoring periods using a cross-sectional observational design. Between September 2016 and January 2018, de-identified data from 2,836 users having 2 sequential sensors (at least 5 days each) were divided by the 1st sensor above and below an estimated A1c (eA1c) of 7.5%. Glucose metrics for the two sensors were compared. For those starting above an eA1c of 7.5%, the eA1c reduced from 9.6% to 8.7% (-0.9%, p<0.001), and time in range (70-180 mg/dL) increased from 7.8 to 10.5 h/day (2.7 h/day, p<0.001). Time above 180 mg/dL decreased from 15.7 to 12.5 h/day (-3.2 h/day, p<0.001), while hypoglycemia below 70 mg/dL increased but stayed below 5.0% (29 to 59 minutes/day, 30.1 minutes/day change, p<0.001). For those at an eA1c of 7.5% or lower, eA1c increased but stayed in target (6.4% to 6.9%, 0.5% change, p<0.001), while time below 70 mg/dL reduced by 22%, from 115 to 91 minutes/day (-24.8 minutes/day, p<0.001). Professional glucose monitoring in clinical practice aids in the reduction of hyperglycemia and increased time in range while maintaining minimal hypoglycemia for those with average levels above target. Those with average levels in target benefit by reduced exposure to hypoglycemia.

Table.

	Sensor 1 eA1c ≤ 7.5%					Sensor 1 eA1c > 7.5%				
Number of Individuals	1,155					1,681				
Days between Sensor Applications	144 (88)					153 (90)				
	Sensor 1	Sensor 2	Mean Difference	Relative Change	p value	Sensor 1	Sensor 2	Mean Difference	Relative Change	p value
eA1c (%)	6.4 (0.8)	6.9 (1.5)	0.5 (0.04)	8%	<0.001	9.6 (1.9)	8.7 (2.1)	-0.9 (0.05)	-9%	<0.001
Time in range 70-180 mg/dL (%)	72.9 (14.6)	67.1 (21.7)	-5.8 (0.6)	-8%	<0.001	32.5 (17.1)	43.8 (23.8)	11.3 (0.6)	35%	<0.001
Time above 180 mg/dL (%)	19.2 (12.1)	26.7 (22.5)	7.5 (0.6)	39%	<0.001	65.4 (17.9)	52.1 (25.8)	-13.3 (0.6)	-20%	<0.001
Time below 70 mg/dL (%)	8.0 (9.7)	6.3 (8.5)	-1.7 (0.3)	-22%	<0.001	2.0 (3.4)	4.1 (6.0)	2.1 (0.1)	105%	<0.001
SD (mg/dL)	48 (18)	50 (21)	2.4 (0.48)	5%	<0.001	76 (23)	71 (25)	-5.3 (0.48)	-7%	<0.001
CV (%)	34.8 (11.0)	33.2 (10.0)	-1.6 (0.25)	-5%	<0.001	34.0 (9.8)	35.7 (10.3)	1.7 (0.21)	5%	<0.001

Data are means and in parentheses are SDs, except for Mean Difference where they are SEs.

Supported By: Abbott Diabetes Care

75-LB

Real-World Flash Glucose Monitoring in a Developing Country

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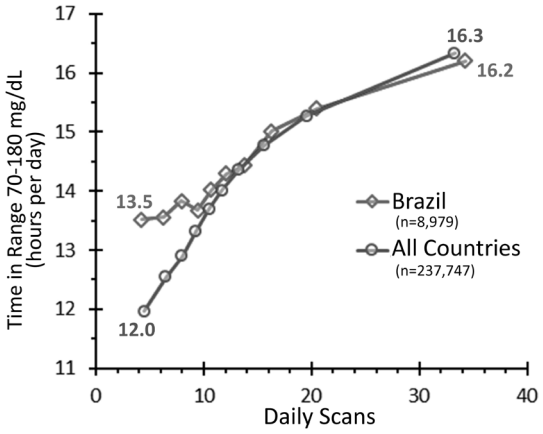
Previous studies showed results of flash glucose monitoring (FreeStyle Libre™) in European countries. This study evaluated real-world impact of device use and glucose metrics using a cross-sectional observational design in a developing country, Brazil. A server collected de-identified data from readers, and completed sensors (>120 hours of operation) were analysed. Comparison of 1,569,588 sensors (237,747 readers) worldwide were made with 57,713 sensors (8,979 readers) from Brazil. Readers were divided into 10 rank-ordered groups by daily scan rate. Users worldwide performed a mean (±SD) of 13.2±8.9 daily glucose scans and a rate of 13.5±9.1/day in Brazil (p=0.002). Time in range (70-180 mg/dL) increased from 13.5 to 16.2 h/day (20% increase, p<0.001) comparing the lowest and highest scan groups in Brazil, with a similar association worldwide (12.0 to 16.3 h/day; 35% increase; p<0.001). Time in hyperglycemia decreased from 10.6 to 6.4 h/day (40% decrease, p<0.001) comparing low with high frequency users worldwide. Brazil users had a similar decrease, though the lowest scan group was 90-minutes lower (9.2 and 6.4 h/day; 30% decrease; p<0.001). Similar daily scan rates were observed in Brazil and worldwide, and those users having

the highest daily scans also had the most time in range and least time in hyperglycemia. This is the first study showing that a developing country in Latin America can also benefit from flash glucose monitoring.

Figure.



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76-LB

T2D Users of a Digital Diabetes Management System Experience a Shift from Greater than 180 mg/dL to Normal Glucose Levels with Sustainable Results

YIFAT HERSHCOVITZ, EITAN FENIGER, SHARON DAR, SR., *Caesarea, Israel*

One of the goals of a digital diabetes management system is to improve the patient's self-management and control of their condition. Blood glucose level reduction and sustainment of lower levels of blood glucose is one of the greatest challenges in managing diabetes. Digital engagement can play a pivotal role in the care of patients with diabetes and other chronical conditions, potentially improving patient's compliance. The Dario™ Blood Glucose Monitoring System (BGMS) connects physically to a smart mobile device and automatically logs blood glucose measurements into a designated application (App). Data is transmitted to the Dario cloud.

Method: A retrospective data evaluation study was performed on the Dario™ cloud data base. A population of all active type 2 diabetic (T2D) users that took measurements with Dario™ BGMS on average of 20 measurements per month during 2017. The study assessed the ratio of all high blood glucose readings (180-400 mg/dL) and the ratio of all normal blood glucose readings (80-120 mg/dL) in their first month of use to their last month of use during 2017 as recorded in the database.

Results: For 17,156 T2D users activated during 2017 the average ratio of high events (180-400 mg/dL) was reduced by 19.3% (from 28.4% to 22.9% of the entire measurements). While at the same time, the ratio of normal range readings (80-120 mg/dL) was increased in 11.3% (from 25.6% to 28.5% of the entire measurements). The most significant shift occurred after one month of usage (14% decrease) and maintained stability over the following months throughout the full year.

Conclusion: The combination of a glucose meter and an App may promote behavioral modification and enhanced adherence to diabetes management, demonstrating improvement in glycemic outcomes and sustainment for a long period of time.

77-LB

Decrease in High Readings and Severe Hyperglycemic Events for People with T2D over the Full Year of 2017 in Users Monitoring with a Digital Diabetes Management System

YIFAT HERSHCOVITZ, SHARON DAR, SR., EITAN FENIGER, *Caesarea, Israel*

One of the goals of a digital diabetes management system is to improve patient's self-management and control of their condition. High blood glucose level is defined as 180-400 mg/dL while severe hyperglycemia (above 400 mg/dL) is considered a medical emergency. Digital engagement can play a pivotal role in the care of patients with diabetes and other chronical conditions, assisting patients to enhance their compliance. The Dario™ Blood Glucose Monitoring System (BGMS) connects physically to a smart mobile device and automatically logs blood glucose measurements into designated App. Data is transmitted to the Dario cloud.

Method: A retrospective data evaluation study was performed on the Dario™ cloud database. A population of active type 2 diabetic (T2D) users that continuously measured their blood glucose using Dario™ BGMS during the full year of 2017 was evaluated. The study assessed the ratio of high (180-400 mg/dL) and hyperglycemic (>400mg/dL) blood glucose readings during full year of 2017 as recorded in the database. The average of high and hyperglycemic glucose readings were calculated in periods of 30-60, 60-90, 90-120, 120-150, 150-180, 180-210, 210-240, 240-270, 270-300, 300-330, 330-360 days and compared to first 30 days as a starting point of analysis.

Results: For 225 T2D active users the ratio of high events (180-400 mg/dL) was reduced gradually in 19.6% (from 23.4% to 18.8% of the entire measurements) from baseline compared to the 12th month of the year. Moreover, the ratio of severe hyperglycemia events (>400 mg/dL) was decreased in 57.8% (from 0.90% to 0.38% of the entire measurements) at the same period.

Conclusion: By means of glucose meter and App patients have the potential to promote behavioral modification and enhance adherence to diabetes management, demonstrating better glycemic control.

78-LB

Continuous Reduction of Blood Glucose Average during One Year of Glucose Monitoring Using a Digital Monitoring System in a High-Risk Population

YIFAT HERSHCOVITZ, SHARON DAR, SR., EITAN FENIGER, *Caesarea, Israel*

Patients with high average of blood glucose levels (above 180mg/dL) are at high risk for developing clinical complications. Digital engagement is playing a pivotal role in the care of patients with diabetes, assisting to enhance their compliance. The Dario Blood Glucose Monitoring System (BGMS) connects physically to a smart mobile device and automatically logs blood glucose measurements into designated App. The data captured on the App is transmitted to the Dario cloud. The study is looking at high risk patients' data over one year of Dario use.

Methods: An exploratory data analysis study reviewed a population of high risk active type 2 diabetic users with initial 30 days glucose average above 180 mg/dL during a full calendar year. The study assessed the average blood glucose readings along a year of usage. The average of glucose readings was calculated per user in periods of in 30 days intervals from 30-60 to 330-360 days and compared to the first 30 days as the starting point baseline of analysis.

Results: Overall of 238 highly engaged T2D users (more than one daily measurement in average) whose average blood glucose level was above 180mg/dL in the first 30 days of measurements (225±45 mg/dL) showed continuous reduction in glucose level average vs. baseline. Reduction in blood glucose average level was demonstrated gradually, in the succeeding 3, 6 and 12 months showing average decrease of 7%, 11% and 14% vs. baseline, respectively. Furthermore, 76% of the entire population (180 out of 238 users) improved their average blood glucose level over a year. Those 180 users (average blood glucose 228±46) showed an average decrease of 10%, 16% and 24% in their glucose average following 3, 6 and 12 months, respectively.

Conclusions: The use of a digital smartphone-based blood glucose monitoring system in high risk patients has the potential to promote behavioral modification and enhanced adherence to diabetes blood glucose levels management in T2D patients.

79-LB

Detecting Insulin Sensitivity Changes for Individuals with Type 1 Diabetes

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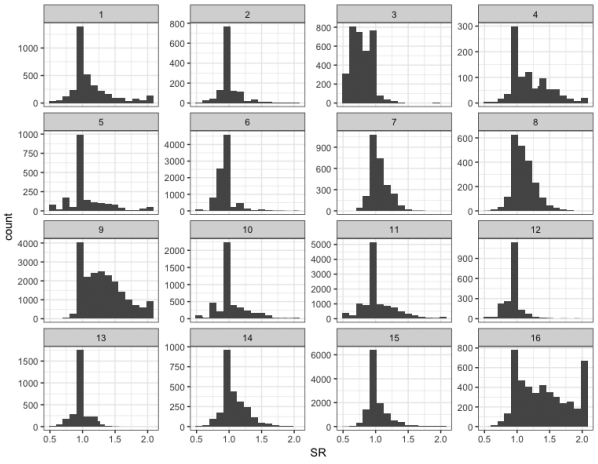
Background: A method to calculate changes in insulin needs was developed in the OpenAPS (Open Source Artificial Pancreas System) community. Individuals have natural fluctuations in insulin needs, but excessive periods of sensitivity or resistance may indicate ongoing physiological trends and therefore impact T1D management.

Methods: Autosens analyzes each CGM data point for 24 hours, comparing observed change to expected impact from insulin. Autosens calculates the deviation for the median of the last 8 and 24 hours of CGM data points and determines the sensitivity ratio (SR) required to neutralize the median deviation. Autosens was run retrospectively to obtain an hourly SR value (first calculated SR every hour) for (N=1)*16 individuals using OpenAPS; with M=5393 data points, and range=922 to 20,473. A SR of >1.0 indicates resistance; <1.0 indicates sensitivity. Histograms were created to visualize SR for each participant. Mean SR ± SD was calculated and those falling beyond ± 10% of 1.0 were classified as being resistant and sensitive respectively.

Results: Mean SR for 12 individuals fell within ±10% of 1.0. 1 individual tended toward sensitivity [0.79 ± 16]. 3 individuals tended toward resistance [1.2 ± 0.28; 1.33 ± 0.30; 1.41 ± 0.37].

Conclusion: Such idiographic visualization of SR can be useful for detecting overall patterns of sensitivity/resistance potentially unaccounted for by the user's pump settings.

Figure.



Supported By: Robert Wood Johnson Foundation

80-LB

Glycemic Variability Associated with Time Spent in Hypoglycemia in Type 1 Diabetes—Explorative Data in Real-World, Real-Time Continuous Glucose Monitoring

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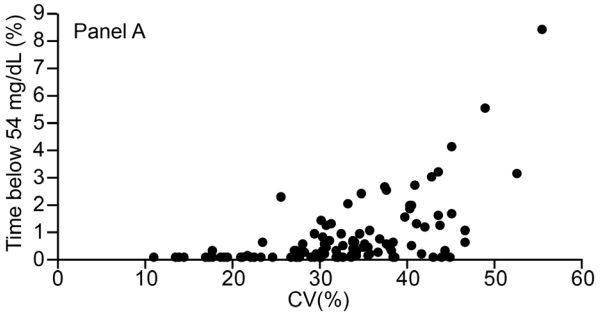
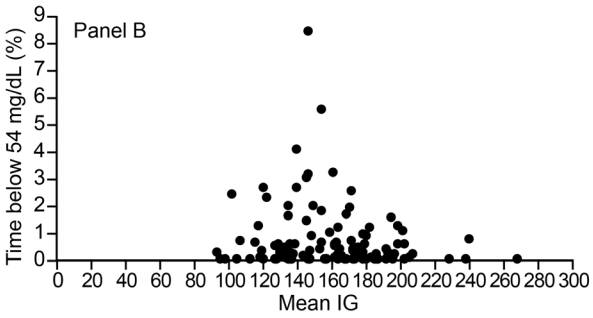
Glycemic variability has previously been associated with risk of hypoglycemia. Cornerstone4Care (C4C), a digital patient management program for diabetes mellitus, supports diabetes self-managing and captures patient data inclusive real-world real-time continuous glucose monitoring (CGM) data. The objective was to explore the association between glucose variability and time spent in hypoglycemia (TIH; percent time with interstitial glucose (IG) <54 mg/dL [3.0mmol/L]) and the association between mean IG and TIH in real-world CGM data. Glucose variability was determined based on CGM data from 112 type 1 diabetes (T1D) patients uploaded via the C4C app and calculated as the coefficient of variation (CV) based on the last 14 days' available CGM data. For each patient a CV-index, mean IG, and proportion of TIH was determined. The variability CV-index ranged from 11% to 56%. Increase in CV appeared to increase TIH. Mean IG did not seem to influence the time spent in hypoglycemia as much. In addition, when CV exceeded the newly recommended cut-off of 36%, the TIH seemed to increase.

In conclusion, higher glucose variability (CV) based on CGM data from T1D was observed to increase the time spent in hypoglycemia. The increase seemed to occur with a CV around 30-36% and seemed to be more independent of mean IG.

Data source: https://www.cornerstones4care.com/.

Figure: Relationship between CV(%) (panel A) / mean IG (panel B) and time spent in hypoglycemia (IG <54 mg/dL [3.0 mmol/L])





CV(%), coefficient of variation; IG, interstitial glucose.

Supported By: Novo Nordisk

81-LB

Accuracy Evaluation of the WaveForm Cascade CGM System vs. Dexcom G5 Sensors

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Objective: WaveForm is actively pursuing a commercial launch with a new trocar-free CGM system. The Cascade CGM device is based on a variant of an amperometric GOx-based technology. Finishing the algorithm and validating the clinical performance of the device is the final development stage. We are reporting on the outcome of a 10-day clinical study that was used to compare the accuracy of the Dexcom G5 CGM device and our Cascade CGM.

Method: The clinical study that was used to evaluate the two CGM systems included 15 subjects with type 1 and 2 diabetes. On day 1, 4, 7 and 10, 12-hour in-clinic CGM accuracy studies were performed. Each subject wore two Cascade CGM devices and one Dexcom G5 sensor in the abdominal area. YSI glucose measurements were performed on plasma from venous blood sampled every 15 minutes. The Dexcom device was inserted at the beginning of day 4 in-clinic day and was worn through day 10 of the study (7 days). The overall MARD and MAD calculation for the Cascade CGM was evaluated for the four in-clinic days by prospectively applying an advanced algorithm to data generated during the study. The comparison of accuracy performance between the Cascade and the Dexcom G5 sensors was conducted over 7 days which included 3 in-clinic days for each CGM device.

Result: Head-to-head MARD comparison between the WaveForm and Dexcom sensor over 7 days showed that MARD for the Cascade CGM was better (11.0% vs. 12.2%). Consensus error grid analysis for Cascade device showed that 99% of data points were in zone A and B, with the remaining 1% in zone C.

Conclusions: Overall performance of the Cascade CGM device over 10 days meets the clinical expectations of a commercial device. Direct comparison with the Dexcom G5 sensor - regarded as the current benchmark in the CGM market - shows that the WaveForm device met and even surpassed the performance level of it in this study. The Cascade CGM will be launched as 14-day wear CGM system.

82-LB

Glycemic Variability from CGM Correlates with Indices of Glucose Metabolism in Healthy Obesity but Not in Type 2 Diabetes

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We evaluated the relationship between measurements of beta cell function and insulin resistance assessed from OGTT and 2-step glucose clamp data with indices of glucose variability (GV) obtained with a continuous glucose monitor (CGM) in obese subjects with and without type 2 diabetes (T2D). 17 healthy obese (OB) (FPG 91 ± 4.9mg/dl and A1c 5.2 ± 0.4%) and 8 age- and weight-matched participants with T2D treated with diet and/or metformin (FPG 131.5 ± 42.8 mg/dl and A1c 6.8 ± 0.8%) wore CGM (Dexcom®) for up to 5 days. EasyGV® software was used to calculate indices of GV: standard deviation (SD), mean amplitude of glycemic excursions (MAGE), J-Index, continuous overlapping net glycemic action (CONGA), and Glycemic Risk Assessment in Diabetes Equation (GRADE). Indices of glucose metabolism were determined with a 2 hour OGTT and a two-step hyperglycemic-euglycemic clamp. Insulin levels during the hyperglycemic-step of clamp (116 ± 126 vs. 40 ± 23 mU/mL) were equal in both groups, while glucose infusion rate (GIR) (7.7 ± 3.1 vs. 3.9 ± 2.4 mg/kg/minutes) during euglycemia was

as expected significantly lower in the T2D subjects compared to OB subjects. GV indices (SD, CONGA, J-Index, GRADE) were statistically lower in OB vs. T2D (P<0.05). Insulin Sensitivity Index (ISI_{0-120}) and the insulin secretion-sensitivity index-2 (ISSI-2) were also lower in obese than in T2D subjects (P<0.001). CGM indices (mean, CONGA, J-index, and GRADE) correlated with incremental AUC of insulin during the OGTT, but not for glucose; as well as insulin levels during the hyperglycemic-step (r=0.740, P<0.01), and GIR during the euglycemic step of the clamp (r= -0.733, P<0.01). CGM measures of GV (CONGA, J-Index, and GRADE) were lower in obese compared to T2D subjects. These results suggest that GV indices are surrogate measurements of beta cell function and insulin action in obese subjects, and may help determine progression to T2D.

Supported By: National Institutes of Health (K23DK09828602, K08AA023545, DK20495, P30DK45735, T32DK07058, UL1TR00142)

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULIN DELIVERY SYSTEMS

83-LB

Trends in Insulin Pen Priming

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Priming insulin pens is recommended to remove air from needles to ensure full dose administration. Little is known regarding how often or how much patients prime during home use or its relation to glucose control. We evaluated patterns of pen priming in patients with type 1 diabetes using NovoPens for insulin administration. Patients were trained on use of pens including how and why to prime for doses. Two sites taught a 2 unit prime, site 3 until insulin seen. Pens were synced to a study phone via a near field communicator and marked as prime or injection. Records were assessed for prime frequency and amount. For this interim analysis, 16,135 pen records from 25 patients were analyzed. The percent of injections with a prime was 80% overall but ranged from 2-99%. Prime amount varied and did not correlate to HbA1C. For patients who primed until insulin seen, 74% of the primes did not necessitate 2 or more units. Prime frequency was defined as low if <25%, variable if 25-75% or consistent if >75%. The frequencies were not evenly distributed; instead patients would prime the majority of the time or infrequently. Percentage of missed prime did not correlate with HbA1C, but seemed to correlate with male gender and younger age. Missed prime of insulin pens is fairly common, but the frequency is variable. Insulin pens which track doses offer important data regarding appropriate use. This information provides insight for education and treatment.

Table.

	Gender	HbA1c at enrollment	Age (years)	Diabetes duration (years)	No prime (%injections)	<2 units primes (%injections)	≥2 units primes (%injections)
Low primers (<25%)	3 men	7.9%	23	9	90%	5%	5%
Variable (25-75%)	3 men	6.4%	24	10	35%	22%	43%
Consistent (>75%)	6 men 13 women	7.6%	36	20	6%	29%	65%
Overall	12 men 13 women	7.5% (range 5.3-9.3%)	33 (range 17-57)	17 (range 2-44)	Overall: 20%. Sites teaching 2 units: 19%. Site teaching until insulin seen: 21%.	Overall: 25%. Sites teaching 2 units: 7%. Site teaching until insulin seen: 62%.	Overall: 55%. Sites teaching 2 units: 74%. Site teaching until insulin seen: 17%.

Supported By: National Institutes of Health

84-LB

Clinical Experience with the MiniMed 670G System in Children, Adolescents, and Young Adults with Type 1 Diabetes

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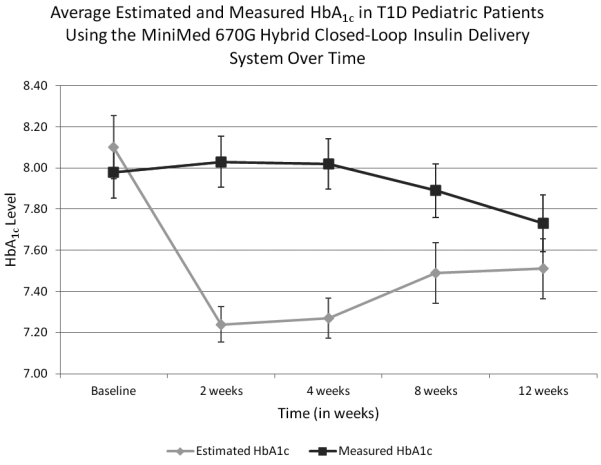
Objective: To compare measured HbA_{1c}, estimated HbA_{1c} and percent time in range before and after the initiation of the Minimed 670G system in children and young adults with type 1 diabetes (T1D).

Methods: Data consisted of 67 T1D patients, aged 5-23 years, who started the MiniMed 670G system and were followed for at least 12 weeks. Data were analyzed at baseline and 2, 4, 8, and 12 weeks following Auto Mode start. Paired t tests and linear mixed regression models were used to evaluate the effect of time on percent of time in Auto Mode, percent of time in range (70-180 mg/L) and changes in most recently measured HbA_{1c} and sensor estimated HbA_{1c}.

Results: Fifteen percent of patients (n=10) were aged 5-9 years, 27% (n=18) were 10-13 years, 30% (n=20) were 14-17 years and 28% (n=19) were ≥ 18 years; average duration of T1D was 5.47 ± 4.26 years. Nearly 96% of patients were Caucasian; 54% were male. Estimated HbA_{1c} levels decreased from 8.10% ± 1.26% at baseline to 7.51% ± 0.88% at 12 weeks (P<0.0001). Measured HbA_{1c} decreased from 7.98% ± 1.03% to 7.73% ± 1.03% (P=0.0008) (Figure 1). Percent time in range increased from 50% at baseline to 61% at 12 weeks (P<0.0001), without significant change in time below range. Time in Auto Mode declined from 75.1% at start to 68.4% at 12 weeks (P=0.0015).

Conclusion: Initiation of the 670G system in a clinical setting led to improved glycemic control in children, adolescents, and young adults.

Figure 1.



85-LB

Greater HbA1c Lowering with Tethered vs. Small Insulin Pumps in a Large UK Insulin Pump Service

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Aim: To examine the impact of different types of insulin pumps (CSII) on HbA1c lowering control in a large UK type 1 diabetes practice.

Methods: Observational retrospective study of electronic database. We identified 597 adults (≥18 years) in our service who started on CSII between 2002 and 2017 with HbA1c data available at baseline and at 6 +/or 12 months after starting CSII. We classified by the starting pump model/manufacturer into traditional "tethered pumps" (Medtronic n=369; Roche n=79; Animas n=60) and "small pumps" (Omnipod n=79 and Cellnovo n=6). We examined change in HbA1c data (shown here in mmol/mol except where otherwise indicated) over the first year of CSII treatment.

Results: In general, CSII improved HbA1c during the first 12 months (72±0.7 to 64±0.6 and 65±0.6 mmol/mol at baseline, 6 and 12 months). Despite similar starting HbA1c, those using tethered pumps achieved a significantly lower HbA1c compared with small pump users after 6 and 12 months CSII therapy.

Conclusions: In real world data from a large pump service, we found significant differences in glycemic outcomes between different pumps. Those starting on tethered pumps had greater HbA1c lowering over first 12 months.

Table. HbA1c Outcomes for Tethered vs. Small Pumps.

Pump type	Initial HbA1c range mol/mol (%)	Baseline HbA1c	6 months HbA1c	p vs. baseline	12 months HbA1c	p vs. baseline
Tethered (n=509)	All starting values	71±0.7	63±0.6*	<0.001	65±0.7*	<0.001
Small (n=85)		71±0.9	70±1.6	NS	69±1.6	NS
Tethered (n=273)	≥69 (85%)	83±0.7	69±0.8**	<0.001	71±0.9*	<0.001
Small (n=43)		83±2.3	77±2	<0.05	77±2.1	<0.05
Tethered (n=132)	59-68 (7.5-8.4%)	64±0.2	59±0.7**	<0.001	59±0.8*	<0.001
Small (n=28)		64±0.5	66±1.4	NS	64±1.4	NS

Data shown as mean±SEM. * p<0.05, ** p<0.001 for tethered vs. small.

86-LB

Exceptional Usability of Tandem t:slim X2 with Basal-IQ Predictive Low-Glucose Suspend (PLGS)—The PROLOG Study

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Background: Our research study group recently evaluated a PLGS system embedded on the Tandem t:slim X2 with Basal-IQ insulin pump. The system was designed to work "in the background" without alarms when suspending and restarting insulin delivery. System usability and effectiveness in decreasing hypoglycemia are both critical to the success of a PLGS device.

Methods: The PROLOG study was a randomized crossover trial conducted at 4 U.S. sites. Participants with type 1 diabetes (age ≥6 years, n=102) previously treated with MDI or CSII (with and without CGM) were randomized to the order of treatment: PLGS during one 3-week period and sensor-augmented pump (SAP) during the alternate 3-week period. We recently reported the primary outcome of the PROLOG study-a reduction of mean sensor time <70 mg/dL by 31% relative to SAP. In addition to glycemic outcomes, usability of the system was evaluated using a validated measure, the System Usability Scale (SUS).

Results: The overall SUS score for at-home use of the Basal-IQ system was 88.8 (out of 100). A score above 68 is considered above average, and 88 is exceptional. Subgroup analyses revealed no differences related to age, baseline glycemic control or baseline diabetes therapy (MDI, CGM or pump use, Table 1).

Conclusions: The t:slim X2 with Basal-IQ was safe, effective, and easy for participants to use, regardless of previous experience with diabetes technology.

Table 1. Subanalyses of SUS scores.

System Usability Scores (SUS) by Subgroup	Composite Score	
	N	Mean
<18 years of age	60	90.7 ± 9.0
≥18 years of age	42	86.0 ± 11.8
Baseline A1c <8.0%	80	89.2 ± 10.1
Baseline A1c ≥8.0%	22	87.0 ± 11.8
<8 years of T1D duration	49	89.9 ± 8.8
≥8 years of T1D duration	53	87.6 ± 11.8
Baseline time <70 mg/dL <5.0% *	71	89.2 ± 10.8
Baseline time <70 mg/dL ≥5.0%	30	87.5 ± 9.8
Injections as current therapy	17	85.3 ± 11.2
Pump as current therapy	85	89.4 ± 10.2
Current CGM User	86	89.6 ±10.2
Not Current CGM User	16	84.1 ± 10.7

*missing for one participant

Supported By: Tandem Diabetes Care, Inc.

87-LB

Adults with T1D Report Half-Unit Pen Prevents Hyperglycemia and Hypoglycemia with Less Worry and Anxiety

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People with type 1 diabetes (PWD) that strive for lower glucose targets are in need of more precise dosing and may require smaller insulin dose adjustments. Most currently available pens deliver insulin in one unit (U) increments, and few deliver half (0.5) U. There is a need to better understand who is using half unit pens (HUP) and their potential benefit for patients in the real world. This study aims to characterize PWD who have used (current/former=EVER users) HUP vs. those PWD that have never used HUP (NEVER users). This research also identified the main factors driving benefit from PWD perspective. An observational, cross-sectional survey was completed through T1D Exchange's online patient community, myGlu.org. Chi square test, Fisher's exact test, and t-tests were used for analyses. A total of 278 PWD (156 EVER, 122 NEVER users) over the age of 18 were recruited for the study (mean age: 42±13 years old, gender: 55% male, mean BMI (kg/m^2): 26.0 ±3.8, and mean A1c (%): 6.3± 0.9), EVER users had diabetes a shorter duration (p<.001). NEVER users were more likely to use an insulin pump (p<.001). EVER users self-reported a significantly lower upper fasting glucose target compared to NEVER users (p<.001), and a lower overall post-prandial glucose target (p<.001). NEVER users were more likely to start to treat low blood sugar at lower readings (p<.001), and they were more confident in avoiding severe hypoglycemia (p<.001). Based on PWD experience, the greatest benefits of using HUP were prevention of hypo and hyperglycemia events and less worry and anxiety. HUP is an option for PWD that wish to maintain tighter management of their diabetes, avoiding hypo and hyperglycemic events while decreasing their level of worry and anxiety about their disease. It is important for PWD and health care providers to understand the benefits of this insulin delivery device to appreciate options for making diabetes management easier.

88-LB

Insulin Pump Therapy with Simple Scheme in Insufficiently Controlled Patients with Type 2 Diabetes on Intensive Injection Therapy—A Real-Life Study

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Background and Aims: Many patients with type 2 diabetes mellitus on intensive insulin injection therapy (MDI) do not reach adequate glycemic control. A randomized controlled trial has shown that continuous subcutaneous insulin infusion (CSII) using a simple scheme with one basal rate, improves glycemic control (Lancet 2014; 384: 1265-72). We studied effectiveness of this scheme in a real life setting.

Materials and Methods: Patients with type 2 diabetes with HbA1c ≥ 64 mmol/mol on MDI with insulin requirement between 0.7 and 2.2 U/day were eligible. Hourly basal rate was 50% of the total daily dose (TDD) divided by 24; 50% of TDD was divided equally between three meals. Trial duration 6 months.

Results: Sixty-seven patients participated. Mean age: 61.3±0.9 years, 42% female; duration of disease: 16.0±7.6 years; weight: 10.7.4±21.9 kg; BMI: 35.8±6.9 kg/m^2, baseline TDD: 135.5±62.3 U/day. Mean HbA1c fell from 80.1 ± 15.2 to 62.4 ±10.0 mmol/mol (p<0.001); mean change in HbA1c -17.7±2.1 mmol/mol. After exclusion 3 outliers (δHbA1c >-50 mmol/mol), the results were comparable: HbA1c fell from 78.0±11.8 to 63.0 ±9.7 mmol/mol (p<0.001); mean change -15.0±1.5 mmol/mol. Total cholesterol decreased slightly (4.33±0.13 to 4.21±0.13 mmol/l, p<0.05); no changes in other lipid parameters or blood pressure. Body weight increased from 106.2±19.5 to 109.3±20.61 kg (p<0.001).

Conclusion: This real-life study shows that introducing CSII with simple insulin schema in patients with insufficiently-controlled type 2 diabetes on MDI, leads to major improvement of glycemic control, at the expense of some weight gain. This approach provides a worthwhile alternative in patient with poorly-controlled DM2 and considerable insulin resistance. Nutritional counselling deserves attention to diminish weight gain.

Supported By: Medtronic

89-LB

Assessment of Infusion Set Survival of the Newly Developed Lantern Catheter in Type 1 Diabetes by Glucose CLA Technique

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The catheter-tissue interface is the bottle neck of insulin pump therapy (CSII). Currently infusion sets shall be changed every 2-3 days to avoid lipohypertrophy, fluctuations in insulin absorption and occlusion. Patients would prefer an extended wear time if stable insulin absorption could be achieved. The novel catheter featuring Lantern Technology shall allow more stable insulin delivery via slots in the shaft of the soft cannula even if kinking or clotting occurs.

The aim of the present study was to investigate clinical performance of the coated Lantern catheter in 16 patients with type 1 diabetes using CSII over a period of up to 7 days. A combined design comprising inpatient (euglycemic clamps on days 1, 4 and 7) and outpatient phases (insulin pump therapy over 7 days) is chosen to allow assessment of performance and survival time of the Lantern catheter. 16 c-peptide negative patients (age 44.2 ± 15.4 years, BMI 24.5 ± 2.3 kg/m^2, HbA1c 55 ± 8 mmol/mol, diabetes duration 20 ± 9 years) completed the 7-day study period. Geometric means of maximum glucose infusion rates (GIR) were similar for days 1, 4 and 7 (6.1 ± 1.5, 7.2 ± 1.3, 5.8 ± 1.4; p=0.14). Time to reach 50% of the maximum GIR were similar over time (31.5 ± 1.6 minutes vs. 29.3 ± 1.3 minutes vs. 27.3 ± 1.3 minutes for days 1, 4 and 7 respectively; p=0.51). Area under the log-transformed GIR curve did not significantly differ for the first 2 hours between days (343.7 ± 1.5 vs. 421.3 ± 1.6 vs. 350.6 ± 1.8; p=0.14; days 1, 4 and 7, respectively); however, there was a trend towards reduced area under the GIR curve over 8 hours over time (874.2 ± 1.4 vs. 744.5 ± 1.7 vs. 509.2 ± 2.0; days 1, 4 and 7, respectively; p<0.05). During outpatient care no severe hypoglycemic event or ketoacidosis occurred. The novel Lantern catheter could be safely used over an extended wear-time of 7 days. There was a trend towards reduced insulin action over time. The findings need to be confirmed in a larger scale trial under routine conditions.

Supported By: ConvaTec

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULINS

90-LB

Insulin-XTEN® Exhibits a Size-Dependent Alteration in Tissue Action in Rats

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To optimize the action of exogenously administered insulin, we employed XTEN® technology to create insulins with variably sized XTEN amino acid polymers. Recombinant fusions of XTEN polymers linked to insulin lispro with an A21G mutation were prepared in various amino acid lengths. Insulin-XTEN molecules demonstrated 15-fold lower potency in binding and receptor phosphorylation than insulin lispro but did not differ from each other. These insulin-XTEN molecules were equally effective in lowering blood glucose at a 100nmol/kg dose in diabetic Sprague-Dawley rats. Furthermore, the larger insulin-XTEN molecules had a longer duration of glucose lowering. Insulin-XTENs were compared to insulin lispro in rat euglycemic clamp studies, using insulin doses that would elicit steady plasma insulin concentrations and equivalent increases in glucose infusion rate. Insulin-mediated suppression of endogenous glucose production was not significantly different among any of the administered insulins. However, plasma free fatty acids and soleus muscle glucose uptake were significantly decreased in an XTEN size-dependent manner when compared to insulin lispro. Additional studies demonstrated equal hepatic pAkt accumulation in rats treated with insulin lispro or any of the insulin-XTENs, but revealed a significant XTEN size-dependent reduction in skeletal muscle pAkt in rats administered insulin-XTENs compared to insulin lispro. These data suggest a possible XTEN size-dependent regulation of insulin action and that the differing sizes of the XTEN polymer may convey preferential tissue action.

In conclusion, XTEN technology may permit "tuning" of the glucodynamic effects of the insulin, leading to an enhanced time extension and improved hepatic and peripheral pharmacodynamic action that could more closely mimic the action of endogenously secreted insulin into the portal circulation.

91-LB

Insulin Degludec/Insulin Aspart (IDegAsp) Twice Daily (BID) vs. Biphasic Insulin Aspart 30 (BIAsp 30) BID—A Randomized Trial in Chinese Patients with Type 2 Diabetes

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IDegAsp is the first coformulation of long-acting basal (degludec) and bolus (IAsp) insulin with no need for re-suspension. This 26-week, phase 3, open-label, treat-to-target, 2:1, randomized trial assessed the efficacy and safety of IDegAsp BID vs. BIAsp 30 BID ±metformin in Chinese adults (N=541) with T2D inadequately controlled on pre-/self-mix or basal insulin ±metformin. Hierarchical testing was used with non-inferiority of A1C change from baseline to week 26 as the primary endpoint and superiority for secondary endpoints. Non-inferiority of A1C change from baseline to week 26 and statistical superiority of IDegAsp BID vs. BIAsp 30 BID for change in fasting plasma glucose, nocturnal (00:01-05:59 hours inclusive) confirmed hypoglycemic and confirmed hypoglycemic episodes (severe or plasma glucose <56mg/dL with or without symptoms) was confirmed (Table). Significantly more patients reached A1C <7% without confirmed hypoglycemia with IDegAsp BID vs. BIAsp 30 BID by week 26. Daily insulin dose (U/kg [SD]) was lower in patients receiving IDegAsp BID vs. BIAsp 30 BID at week 26 (0.78 [0.35] vs. 0.95 [0.35]). No new safety signals were identified. These results demonstrate the efficacy and safety of IDegAsp in Chinese patients with T2D, confirming results from other international trials comparing the two treatment modalities (NCT02762578).

Table.

Summary of results of hierarchical testing

	IDegAsp BID (n=360)			BIAsp 30 BID (n=181)			Conclusion* (LS Mean Treatment contrast [95% CI])
	Baseline	End of trial (LOV)	Mean change from baseline	Baseline	End of trial (LOV)	Mean change from baseline	
Mean A1C (% [SD])	8.31 [0.76]	6.95 [0.77]	-1.37 [0.94]	8.33 [0.77]	7.01 [0.72]	-1.32 [0.81]	Non-inferiority (-0.08 [-0.20; 0.05], p<0.0001)
Mean FPG (mg/dL [SD])	163.42 [39.90]	109.40 [31.30]	-53.91 [46.68]	163.43 [44.82]	134.80 [36.15]	-28.25 [46.47]	Superiority (-1.42 [-1.74; -1.10], p<0.0001)
Nocturnal confirmed hypoglycemia[1]	34.86			61.02			Superiority (0.53 [0.33; 0.87], p=0.0056)
Confirmed hypoglycemia[1]	237.16			412.16			Superiority (0.57 [0.42; 0.77], p=0.0001)
Mean body weight (lb [SD]; kg [SD])	150.82 [25.42]; 68.41 [11.53]	157.01 [26.39]; 71.22 [11.97]	6.19 [5.65]; 2.81 [2.56]	153.15 [27.30]; 69.47 [12.38]	158.13 [27.42]; 71.73 [12.44]	4.98 [5.95]; 2.26 [2.70]	Test process stopped (0.61 [0.15; 1.08]), p=0.9954)
A1C <7% without confirmed hypoglycemia[1] at end of trial (% of patients)	42.4			26.4			Inconclusive (2.22 [1.47; 3.35], p<0.0001)

[1]Rate (number of events divided by PYE multiplied by 100) for total treatment period. *A patient who meets the A1C target (<7%) at end of trial without confirmed hypoglycemia during the last 12 weeks of treatment or within 7 days after the last randomized treatment. The endpoint is only defined for patients who have been exposed for at least 12 treatment weeks.*p-values are from the 1-sided test for non-inferiority and superiority. BIAsp 30, biphasic insulin aspart 30; BID, twice daily; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart; LOV, last observed value; LS, Least squares; PYE, patient years of exposure; SD, standard deviation

Supported By: Novo Nordisk

92-LB

Stepwise Intensification of Prandial Insulin in Taiwanese Patients with T2DM—Final Analysis Report of the SPIRIT Study

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Aim: Addition of 1-3 dose of bolus insulin is recommended by ADA/EASD guidelines when basal insulin (BI) therapy becomes insufficient for T2DM

patients to achieve HbA_{1c} target of <7%. This prospective registry study examined the effect of stepwise intensification of prandial insulin (PI) on top of BI over 48 weeks across multi-centers in Taiwan.

Method: 328 T2DM patients completed 48 weeks of stepwise intensification of PI + BI therapy (Main group). The primary objective of the study was to determine the mean change in HbA_{1c}. Secondary objectives included; evaluation of change in FPG, 2h-PPG, PI and BI dose and the rate of HbA_{1c} <7% achievement and hypoglycemic events. Results of BI intensification with PI were retrospectively analyzed against a BI alone group (Control group, n=113). Statistical analysis was performed using T-tests.

Result: Mean HbA_{1c} was 9.16% in Main group at baseline. At week 48, significant difference in mean HbA_{1c} change (-0.59 ± 1.16% vs. -0.07 ± 1.06%; p<0.0001) but not in mean FPG change (-10.99 ± 70.06 mg/dL vs. -6.53 ± 50.58 mg/dL; p=0.054) was observed between Main group and Control group; 5.49% and 2.65% (p=0.0318) of patients achieved HbA_{1c} <7%, respectively. In Main group, mean BI dose was 26.43 ± 12.35 IU/day (p<0.05 vs. baseline); mean PI dose was 10.16 ± 7.90 IU/day (p <0.0001 vs. baseline). In Control group, mean BI dose was 24.95 ± 13.92 IU/day (p=0.0986 vs. Main group). Overall, 31 hypoglycemic episodes related to PI (9) and BI (22) use were reported as treatment-emergent adverse events in Main group. No significant difference was observed in the frequency of documented symptomatic or severe hypoglycemic episodes between Main group and Control group at baseline and at week 48.

Conclusion: This study demonstrated the introduction of stepwise intensification of prandial insulin leads to greater improvements in HbA_{1c} levels than basal insulin monotherapy in T2DM patients in Taiwan and this effect can be maintained during the study period of 48 weeks.

Supported By: Sanofi Taiwan

93-LB

Evaluation of a New Protocol of Insulin Dose Adjustment in a Low-Resource Setting

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Glycemic Control (GC) is difficult to achieve in settings where only NPH, R and pre-mixed insulins are available, test strips are scarce, and food insecurity is common.

We evaluated the impact of a sliding-scale based insulin adjustment protocol in Haiti. Thirty youth aged 11-28 years with T1D treated with 70/30 Mixtard were randomized to remain on 70/30 (G70, n=15) or switch to self-mixed NPH+R (GNR, n=15). Carbohydrate (CHO) ratio and insulin sensitivity factor were calculated based on total daily insulin dose (TDD), and translated into sliding scales with either insulin correction dose (ICD) only (G70), or the sum of a 60 g CHO meal dose and ICD (GNR). Self-monitored blood glucose (SMBG) and insulin were administered before AM and PM meals. All had bi-monthly visits for 12 weeks. In G70 vs. GNR, age (19.3±4.5 vs. 19.2±5.4 years), sex (40 vs. 53% m), normal BMI (87 vs. 80%), diabetes duration (5.3±4.2 vs. 5.3±4.5 years), and baseline A1c (9.8±2.1 vs. 10.8±2.9%, p=0.27) did not differ. A1c declined to 8.0±1.3% (-1.8%, p<0.006) vs. 8.9±1.2% (-1.9%, p<0.02), p=0.83, without severe acute complication. Skipped meals per week (3.7±2.9 vs. 4.1±3.3), missed SMBG (3.5±3.4 vs. 7.4±7.6%, p=0.07), and increase of TDD (7.7±7.8 vs. 6.6±9.6 units) were similar. Use of sliding scales adjusted for SMBG and meals omission, and frequent clinic visits significantly improved GC in youth with T1D in a low-resource setting, regardless of pre- or self-mixed insulin.

Table. Insulin Dose Adjustment According to Presence of Pre-meal BG Tests and Meals.

		Pre-Mix		Self-Mix	
	BG range[a]	Meal[b]	No Meal[c]	Meal[b]	No Meal[c]
AM	No test	Planned dose[d]	3 x ICD value of 151-180 mg/dl sliding scale range	N: Planned dose[d] R: MID	N: 1/3 or 1/2 of planned dose[d] R: none
	< 80 mg/dl	Treat hypoglycemia PRN		Treat hypoglycemia PRN	
		Planned dose[d]	No insulin	N: Planned dose[d] R: MID	No insulin
	≥ 80 mg/dl	Planned dose[d]	3 x ICD value as per sliding scale[e]	N: Planned dose[d] R: MID + ICD as per sliding scale[e]	N: 1/3 of planned dose[d] R: ICD as per sliding scale[e]
Mid-day	No test	No insulin		No insulin	
	< 80 mg/dl	Treat hypoglycemia PRN		Treat hypoglycemia PRN	
	80-240 mg/dl	No insulin		No insulin	
	≥ 240 mg/dl	2 x ICD value as per sliding scale[e]	2 x ICD value as per sliding scale[e]	R: ICD as per sliding scale[e]	R: ICD as per sliding scale[e]
PM	No test	Planned dose[d]	No insulin	N: Planned dose[d] R: MID	No insulin
	< 80 mg/dl	Treat hypoglycemia PRN		Treat hypoglycemia PRN	
		Planned dose[d]	No insulin	N: Planned dose[d] R: MID	N: none R: ICD
	≥ 80 mg/dl	Planned dose[d]	1 x ICD value as per sliding scale[e]	N: Planned dose[d] R: MID + ICD as per sliding scale[e]	N: none R: ICD as per sliding scale[e]

[a]Pre-meal glycemic target: 80-130 mg/dL. [b]Additional instructions are given on pre-meal insulin dose adjustment according to the estimated loads of carbohydrate that are different from 60 g. [c]Patients are encouraged performing SMBG for any skipped meal. [d]Planned dose is defined as previous dose adjusted, when needed, to its effect on BG. [e]Sliding scale [mg/dl]: <80; 80-150; 151-180; 181-210; 211-240; 241-270; 271-300; >300.
BG, blood glucose; ICD, insulin correction dose; MID, meal insulin dose.

94-LB

Glycemic Parameters for Clinical Shifting to Glargine 300 U/mL (Gla-300) Basal-Plus/Basal-Bolus Insulin Therapies in Asian Patients with Poorly Controlled T2DM

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Aim: T2DM patients are shifted to long-acting insulin analogs when premixed insulin therapy becomes insufficient for individuals to achieve glycemic control. The objective of this study was to investigate glucose patterns from continuous glucose monitoring (CGM) for the clinical assignment of Asian T2DM patients with poor glucose control to Gla-300 basal-plus or Gla-300 basal-bolus therapy.

Method: 20 T2DM premixed insulin outpatients requiring therapy change were enrolled in the study. Based on clinical judgment during routine follow-up, patients were switched to Gla-300 basal-plus or Gla-300 basal-bolus therapy by clinicians. Adjustments were not made to patients' diet or daily routines. Non-real time CGM was prospectively applied at baseline and one month after switching insulin therapy regimens. Mean fasting and postprandial glucose levels, glucose excursion markers, including mean amplitude of glucose excursion (MAGE) and standard deviation of plasma glucose (SDPG), estimated A1C from CGM and frequency of hypoglycemia were recorded for computer-assisted analysis.

Result: Baseline CGM data indicated that pre-meal (dinner) glucose levels (129 ± 33 vs. 204 ± 92 mg/dL, p=0.046), SDPG (52 ± 11 vs. 72 ± 21 mg/dL, p=0.029) and MAGE (119 ± 26 vs. 174 ± 32 mg/dL, p=0.038) were statistically lower in patients shifted to basal-plus therapy than those shifted to basal-bolus therapy. One month after initiating Gla-300-based insulin therapies, glucose excursion manifestations, estimated A1C levels and hypoglycemia occurrences were shown to decrease in both treatment groups; though without statistical significance between groups.

Conclusion: The baseline glucose excursion markers (i.e., SDPG and MAGE) as well as pre-dinner glucose levels are significant glycemic parameters that can be assessed for the clinical shifting of T2DM Asian patients from premixed insulin to Gla-300 based basal-plus or basal-bolus therapies.

Supported By: Sanofi Taiwan

95-LB

Pharmacokinetic and Pharmacodynamic Properties of a Novel "Superfast" Insulin Aspart Formulation

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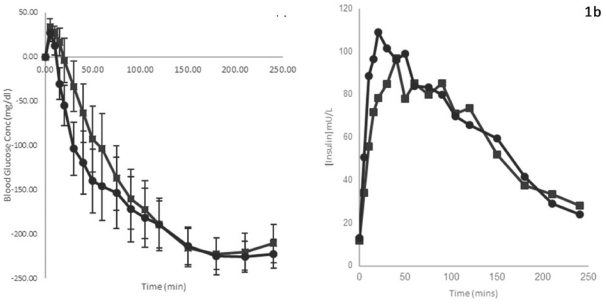
Background: An insulin with a significantly faster onset of action compared to current state-of-the-art products will improve postprandial glycaemic control, reduce variability, improve HbA1c and increase flexibility. A superfast insulin is a key component for the development of efficient closed-loop pump systems.

Method: A superfast formulation, utilising excipients with metal ion binding constants critical in controlling injection site absorption, was investigated in diabetic mini swine in a randomized, cross-over experiment. Ten male animals received 0.2 U/kg insulin via subcutaneous injection. At standardized intervals post-injection, blood glucose and insulin were measured.

Results: Pharmacodynamic (PD) and pharmacokinetic (PK) properties of Superfast insulin were compared to an ultra-rapid control composition including nicotinamide. Tmax (22.5 minutes vs. 41.9 minutes) and T1/2max (7.9 minutes vs. 11.9 minutes) were significantly (P<0.01 and P<0.02) shorter for Superfast insulin, with a correspondingly faster glucose lowering action (Figure 1). Figure 1a) PD and 1b) PK profile of 100U/mL Superfast insulin (red) in comparison to an ultra-rapid acting insulin control containing nicotinamide (blue)1a.

Conclusion: This novel formulation represents a unique superfast prandial insulin that more closely matches a physiological response to blood glucose with the potential to be a major advancement for diabetes care.

Figures 1a-1b.



ADA-Supported Research

96-LB

Hypoglycemia with Mealtime Fast-Acting Insulin Aspart vs. Insulin Aspart Across Two Large Type 1 Diabetes Trials

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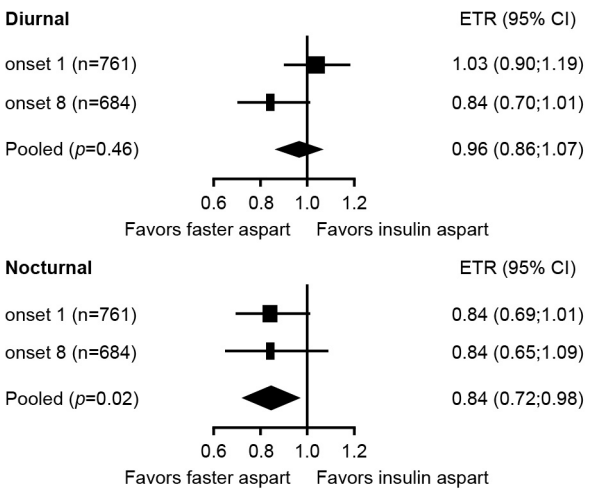
Hypoglycemia is a ubiquitous challenge with insulin treatment in type 1 diabetes (T1D), with nocturnal episodes of particular concern. Severe (as defined by the ADA) or blood glucose-confirmed (<56 mg/dL [3.1 mmol/L]) hypoglycemia was investigated across two double-blind, treat-to-target, randomized trials assessing the efficacy and safety of mealtime fast-acting insulin aspart (FA) vs. insulin aspart (IAsp) by multiple daily injections in adults with T1D: a 52-week trial in combination with insulin detemir (onset 1; n=761), and a 26-week trial in combination with insulin degludec (onset 8; n=684). FA was confirmed to be non-inferior to IAsp regarding change from baseline in A1C in both trials, with a statistically significantly greater A1C reduction with FA in onset 1. Importantly, nocturnal hypoglycemia rates were consistently lower with FA vs. IAsp in both trials (pooled estimated treatment rate ratio [ETR] 0.84 [95% CI 0.72;0.98]; p=0.02) (Figure), while no significant difference was observed for overall (pooled ETR 0.94 [95% CI: 0.85;1.05]) and diurnal hypoglycemia (pooled ETR 0.96 [95% 0.86;1.07]) (Figure) with some heterogeneity across trials.

In summary, analysis across two large trials supports the safety of mealtime FA, with lower rates of nocturnal hypoglycemia with FA vs. IAsp. ClinicalTrials.gov: NCT01831765; NCT02500706.

Figure: Diurnal and nocturnal severe or blood glucose-confirmed hypoglycemic events[a]



[a]An episode that is severe (requiring assistance of another person to actively administer carbohydrate or glucagon, or take other corrective actions) or blood glucose-confirmed by a plasma glucose value <56 mg/dL (3.1 mmol/L) with or without symptoms consistent with hypoglycemia.
Pooled ETR and CI is obtained from a fixed-effects meta-analysis. Study duration of onset 1 was 52 weeks and onset 8 was 26 weeks. For onset 1, weighted contribution is 63.5% for diurnal hypoglycemia and 65.2% for nocturnal hypoglycemia. For onset 8, weighted contribution is 36.5% for diurnal hypoglycemia and 34.9% for nocturnal hypoglycemia.
CI, confidence interval; ETR, estimated treatment rate ratio; faster aspart, fast-acting insulin aspart; N, total number of subjects in faster aspart/insulin aspart arm.

Supported By: Novo Nordisk

97-LB

Comparable Rates of Severe Hypoglycemia in People with Type 2 Diabetes (T2DM) at High Risk of Hypoglycemia Switching to either Insulin Glargine 300 U/mL (Gla-300) or Insulin Degludec (IDeg)—The Lightning Real-World Predictive Modeling Study

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Hypoglycemic events during basal insulin (BI) treatment, recorded by physicians in U.S. electronic health records in real-life practice, were used to predict hypoglycemia rates in people with T2DM prescribed BI analogs. Based on large-scale real-world data (Optum Humedica), a predictive model (implementing machine learning and controlling for >160 baseline demographic and clinical variables) was developed and validated for each drug-specific cohort (patients treated with a specific BI). Overall, models predicted similar severe hypoglycemia rates when switching from another BI to second-generation BI analogs Gla-300 or IDeg. This subanalysis focuses on severe hypoglycemia rates in clinically vulnerable subgroups of patients. Numerically, the highest rates were found in the subgroup with prior hypoglycemic events (Table). The models predicted no statistically significant differences in severe hypoglycemia rates between Gla-300 and IDeg in any of the at-risk subgroups (Table).

In summary, using real-world data, these predictive modeling results show similar rates of severe hypoglycemia when switching to either Gla-300 or IDeg, in subgroups of patients with T2DM at high risk of hypoglycemia.

Table. Predicted rates of severe hypoglycemia in different subgroups of BI switchers

Subgroup (proportion of total population, %)	Basal insulin	Median hypoglycemia rate (PHPY)	Difference versus Gla-300 (95% CI)	p[a]
Overall n=42,001 (100%)	Gla-300	21.00	–	–
	IDeg	21.15	−0.11 (−5.94 to 6.47)	0.492
Increased hypoglycemia risk[b] n=13,668 (33%)	Gla-300	52.01	–	–
	IDeg	43.64	8.26 (−6.44 to 26.67)	0.859
Moderate/severe renal impairment[c] n=15,889 (38%)	Gla-300	30.75	–	–
	IDeg	31.64	−0.89 (−10.03 to 10.32)	0.430
Basal-bolus regimen n=20,137 (48%)	Gla-300	28.62	–	–
	IDeg	28.31	0.12 (−8.80 to 9.81)	0.512
≥65 years of age n=15,837 (38%)	Gla-300	22.52	–	–
	IDeg	26.43	−3.75 (−11.28 to 5.66)	0.200
≥75 years of age n=5,654 (13%)	Gla-300	26.55	–	–
	IDeg	32.30	−5.76 (−16.43 to 7.80)	0.200

Severe hypoglycemia was defined by: ICD 9/10 codes; or blood glucose <54 mg/dL; or intramuscular glucagon administration; or mention of hypoglycemia in patient notes with a descriptor denoting severity or on the same day as an emergency department visit/inpatient admission. The unit of analysis was the patient-treatment (a period during which a patient was using a BI).
[a]1-sided p-values. [b]≥1 hypoglycemic episode within last year, moderate renal impairment, >5 years of insulin exposure, hypoglycemic episode within last 12 weeks. [c]Compromised estimated glomerular filtration rate, nephropathy, proteinuria, dialysis.
BI, basal insulin; CI, confidence interval; ICD, International Classification of Diseases; PHPY, per hundred patient-years

Supported By: Sanofi

98-LB

Clinical Outcome Assessment of the Effectiveness of Insulin Degludec (Degludec) in Real-life Medical Practice (CONFIRM)—A Comparative Effectiveness Study of Degludec and Insulin Glargine 300U/mL (Glargine U300) in Insulin-Naïve Patients with Type 2 Diabetes (T2D)

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The CONFIRM study compared the real-world effectiveness of degludec and glargine U300 in insulin-naïve patients with T2D. This retrospective, non-interventional comparative effectiveness study used electronic health records of U.S.-based patients from Explorys, with propensity-score matching to balance baseline characteristics between cohorts. The primary endpoint, ΔA1C from baseline to 6 months follow-up, was estimated using a repeated-measure analysis with subject as random effect. Rate of hypoglycemic episodes (defined using International Classification of Diseases codes 9/10) and proportion of patients with hypoglycemia were estimated using negative binomial and logistic regression, respectively. Time-to-discontinuation of basal insulin was analyzed using a Cox Proportional Hazard model. This study included adults with T2D treated with oral antidiabetic drugs, intensified with either degludec or glargine U300. Data from 4056 patients were analyzed. After matching, baseline characteristics of the groups were comparable (n=2028 in each group). At follow-up ΔA1C was significantly lower with degludec (–1.5%) vs. glargine U300 (–1.2% [treatment difference, −0.3%, p=0.029]). Rates of hypoglycemia were significantly lower with degludec vs. glargine U300, (rate ratio: 0.70, p=0.045) similarly the proportion of patients experiencing hypoglycemia was significantly lower with degludec (odds ratio: 0.64; p<0.01). Patients treated with glargine U300 had a 37% higher risk of treatment discontinuation vs. degludec (hazard ratio: 1.37, p<0.01). Data from the largest real-world comparative effectiveness

study of degludec and glargine U300 to date, demonstrated improved glycemic control, lower rates of hypoglycemia and risk of discontinuation with degludec vs. glargine U300.

Supported By: Novo Nordisk A/S

99-LB

Impact of Switching from Twice-Daily Basal Insulin to Once-Daily Insulin Glargine 300 U/mL (Gla-300) in Patients with Type 1 Diabetes (T1DM)—Phase 4 OPTIMIZE Study, Belgian Cohort

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The 28-week, prospective, multicenter, open-label OPTIMIZE study, conducted in Belgium and Canada, evaluated treatment optimization with once-daily (OD) Gla-300 in combination with a prandial rapid-acting insulin analog in adults with T1DM previously uncontrolled (HbA_{1c} 8-10%) on twice-daily (BID) basal insulin as part of basal-bolus therapy.

The Intent-to-Treat (ITT) and safety populations of the Belgian cohort comprised 48 patients (52.1% women); mean (SD) age 51.7 (12.8) years and mean (SD) body mass index 28.2 (4.9) kg/m^2. Prior to the study, 37.5% were on insulin glargine 100 U/mL and 62.5% were on insulin detemir. There was a statistically significant reduction in HbA_{1c} from baseline to month 6 (primary endpoint, p<0.0001). No significant changes were observed in basal or prandial insulin dose, or in total or nocturnal hypoglycemic event rates. Statistically significant improvements were seen in the Diabetes Treatment Satisfaction Questionnaire (DTSQ) total and perceived hyperglycemia scores (p<0.05) (Table), and in the patient satisfaction score for number of injections (p=0.004).

Switching from a BID basal insulin analog to OD Gla-300 in this challenging T1DM population was associated with a statistically significant improvement in HbA_{1c} levels and better overall treatment satisfaction.

Table. Outcomes

Outcomes	Time points	N	Mean (SD)	Mean difference (95% CI)	P value
HbA_{1c}, %	Baseline	48	8.48 (0.62)	0.34 (0.17, 0.51)	**<0.0001**
	Month 6 (LOCF)	48	8.14 (0.53)		
Basal insulin dose, Units	Baseline	43	37.45 (19.11)	-	0.081
	Last phone call	43	40.87 (20.02)		
Total number HE, per patient/year	Run-in	41	122.25 (76.80)	-	0.527
	Last 4 weeks	41	131.84 (81.05)		
Total number nocturnal HE, per patient/year	Run-in	41	16.03 (23.02)	-	0.826
	Last 4 weeks	41	14.92(25.09)		
DTSQ total	Baseline	46	25.46 (6.26)	-	**0.001**
	Month 6	46	28.89 (5.26)		
DTSQ perceived hyperglycemia	Baseline	48	4.00 (1.40)	-	**0.016***
	Month 6	46	3.67 (1.12)		(>0.05**)
DTSQ perceived hypoglycemia	Baseline	48	3.13 (1.50)	-	0.102*
	Month 6	46	3.59 (1.15)		
HFS total	Baseline	46	37.25 (22.48)	-	0.651
	Month 6	46	36.06 (21.31)		
HFS behavior	Baseline	46	17.26 (9.16)	-	0.977
	Month 6	46	17.22 (10.21)		
HFS worry	Baseline	46	19.98 (15.93)	-	0.522
	Month 6	46	18.84 (14.97)		

DTSQ, Diabetes Treatment Satisfaction Questionnaire; HE, hypoglycemic events; HFS, hypoglycemia fear score; LOCF, last observation carried forward

Statistically significant results are indicated in bold

*Friedman's test comparing baseline, month 3 and month 6 time points

**Post hoc Wilcoxon's test comparing baseline to month 6 when Friedman's test is statistically significant (p<0.05)

Supported By: Sanofi (EudraCT 2015-001186-46)

100-LB

Use of Big-Data Algorithms to Characterize Patients with T2D on Basal Insulin (BI) Who Add a Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) and Predict Their A1C Response

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Machine learning allows extensive analysis of big complex data. This study had two aims: 1.) characterize patients on BI who add a GLP-1RA and 2.) identify predictors of ≥1% decline in A1C. Patients with T2D who were prescribed BI for ≥90 days but not GLP-1RA for 180 days beforehand (in the U.S. IBM Explorys database between 2010 and 2016) were included (N=80,019). For the A1C analysis, A1C readings ≤180 days before, and 180-360 days after initiating GLP-1RA were required (N=8731). Logistic regression with 23 pre-specified variables, and subsequent hypothesis-free machine learning models, with 155000 additional variables covering clinical, claims and billing data addressed both aims. GLP-1RA initiators were characterized by a BI duration of >180 days (vs. ≤180 days) estimated odds ratio (OR) 5.87 (95% CI: 5.49-6.27), receiving oral antidiabetic drugs(s) OR 1.70 (1.64-1.77) and co-medication(s) (both vs. none) OR 3.22 (2.96-3.50), a BMI >30 kg/m^2 (vs. <30 kg/m^2) OR 1.93 (1.84-2.03), age <75 years (vs. ≥75 years) OR 3.63 (3.37-3.92) and private insurance (vs. non-private) OR 2.2 (2.10-2.31). Variable selection via machine learning confirmed the importance of these variables. Baseline A1C was the only strong predictor of ≥1% decline in A1C, ORs (95% CI) compared with A1C <7% were 4.99 (3.29-7.57), 7.04 (4.77-10.39), 14.56 (9.98-21.24), 23.21 (15.92-33.85), 36.28 (25.05-52.54), 73.14 (50.32-106.32) for categories 7-<7.5, 7.5-<8, 8-<8.5, 8.5-<9, 9-<10, ≥10%, respectively. Machine learning, applying 155000 variables, confirmed the importance of baseline A1C. On average, patients who improved lowered A1C from 10.0% (interquartile range [IQR]: 8.6-11.0) to 7.7% (IQR 6.7-8.4). Patients with T2D on BI who added a GLP-1RA were likely to be <75 years old and had characteristics of progressed disease. Baseline A1C determined a ≥1% decline in A1C, suggesting patients on BI with high A1C would benefit from combination treatment with GLP-1RA.

Supported By: Novo Nordisk A/S

101-LB

Patient-Reported Outcomes (PROs) for Insulin Degludec/Liraglutide (IDegLira) vs. Insulin Glargine (IGlar U100) as Add-On to Sodium-Glucose Co-Transporter-2 Inhibitor (SGLT2i) ± Oral Antidiabetic Drug (OAD) Therapy in Patients with Type 2 Diabetes (T2D)—DUAL IX Trial

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In DUAL IX, a 26-week, phase 3b, treat-to-target, open-label trial, patients with uncontrolled T2D on SGLT2i ± OADs (N=420) were randomized 1:1 to once-daily IDegLira or IGlar U100 (100 units [U]/mL) add-on therapy. IDegLira was superior to IGlar U100 for A1C (1.9 vs. 1.7% reduction), body weight (0.0 vs. 2.0 kg gain) and hypoglycemia rate (58% lower with IDegLira). PROs were measured at baseline and week 26 with the 5-domain Treatment Related Impact Measure-Diabetes (TRIM-D) questionnaire, with higher scores indicating better outcomes. After 26 weeks, improvements were significantly greater with IDegLira vs. IGlar U100 in total TRIM-D, Treatment Burden domain and especially Diabetes Management domain (Table), including 4 of the 5 individual items (estimated treatment ratio [95% confidence interval]): help you control your diabetes: 2.17 [1.47; 3.21], p<0.0001; help you avoid hyperglycemia: 1.95 [1.32; 2.87], p=0.0007; help you avoid hypoglycemia: 1.62 [1.12; 2.36], p=0.0105; help you manage your weight: 2.44 [1.69; 3.52], p<0.0001; help you prevent feeling tired/lack of energy: 1.36 [0.95; 1.96], p=0.0945.

In conclusion, vs. IGlar U100, IDegLira treatment resulted in better clinical and treatment management outcomes.

Table.

	Baseline score[1] (SD)		Change (SD) from baseline at week 26		ETD [95% CI]	*p*-value
	IDegLira	IGlar U100	IDegLira	IGlar U100		
Total TRIM-D	75.8 (12.4)	75.3 (12.7)	8.3 (12.6)	5.4 (11.7)	2.78 [0.83; 4.73]	**0.0052**
Treatment Burden	70.6 (19.0)	70.7 (18.9)	7.8 (20.7)	4.0 (19.7)	3.18 [0.12; 6.24]	**0.0414**
Daily Life	85.3 (15.4)	83.1 (16.7)	2.5 (17.3)	2.9 (17.0)	0.85 [–1.96; 3.66]	0.5546
Diabetes Management	56.9 (20.1)	56.3 (20.9)	17.4 (20.8)	9.3 (23.6)	7.27 [3.98; 10.57]	**<0.0001**
Compliance	80.6 (16.5)	82.5 (16.8)	8.8 (17.4)	6.2 (17.4)	1.00 [–1.62; 3.62]	0.4564
Psychological Health	83.3 (15.2)	82.1 (16.2)	6.4 (15.4)	5.2 (14.9)	1.64 [–0.74; 4.03]	0.1767

[1]All scores were based on a 0–100 scale with higher values representing better outcomes.
CI, confidence interval; ETD, estimated treatment difference; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; SD, standard deviation; TRIM-D, Treatment Related Impact Measure – Diabetes

Supported By: Novo Nordisk A/S

102-LB

Total and Severe Hypoglycemia Is Reduced with Use of Inhaled Technosphere Insulin (TI, Afrezza®) Relative to Insulin Aspart in Type 1 Diabetes

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Hypoglycemia (HG) and fear of HG limit effective insulin therapy and contribute to suboptimal glycemic control. Ultra-short acting insulins reduce HG risk by providing their glucose-lowering effect early and reducing the risk of late postprandial HG. AFFINITY-1, a treat-to-target study in T1D on multiple daily injection therapy, demonstrated one such ultra-short acting insulin, TI (Afrezza®), was non-inferior to SC aspart in A1C reduction (Bode et al, Diabetes Care 2015). Consistent with its action profile, a lower rate of HG was observed in TI users overall, particularly in the 2-5 h post-meal interval and in those achieving target A1C <7%.

In this post-hoc analysis of patients with reported A1C values at end of treatment, mean rates for all HG and severe HG obtained from combined SMBG and AE reporting were significantly lower with TI than with aspart (Figure). A negative binomial regression including treatment, region, type of basal insulin, and A1C at end of treatment yielded an LS-mean HG rate for patients on TI 26% lower than comparable patients on aspart across the entire A1C range (mean ratio:0.74, 95% CI: 0.68-0.81).

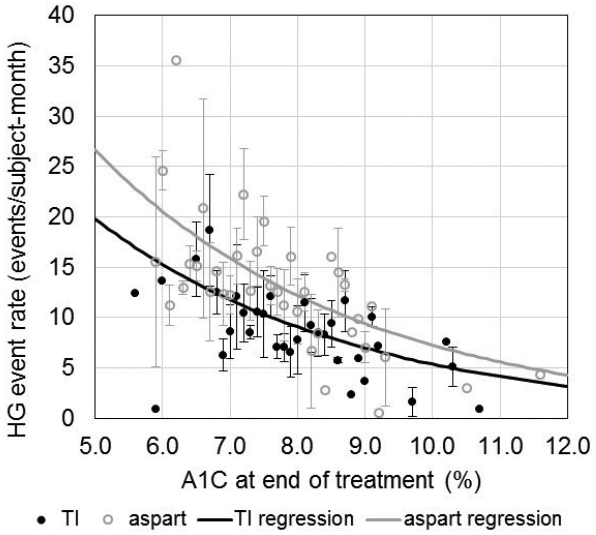
TI's rapid onset and ultra-short action provide insulin when needed at meals and between meals.

This profile improves overall and prandial glucose control and, as demonstrated in AFFINITY-1, has the potential to reduce the risk of late post-meal HG.

Table.

		all HG events		severe HG events	
Treatment	N	No. of events	Events per subj	incidence subj (%)	No. of events
TI	129	6983	54.1	28 (21.7)	59
aspart	150	11723	78.2	47 (31.3)	127
TOTALS	279	18706		75	186

Figure.



CLINICAL THERAPEUTICS/NEW TECHNOLOGY—NONINSULIN INJECTABLES

103-LB

Once-Weekly Dulaglutide (DU) and Canagliflozin (CAN) Combination Therapy in Obese T2 Diabetes (T2D) Patients—One Year Real-World Evidence from India

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Objective: To assess the effects of addition of a combination of GLP-1 receptor agonist (GLP-1RA), injection DU 1.5 mg weekly and SGLT2 inhibitor (SGLT2i), CAN 100mg/day in T2D obese Asian Indian patients sub-optimally controlled on metformin and other agents [sulfonylurea (SU) 71%, insulin 29%].

Methods: Impact of DU and CAN on HbA1c (A1c), weight (wt.), systolic blood pressure (SBP), lipids and dose of previous antidiabetic agents at week 16, 32 and 52 was analyzed retrospectively.

Results: Fifty-five patients (31M/24F, age 51±5.8 years, wt. 92.6±3.4 kg, BMI 31.1±2.1kg/m^2, SBP 142.4±3.9mmHg, eGFR 62± 5mL/minutes/1.73m^2, with 8.4±3.3 years duration of diabetes) met the inclusion criteria. In 71% subjects, A1c decreased by 1.6% [8.5±0.4 to 7.1±0.2, P<0.0001] at week 16 and dropped to 6.8±0.3 (P=0.0002) in 18% (week 32) but rose by 0.26% (P=0.0056) in 11% (week 40-52). At week 16, wt. was - 4.1 kg (92.6±3.4 to 88.5±3.6, P<0.0001). By week 32, 68% lost another 3.3±0.7 kg (P<0.0001) while 10% regained 1.1±0.6 kg (P=0.077). A drop in SBP of 4.1±0.8 mmHg (P<0.0001) was seen in 74.5% patients and 53% of these needed reduction in doses. A decrease in triglyceride (189.6±8.1 to 168.4±6.9 mg/dL, P<0.0001) and LDL-cholesterol (107.5±4.7 to 104.2±4.9 mg/dl, P=0.0004) occurred. At week 16, 50% required reduction in insulin dose and 15% stoppage. Increase in basal insulin dose/addition of prandial insulin was needed in 5% (week 39-52). By week 16, SU dose had to be halved in 56% and discontinued in others because of minor episodes of hypoglycemia. With CAN, genital and urinary tract infections were seen in 5.9% (2 F/1M) and 3.6% respectively. None had to stop therapy. With DU, nausea (18.1%), vomiting (14.5%) and diarrhea (7.2%) occurred but none had to stop therapy.

Conclusion: Combination Therapy of GLP-1 RA and SGLT2i in obese T2D patients provides statistically significant and durable glycemic control, with favorable effects on weight, BP and lipids and is also well tolerated.

104-LB

DURATION-8 Randomized Controlled Trial 104-Week Results—Once-Weekly Exenatide (ExQW) plus Once-Daily Dapagliflozin (DAPA) vs. ExQW or DAPA Alone

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In patients with T2D uncontrolled on metformin alone, ExQW + DAPA significantly reduced glycemia, body weight and systolic blood pressure compared to ExQW + placebo (PBO) or DAPA + PBO at 28 weeks (NCT02229396).

Here, we examined efficacy and safety after 104 weeks of double-blind therapy. Of 695 patients randomized, 431 (62%) completed 104 weeks; 4.3% withdrew due to adverse events (AEs). Absolute reductions and between-group differences in A1C were maintained over 104 weeks (Figure). Clinically relevant changes vs. baseline in other efficacy end points were also observed (Table). AEs and serious AEs were balanced across treatment groups. Hypoglycemia incidence was low (Table).

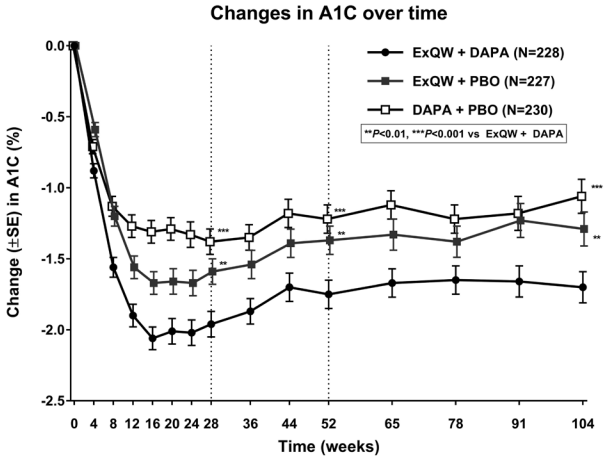
In conclusion, ExQW + DAPA maintained efficacy over 104 weeks with no unexpected safety concerns.

Table. Changes in Efficacy End Points and Hypoglycemia Incidence from Baseline Through Week 104.

	ExQW+DAPA N=228 n=147	ExQW+PBO N=227 n=132	DAPA+PBO N=230 n=152	ExQW+DAPA vs ExQW+PBO	ExQW+DsAPA vs DAPA+PBO
A1C, %					
BL mean (SD)	9.29 (1.06)	9.26 (1.08)	9.25 (1.02)		
28 week LSM change from BL (SE)	–1.98 (0.09)	–1.60 (0.10)	–1.39 (0.09)	–0.38 (0.13)**	–0.59 (0.13)***
52 week LSM change from BL (SE)	–1.75 (0.10)	–1.38 (0.10)	–1.23 (0.10)	–0.37 (0.14)**	–0.52 (0.13)***
104 week LSM change from BL (SE)	–1.70 (0.11)	–1.29 (0.12)	–1.06 (0.12)	–0.42 (0.15)**	–0.64 (0.15)***
FPG, mg/dL					
BL mean (SD)	195.0 (53.5)	189.3 (49.8)	188.5 (44.2)		
28 week LSM change from BL (SE)	–65.8 (2.9)	–45.8 (3.0)	–49.2 (2.9)	–20.1 (4.0)***	–16.6 (3.9)***
52 week LSM change from BL (SE)	–63.0 (2.9)	–45.4 (3.1)	–39.8 (3.0)	–17.6 (4.1)***	–23.3 (4.0)***
104 week LSM change from BL (SE)	–49.0 (4.1)	–29.8 (4.5)	–21.9 (4.6)	–19.2 (5.9)***	–27.1 (6.0)***
2h-PPG, mg/dL					
BL mean (SD)	268.5 (67.5)	266.1 (67.2)	261.5 (60.2)		
28 week LSM change from BL (SE)	–87.8 (4.1)	–60.1 (4.3)	–61.1 (4.1)	–27.7 (5.2)***	–26.8 (5.1)***
52 week LSM change from BL (SE)	–82.4 (4.8)	–64.0 (5.1)	–59.6 (5.0)	–18.4 (6.3)**	–22.8 (6.2)***
104 week LSM change from BL (SE)	–86.2 (5.9)	–79.0 (7.0)	–64.0 (6.6)	–7.2 (7.9)	–22.2 (7.9)**
Body weight, kg					
BL mean (SD)	92.1 (21.8)	89.1 (18.7)	90.9 (19.6)		
28 week LSM change from BL (SE)	–3.6 (0.3)	–1.6 (0.3)	–2.2 (0.3)	–2.0 (0.4)***	–1.3 (0.4)***
52 week LSM change from BL (SE)	–3.3 (0.4)	–1.5 (0.4)	–2.3 (0.4)	–1.8 (0.5)***	–1.0 (0.5)
104 week LSM change from BL (SE)	–2.5 (0.4)	–0.8 (0.5)	–3.0 (0.5)	–1.7 (0.6)**	+0.5 (0.6)
Systolic BP, mmHg					
BL mean (SD)	130.7 (12.1)	129.3 (12.5)	129.6 (12.8)		
28 week LSM change from BL (SE)	–4.3 (0.8)	–1.2 (0.8)	–1.8 (0.8)	–3.0 (1.1)**	–2.4 (1.1)*
52 week LSM change from BL (SE)	–4.5 (0.8)	–0.7 (0.9)	–2.7 (0.8)	–3.9 (1.1)***	–1.8 (1.1)
104 week LSM change from BL (SE)	–3.1 (1.0)	–0.1 (1.1)	–1.1 (1.0)	–3.0 (1.4)*	–2.0 (1.4)
Hypoglycemia† through 104 weeks	**N=231**	**N=230**	**N=233**		
Major, % pts	0	0	0		
Minor, % pts	1.7	0	0.4		
Other, % pts	6.9	3.5	3.4		

*P<0.05, **P<0.01, ***P≤0.001 (P-values at week 52 and week 104 are nominal). BL, baseline, BP, blood pressure; FPG, fasting plasma glucose; LSM, least-squares mean; N, number comprising the intention-to-treat analysis set; n, number completing 104 weeks of treatment; 2h-PPG, 2-hour post-prandial glucose; pts, patients; SD, standard deviation; SE, standard error; wk, week.
†Major hypoglycemia: loss of consciousness, seizure or coma resolving after glucagon or glucose administration or events requiring third-party assistance due to severe impairment of consciousness or behavior with blood glucose concentration <54 mg/dL. Minor hypoglycemia: non-major event with symptoms consistent with hypoglycemia and blood glucose concentration <54 mg/dL. Other hypoglycemia: events not meeting major or minor hypoglycemia criteria.

Figure.



Supported By: AstraZeneca

105-LB

Results of an Interim Analysis of a Phase 2, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of ZGN-1061 in Patients with Obesity and Type 2 Diabetes

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ZGN-1061 (1061) is a methionine aminopeptidase 2 (MetAP2) inhibitor being developed to improve glycemic control in type 2 diabetes. This clinical trial investigated the effect of 12 weeks of subcutaneous (SC) 1061 (0.05, 0.3, 0.9 mg or placebo) administered every 3 days on A1C, safety, and tolerability. Stable noninsulin diabetes therapy was permitted. The study included 129 patients; an interim analysis was conducted on a subset of patients at week 8. Baseline characteristics of the interim ITT population (N=57): 54% male, 77% white, (mean±SD) age 54±8 years, A1C 8.7±1.0%, BMI 37.2±6.4 kg/m^2. At week 8, the LS mean±SE change in A1C for placebo was 0.2±0.1% (N=13) vs. -0.4±0.2% with 0.9 mg 1061 (N=13, LS mean±SE difference -0.6±0.2%, p<0.02). In patients with week 12 measurements, the change in A1C was 0.4±0.2 (N=12) vs. -0.5±0.2 (N=8, difference -0.9±0.3, p<0.01). There were trends for weight loss and improved fasting plasma glucose with 0.9 mg 1061 vs. placebo as well as improvements in biomarkers, including hsCRP (week 8 -2.1±2.2 mg/L vs. 1.0±2.1, ns), adiponectin (1.0±0.3 ug/mL vs. -0.1±0.3, p<0.05), leptin (-6.9±1.9 ng/mL vs. 2.1±1.7, p<0.05), FGF-21 (0.026±0.014 ng/mL vs. 0.000±0.013; ns), and postprandial glucose AUC (p<0.01). Improvements in efficacy measures with the lower doses of 1061 were variable. There were no serious or severe adverse events (AEs) and no subjects withdrew due to an AE. The most common AE (1061>placebo) was upper respiratory tract infection. The 1061 pharmacokinetic profile indicated that exposure was within target levels for efficacy and safety and there were no changes in thrombosis markers (e.g., D-dimer). In this interim analysis, 1061 produced improvements in glycemic control and metabolic biomarkers consistent with MetAP2 inhibition. 1061 was also well tolerated with no safety signals in all doses tested. Week 12 results from the full analysis dataset will be presented.

Supported By: Zafgen, Inc.

106-LB

Effect of Leptin Replacement Therapy (LRT) on Survival and Disease Progression in Generalized and Partial Lipodystrophy (GL, PL)

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Lipodystrophy (LD) is an ultra-rare disease associated with significant morbidity and mortality. Effects of LRT on metabolic disease in GL and PL have been studied; but effects on mortality are unknown. We investigated these effects using data from GL and PL patients treated with LRT at NIH (N=114) and cared for but not treated with LRT at 3 centers in the U.S. and Turkey (N=178).

Four abnormalities (liver, kidney, heart, and HbA1c ≥6.5%) were considered. LRT patients had a mean of 2.8 abnormalities prior to treatment, while the mean for untreated patients was 0.7 at a similar age. We used a matching approach to create comparable samples of treated and untreated patients. Each treated patient was matched (using Mahalanobis distance) to an untreated patient to balance across age, gender, type of LD, and number of abnormalities. LRT treatment effect was examined via Cox proportional hazards models of 1.) mortality and 2.) development of subsequent abnormalities. Additionally, the relationship between abnormalities and mortality was studied in the sample of untreated patients.

Results: A Cox proportional hazards model relating treatment to mortality yielded a hazard ratio (HR) for LRT of 0.34 (p=0.047), meaning that LRT was associated with a 66% decrease in mortality risk. Adjusting for covariates including gender, type of LD, and type of abnormality resulted in a larger decrease in mortality risk (HR 0.21, p<.01).

One possible mechanism for the effect of LRT on mortality is its role in mitigating or resolving abnormalities. A time-varying Cox proportional hazards model relating number of abnormalities present (0 to 4) to mortality among untreated patients found a positive relationship between additional abnormalities and mortality (HR 3.2, p<.01). Separately, we found that LRT reduced the likelihood of developing a third (HR 0.47, p<.01) or fourth abnormality (HR 0.46, p<.05).

In conclusion, these are the first data suggesting that LRT reduces mortality in LD.

107-LB

ZGN-1061 Improves Metabolic Parameters and Hepatic Pathology in an Obese Mouse Model of Diet-Induced and Biopsy-Confirmed Nonalcoholic Steatohepatitis

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ZGN-1061 (1061) is a methionine aminopeptidase 2 (MetAP2) inhibitor being developed to improve glycemic control in type 2 diabetes. In diet-induced obese mice, 1061 reduces fat mass and improves glycemic control, lipid metabolism, and other metabolic parameters. This study investigated 8 weeks of treatment with 1061 (0.3 mg/kg, SC, N=11) or vehicle (N=10) on metabolic parameters, hepatic pathology, and nonalcoholic fatty liver disease (NAFLD) activity score (NAS; composite measure of steatosis, inflammation, and ballooning degeneration; range 0-8) in male mice with diet-induced and biopsy-confirmed nonalcoholic steatohepatitis (DIO-NASH). At week 8, there was a vehicle corrected weight loss of 13.1% with 1061 ($p<0.001$). 1061-treated mice had reduced liver weight (mean±SE: 2.6±0.4 g) vs. vehicle (3.8±0.8 g, $p<0.001$) and 21% reduction of liver triglyceride ($p<0.05$). There was no change in food intake. NAS was unchanged in vehicle-treated mice (BL 6.2±0.1, Wk8 6.4±0.2, ns). 1061-treated mice had reduced NAS (BL 6.2±0.2, Wk8 5.0±0.3, $p=0.002$). Two of the NAS component measures improved: steatosis in vehicle-treated mice was unchanged (BL 3.0±0.0, Wk8 3.0±0.0, ns), whereas ZGN-1061 reduced steatosis (BL 2.9±0.1, Wk8 2.5±0.2, $p=0.02$), and hepatocellular ballooning was unaffected in vehicle-treated mice (BL 0.7±0.2, Wk8 0.6±0.2, ns), whereas 1061 significantly reduced ballooning severity (BL 0.6 ± 0.2, Wk8 0.0 ± 0.0, $p=0.006$). There was no treatment effect on fibrosis stage or liver collagen 1A. However, liver galectin-3 was reduced with 1061 vs. vehicle. 1061 produced a reduction in terminal plasma ALT and AST vs. vehicle. In DIO-NASH mice, 1061 markedly reduced body weight in conjunction with liver weight and triglyceride content. Importantly, 1061 improved liver function, steatohepatitis and NAS composite score. These findings introduce 1061 as a promising therapy for obesity-related NASH.

Supported By: Zafgen, Inc.

108-LB

ZGN-1061, a Novel MetAP2 Inhibitor, and Liraglutide Combine to Improve Glycemic Control and Reduce Body Weight in a Rat Model of Diet-Induced Obesity

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ZGN-1061 (1061) is a methionine aminopeptidase 2 (MetAP2) inhibitor being developed to improve glycemic control in T2D. This study investigated 5 weeks (weeks) of once-daily SC treatment with a submaximal 0.3 mg/kg dose of 1061, a maximal 0.4 mg/kg dose of liraglutide (lira), 1061+lira, or vehicle (N=10/group) on body weight (BW), food intake/preference, and glycemic control in the Gubra diet-induced obese (DIO) rat model (ad libitum fed chow and highly palatable high-fat, high-sugar [HFHS] diet). Fasting (4 hour) blood glucose (FBG) was collected weekly and a semifasted (16 hour access to 50% of daily energy requirement) OGTT was performed at week 4. At week 5 (day 33), BW changed by +1.7% with vehicle vs. -6.0% with 1061, -9.1% with lira, and -16.9% with 1061+lira (all $p<0.001$). BW loss occurred earlier with lira (day 1) than 1061 (day 5). Starting at day 6, intake of the HFHS diet was modestly reduced (15-30%) with 1061 vs. vehicle. In contrast, lira and 1061+lira induced rapid and sustained 40-50% and 50-80% reductions in intake of the HFHS diet, respectively, over the first 8-9 days. Cumulative (day 0-35) HFHS diet intake was reduced vs. vehicle by 1061 (13.4%, $p=0.07$), lira (17.8%, $p<0.01$), and 1061+lira (38.2%, $p<0.001$). Cumulative chow intake was increased by 1061 and 1061+lira but not lira alone. There was a modest reduction in FBG (mean week 1-5) with 1061 vs. vehicle ($p=0.08$), a significant reduction with lira, and 1061+lira produced the largest reduction (both $p<0.001$) that was significantly lower than either agent alone (both $p<0.01$). In the OGTT, 1061 reduced the glucose AUC vs. vehicle by 37% ($p=0.07$), lira by 60% ($p<0.001$), and 1061+lira by 80% ($p<0.001$), achieving an AUC that was no different from lean rats. In this DIO rat model, 1061 and lira had complementary effects on reducing BW and normalizing glycemic control. Combination treatment with 1061 and liraglutide may yield greater weight loss and glycemic control than either agent alone in patients with T2D.

Supported By: Zafgen, Inc.

109-LB

Repeat BCG Vaccination Creates Lasting Reductions of HbA1c in Subjects with Long-Term Type 1 Diabetes—Long-Term Clinical Trial Follow-up

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We report on a randomized, placebo-controlled prospective examination of adult subjects with long-term type 1 diabetes who received 2 bacillus Calmette-Guerin (BCG) vaccine doses 4 weeks apart and were studied for up to 5 years. All enrolled subjects had disease >10 years duration without complications. Starting after year 3 of follow-up, only BCG vaccinated subjects had lowered HbA1c for 1 year (Year 05 data: BCG-treated HbA1c 6.18+/-.34 [n=9], placebo 7.07+/-.41 [n=3], reference subjects with type 1 diabetes 7.22+/-.17 [n=34, $p=0.02$]). Continuing follow-up of 6 subjects who have been followed for a total of 8 years, 4 years after the first documented lowering of HbA1c (Phase 1 trial participants), confirms the ability of repeat BCG vaccination to maintain lowered HbA1c levels without hypoglycemia in long-term disease (BCG-treated HbA1c 6.65+/-.26 vs. placebo 7.22+/-.38, $p=0.0002$) for a total of 5 continuous years. For all BCG-treated subjects, the stable reductions in HbA1c were not associated with hypoglycemia. BCG-treated subjects had no change in their enrollment use of insulin pumps and none utilized a CGM device. The apparent stable and long-lasting impact of BCG on blood sugars in humans with type 1 diabetes appears to be the result of a novel mechanism, as documented with metabolomics, mRNAseq, and epigenetic methods; namely, a systemic shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis, a state of high glucose utilization on cellular levels. BCG via epigenetics also resets T-regulatory genes for genetic reprogramming of tolerance. Trials are being designed to confirm the value of BCG for blood sugar control in humans. The identification of a novel mechanism for blood sugar lowering with BCG opens the door for future trials in both type 1 and 2 diabetes with a safe, novel and affordable approach.

110-LB

Addition of GLP-1 Therapy to Insulin in C-Peptide-Positive Patients with Type 1 Diabetes

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We have previously demonstrated that the addition of liraglutide to insulin significantly improves the glycemic control in patients with type 1 diabetes (T1D) with undetectable c-peptide. We have now investigated whether the addition of GLP-1 therapy to insulin in c-peptide positive patients with T1D will increase the c-peptide concentrations and improve the glycemia further with reduced insulin requirements. We conducted a retrospective analysis of 11 Caucasian patients with detectable c-peptide and positive GAD-65 antibodies treated with GLP-1 therapy for 12±1 weeks (baseline c-peptide: 0.43±0.09 ng/ml; baseline HbA1c: 10.63±0.87%; mean age: 43±5 years; mean age of diabetes diagnosis: 37±5 years; mean duration of diabetes: 6±2 years; mean BMI: 23± 1Kg/m^2; mean body weight: 71±2 kg; 6 females, 5 males). At the end of 12± 1 weeks of GLP-1 therapy; c-peptide concentrations increased significantly from 0.43±0.09 to 1.42±0.42ng/ml ($p=0.01$); HbA1c fell from 10.63± 0.87% to 7.45± 0.52% ($p<0.01$), body weight fell from 71±2.0 kg to 69±2 kg ($p=0.06$) and total insulin dose fell by 64% from 34.45±5.73 to 12.27±4.01 units ($p<0.01$). 5 out of 11 patients did not require any insulin. 9 patients were initiated on liraglutide: 0.6 mg subcutaneous (sc) daily for one week, 1.2 mg daily for second week and then 1.8 mg daily thereafter. One out of these 9 patients did not tolerate 0.6 mg daily dose and stopped it due to nausea in the first week. 2 patients were initiated on dulaglutide (0.75 mg sc once a week for 2 weeks and then 1.5 mg once a week thereafter). We conclude that addition of GLP-1 therapy in GAD-positive and C-peptide positive patients with type 1 diabetes (T1D) results in 3.5 fold increase in c-peptide concentrations with improved glycemic control and more than 60% reduction in insulin requirements over a period of 12 weeks. Long term studies are needed to establish the durability of these benefits.

111-LB

Improvement of Type 2 Diabetes (T2DM) and Reduction of Major Adverse Cardiovascular Events and Mortality in Hypogonadal Men Receiving Long-Term Treatment with Injectable Testosterone Undecanoate (TU)—Real-Life Evidence from a Urological Registry Study

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Background: Hypogonadism is highly prevalent in men with T2DM.

Methods: Of 805 hypogonadal men in a urological registry, 311 men (39%) had T2DM diagnosed and treated elsewhere. 141 received TU 1000 mg/12 weeks (T-group), 170 opted against treatment (CTRL). Mean changes over time between groups were compared by mixed effects model. Changes were adjusted for age, weight, waist circumference, HbA_{1c}, blood pressure (BP), lipids to account for baseline differences between the two groups.

Results: Mean follow-up 7.5 years for 2.319 patient-years. Age: 62.8±5.1 years. T-group: HbA_{1c} progressively decreased from 9.0±1.2 to 5.9±0.3% at 10 years ($p<0.0001$) with statistical significance vs. previous year for the first 7 years. CTRL: HbA_{1c} increased from 7.8±0.7 to 10.6±1.7% ($p<0.0001$). Estimated adjusted difference between groups; -6.2% ($p<0.0001$). T-group: fasting insulin decreased from 29.6±4.1 to 13.5±5 µU/mL ($p<0.0001$) with statistical significance vs. previous year for the first 6 years. CTRL: fasting insulin increased from 26.1±2.7 to 36.7±2 µU/mL ($p<0.0001$). Estimated adjusted difference between groups: -28 µU/mL ($p<0.0001$). T-group: HOMA-IR decreased from 10.2±2.1 to 3.3±1.2 after 10 years ($p<0.0001$). The decrease was statistically significant vs. previous year for the first 6 years. CTRL: HOMA-IR increased from 7.5±1.3 to 17.1±6.3 ($p<0.0001$). Estimated adjusted difference between groups: -14.8 ($p<0.0001$). Since injections were administered in the doctor's office and no patient dropped out, there was a 100% adherence to TTh. 8 patients (5.7%) in T-group died. In CTRL, 47 myocardial infarctions (27.6%), 37 strokes (21.8%), and 41 deaths (24.1%) occurred.

Conclusions: Long-term TTh with TU in hypogonadal men with T2DM improved diabetic measures and reduced MACE compared to untreated controls.

Supported By: Bayer AG

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—ORAL AGENTS

112-LB

Efficacy and Safety of Continuing Sitagliptin when Initiating Insulin Therapy in Subjects with Type 2 Diabetes Mellitus

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DPP-4 inhibitors (DPP-4is) are often discontinued with initiation of insulin therapy but the impact of this discontinuation on efficacy and hypoglycemia has not been studied. In this double-blind trial the safety and efficacy of initiating insulin while continuing sitagliptin (SITA) was evaluated. Eligible patients had inadequately controlled T2DM on metformin (MET, ≥ 1500 mg/day) in dual or triple combination therapy with a DPP-4i and/or sulfonylurea. Those on MET + SITA (100 mg/day) directly entered the trial; all others were switched to MET + SITA and stabilized during a run-in period. Subjects were randomized to continuing SITA or discontinuing SITA and switching to matching placebo, with both groups initiating insulin (LANTUS®), which was titrated based on fasting glucose.

746 subjects (mean A1C 8.8%, disease duration 10.6 years) were randomized. After 30 weeks, continuing SITA was superior to discontinuing SITA in reducing A1C ($p<0.001$). Patients who continued SITA had a lower event rate of documented symptomatic hypoglycemia (blood glucose ≤70 mg/dL) and daily insulin dose compared to patients who discontinued SITA. Summary adverse event measures and change in body weight (week 30) were similar in the 2 treatment groups.

In summary, with the initiation of insulin therapy, continuation of SITA resulted in superior glycemic efficacy and less documented symptomatic hypoglycemia.

Table.

Change from Baseline in A1C (%) [a]		
Treatment	LS Mean (95% CI)	Difference in LS Means (95% CI)
SITA, n= 373	-1.88 (-1.98, -1.78)	-0.46 (-0.58, -0.34)
PBO, n= 370	-1.42 (-1.52, -1.32)	
Event Rate of Documented Symptomatic Hypoglycemia (Blood Glucose ≤70 mg/dL) [b, c]		
Treatment	Event Rate (95% CI)	Event Rate Ratio (95% CI)
SITA, n= 371	1.55 (1.22, 1.96)	0.73 (0.54, 0.98)
PBO, n= 370	2.12 (1.70, 2.66)	
Total Daily Insulin Dose (Units) [a, d]		
Treatment	LS Mean (95% CI)	Difference in LS Means (95% CI)
SITA, n= 365	53.2 (48.5, 58.0)	-8.0 (-14.6, -1.5)
PBO, n= 367	61.3 (56.5, 66.0)	

[a] Analyzed using a longitudinal data analysis model.
[b] Analyzed using a negative binominal regression model.
[c] Two subjects (both in the sitagliptin group) were not included in the analysis due to a missing value of a model covariate (race).
[d] 11 subjects did not have post baseline insulin dose data.

Supported By: Merck & Co., Inc.

113-LB

Dapagliflozin Improves Insulin Sensitivity in the Obese Prediabetic Canine

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SGLT2 inhibition has positive effects on glucose balance, reducing fasting and postprandial glucose levels, however little is known about the effects of SGLT2 inhibitors on lipid levels. PKPD simulation for this canine model was applied for dose selection of dapagliflozin (dapa). Seven dogs were fed a high fat diet for 6 weeks, then received a single low dose of streptozotocin (18.5mg/kg) to induce mild type 2 diabetes. Animals were exposed to dapa (n=4, 1.25mg/kg) or placebo (n=3) once per day for 6 weeks, while remaining on the high fat diet. Animals were then subjected to the intravenous glucose tolerance test (IVGTT) to assess glucose tolerance and insulin response to glucose, and the euglycemic hyperinsulinemic clamp protocol in conjunction with tracer infusions to evaluate adipose tissue, skeletal muscle and hepatic insulin sensitivity. In the IVGTT, modeling techniques are used to estimate the acute insulin response to a glucose bolus, which was not altered with dapa treatment, but insulin sensitivity was significantly improved compared to placebo-treated animals (dapa 0.54 ± 0.22, control $-0.95\pm0.51 mU/l^{-1}.minute^{-1}$, $p=0.05$). The glucose infusion required for euglycemia during steady state in the clamp was decreased with dapa (dapa -3.0 ± 1.05, control 1.53 ± 1.28 mg/minute/kg, change from pre-drug timepoint, $P=0.038$), supporting the IVGTT results. Urinary glucose disposal rate during the clamp was inconsistent. There is a trend towards higher FFA levels in dapa-treated animals under noninsulin stimulated conditions ($P=0.054$). These may be a regulator of hepatic glucose production, or reflect a switch towards lipid utilization. We conclude that 6 weeks of dapa treatment improves insulin sensitivity in a canine model of mild type 2 diabetes. Further studies on lipid metabolism, body fat deposition and insulin clearance are on-going.

Supported By: AstraZeneca

114-LB

LIK066, a Dual SGLT1/2 Inhibitor, Reduces Weight and Improves Multiple Incretin Hormones in Clinical Proof-of-Concept Studies in Obese Patients With or Without Diabetes

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Background: LIK066 is a potent dual inhibitor of SGLT1/2 (IC_{50}: 20.6 and 0.58 nM for SGLT1 and SGLT2). We studied mechanistic effects of dual SGLT1/2 inhibition of SGLT1 in the gut and SGLT1/2 in the kidneys.

Methods: Effects of LIK066 on weight, glucose and a variety of incretin hormones (GLP-1, PYY, GIP, glucagon, insulin) were investigated in: 1.) a single dose cross-over study in T2DM, 2.) a 14 day randomized, double-masked study in T2DM, 3.) a 12-week randomized, double-masked, placebo-controlled study in obese subjects with normoglycemia (NG) or dysglycemia (DG; HbA1c: ≥5.7% and <10%).

Results: LIK066 (2.5, 30, 300 mg single dose) significantly reduced glucose excursion and insulin secretion (p<0.01 at 30 and 300 mg) following oral glucose tolerance test (OGTT) in patients with T2DM (n=12), with the 300 mg dose completely suppressing glucose and insulin excursions. In patients with T2DM (n=30), LIK066 15 mg qd for 14 days reduced blood glucose (41 mg/dL by continuous glucose monitoring) and increased 24-hour urinary glucose excretion (100 g/d on day 14). Furthermore total GLP-1 and PYY increased ($AUC_{0\text{-}3hrs}$ >1.5-fold; p<0.05) post-OGTT, while GIP levels were reduced (>50%; p<0.05). In obese subjects (n=88), LIK066 150 mg qd for 12 weeks reduced weight by 5.70% (p<0.001) compared to placebo, with higher effects in DG (6.85%) vs. NG (4.55%). Additionally multiple metabolic parameters improved (reduced waist circumference, postprandial glucose and insulin, and increased postprandial glucagon). LIK066 was generally safe and well tolerated. The most common AEs were headache, flatulence and diarrhea.

Conclusions: LIK066 treatment leads to favorable changes in a variety of metabolic hormones (increased GLP-1, PYY and glucagon, reduced GIP, glucose and insulin), all contributing to WL effects of LIK066. The dual inhibition of SGLT1/2 in both the gut and kidneys is an attractive strategy for obesity or diabetes treatment.

115-LB

Development of Oral Bioavailable Nicotinamide N-Methyltransferase Inhibitors to Reduce Adiposity, Insulin Resistance, and Hyperglycemia

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There is a critical need for new mechanism-of-action drugs that reduce adiposity, a prime driver of type 2 diabetes. A novel target to treat adiposity and reverse type 2 diabetes is nicotinamide-N-methyltransferase (NNMT), a cytosolic enzyme with newly identified roles in regulating adipose tissue metabolism and energy homeostasis. We have recently developed first-in-class small molecule NNMT inhibitors and characterized physicochemical, pharmacological, pharmacokinetic (PK), and off-target safety profiles of these inhibitors to identify a drug-like efficacious, orally bioavailable, and safe lead candidate for IND-enabling studies. Our first generation of highly selective, stable, and soluble compounds demonstrated excellent PK properties, including high oral bioavailability (>90%) and half-life of 3 hours in rats. Finally, the efficacy of promising NNMT inhibitors at modulating adiposity and type 2 diabetes endpoints (e.g., fat mass, oral glucose tolerance, adipokine levels, circulating lipids) were assessed using diet-induced obese (DIO) mice maintained on a high-fat diet. Systemic treatment of DIO mice with a potent NNMT inhibitor significantly reduced body weight and white adipose tissue mass, decreased adipocyte cell size, and lowered plasma cholesterol levels (p<0.05). Notably, administration of NNMT inhibitors did not alter total food intake nor produce any observable adverse effects. These results support continued development of small molecule NNMT inhibitors as therapeutics to lessen adiposity and lower the burden of adiposity-associated type 2 diabetes.

116-LB

Changes in HbA1c with Optimization of Metformin Dosage in the GRADE Cohort

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Delay in maximizing metformin (MET) therapy is a common problem - attributed to "clinical inertia" - which might be reduced if there were better understanding of the impact of increasing MET in persons already on MET at submaximal dosage. We determined the effect of optimizing MET dosage on glycemic control in GRADE study participants. We examined the HbA1c of 6767 participants before and after a run-in period, during which MET dosage was adjusted to 2000 mg daily, or a maximally tolerated lower dose. The run-in was 6-14 weeks for participants taking MET at a dose other than 2000 mg/day, or >4 weeks if on 2000 mg/day at entry. To be eligible, participants had to have type 2 diabetes <10 years and HbA1c >6.8% while taking >500 mg of MET daily and no other glucose-lowering drug. Participants also received diet and exercise counseling. Increases in MET dosing during run-in were associated with a progressive fall in HbA1c (p<0.001). The mean decrease in HbA1c was 0.5 ± 1.1% (SD) in participants whose MET was increased by <500 mg/day, 0.5 ± 0.9% for an increase of 500-999 mg/day, and 0.7 ± 1% for an increase of >1000 mg/day. There was also a mean HbA1c decrease of 0.4 ± 0.9% if MET dosage was kept at 2000 mg/day (n=3472), and a mean HbA1c decrease of 0.2 ± 0.7% if the daily dose was decreased (from a mean of 2213 to 1612 mg/day, n=187) - possibly reflecting better adherence to medications and/or lifestyle recommendations. In subjects whose MET dosage was increased (n=3108), the decrease in HbA1c was inversely and strongly correlated with the initial HbA1c at entry (p<0.001, r=-0.53).

Conclusions: Maximizing MET dosage can improve glycemic control in persons with type 2 diabetes who have HbA1c values above 6.7% while taking less than 2000 mg of MET daily, and maximizing MET dosage produces a larger fall in HbA1c if the initial HbA1c is higher. Moreover, a decrease in MET dosage did not increase HbA1c. These findings support health policies aimed to improve and optimize use of metformin among persons with type 2 diabetes whose glycemic control is suboptimal.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

117-LB

Suppression of Ketogenesis in Type 1 Diabetes Is Not Delayed by SGLT2 Inhibitor Therapy

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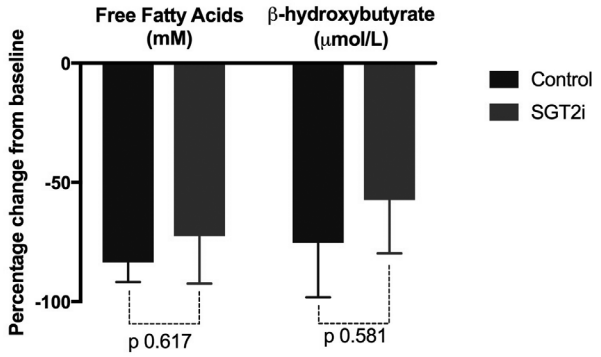
Enthusiasm for SGLT2 inhibitors as adjunctive agents for T1D has been tempered by increased risk of DKA, especially in pump treated patients susceptible to interruptions of basal insulin due to infusion site failures. Our insulin interruption study showed that failure to recognize early metabolic decompensation in SGLT2i-treated T1D patients relates to blunted increases in plasma glucose (PG) rather than accelerated ketogenesis (Δ PG 99±13 vs. 197±24 mg/dL, p<0.002; Δ free fatty acids [FFA] 0.8±0.1 vs. 0.7±0.1 and Δ β-hydroxy-butyrate [BHB] 1.5±0.2 vs. 1.2±0.2 mmol/L) before and after SGLT2i therapy. We report herein whether correction of early ketogenesis by a rescue dose of rapid-acting insulin is adversely affected by SGLT2i use. Ten adults [age 23±5 years, A_{1c} 7.4±0.8%] had insulin interruption studies pre- and post 3 weeks of canagliflozin therapy. After a 6-hour suspension, a 0.2 unit/kg SQ bolus of aspart was given. PG, FFA and BHB levels were monitored for 150 minutes. PG fell from 314±42 to 183±17mg/dl pre- vs. 186±73 to 117±33mg/dL post SGLT2i use. The fall in FFA and BHB levels were unaffected by SGLT2i therapy(Figure). These data indicate that SGLT2i treatment does not impair suppression of increased FFA and BHB levels due to interruption of basal insulin infusion. Turning ketogenesis off, as well as on, does not appear to be affected by SGLT2i use.

Figure.



Supported By: Endocrine Fellows Foundation; JDRF (5-ECR-2014-112-A-N); National Institutes of Health (K12DK094714, UL1TR000142, P30DK45735)

118-LB

Enteral Insulin Attenuates Fatty Liver Signs and Symptoms in Mice on a High-Fat Diet

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Nonalcoholic fatty liver disease (NAFLD) is now the most common liver disorder in the USA, affecting 90% of morbidly obese individuals and often clustering with prediabetes or overt type 2 diabetes mellitus. While its exact pathogenesis remains unclear, insulin resistance and obesity are considered contributing and risk factors, suggesting effective blood glucose control as a means of preventing and managing NAFLD. To assess this treatment avenue, C57b1/6J mice maintained on a high-fat diet (HFD) for 13 weeks, were treated daily with insulin (INS; 3.6 mg/kg), delivered via a feeding tube, or sham-saline treatment for three consecutive weeks. Peripheral blood and liver samples were collected to analyze inflammatory and fibrosis markers and to histologically assess NAFLD activity score (NAS). Following the treatment period, INS HFD mice demonstrated lower body weight (8.6±1.8 g vs. 7.5±4.1

g) and significantly lower NAS (0.11 vs. 3.7; p<0.005) as compared to sham HFD mice. Further, the mean baseline alanine aminotransferase (ALT) levels of 212±223.6 U/L dropped to 38.3±34.5 U/L and 88.4±85.3 U/L in sham and INS animals, respectively. However, post-treatment aspartate aminotransferase (AST) levels were unchanged in sham HFD animals (202.8±83.7 U/L), but were two-fold lower in INS mice (123.2±80.4 U/L; p=0.03). Mean AST/ALT ratios, a reliable indicator of liver disease, were significantly lower among INS, as compared to sham mice (2.6±1.3 vs. 4.7±2.9; p=0.04). Change from baseline alpha smooth muscle actin (αSMA) RNA levels, a hallmark of fibrosis, was lowest among INS (0.31±0.23-fold increase) as compared to saline-treated HFD mice (0.58±0.14). In parallel, a consistently higher percentage of active, antifibrotic ($NKP46^+$) $CD3^+$ natural killer cells were observed among INS vs. sham and untreated NFD mice. These preliminary findings provide a proof of concept for the potentially therapeutic effect of enteral insulin on fibrotic and inflammatory processes in the liver.

119-LB

Long-Term Efficacy and Safety of Dapagliflozin in Patients with Inadequately Controlled Type 1 Diabetes—The DEPICT-1 Study

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In the short term (24-week) period of the Phase 3 study DEPICT-1, treatment with the SGLT2 inhibitor dapagliflozin (DAPA) as adjunct to adjustable insulin (INS) improved glycemic control and was well-tolerated in patients with inadequately controlled T1D (HbA1c 7.5-10.5%) (Lancet Diabetes Endocrinol. 2017;5:864-76). Here we describe the 28-week extension of DEPICT-1, assessing the 52-week efficacy and safety of DAPA in patients who completed the 24-week period. 747 patients in the DAPA 5 mg (n=250), 10 mg (n=270), or placebo (PBO; n=227) plus INS groups entered the long-term period (90% of the randomized patients); 85% completed the study. Reductions in HbA1c and body weight were maintained in the DAPA groups vs. PBO over 52 weeks (Table). The moderate decrease in HbA1c with DAPA was accompanied by a more substantial dose-dependent reduction in body weight. Total events of adjudicated definite DKA increased in the long-term period, with more in the DAPA groups vs. PBO at week 52. Most were mild or moderate, with the primary cause related to missed insulin doses or pump failure. Adverse events (AEs), serious AEs, and hypoglycemic events were balanced between groups (Table).

In conclusion, DAPA plus INS provided a sustained reduction in HbA1c and body weight, and was well-tolerated, but increased events of DKA over 52 weeks in patients with inadequately controlled T1D.

Table.

Efficacy Outcomes at Week 52	DAPA 5 mg + INS n=259*	DAPA 10 mg + INS n=259*	Placebo + INS n=260*
A1c, %	.	.	.
Week 52 adjusted mean change	-0.27 (0.06)	-0.31 (0.06)	0.06 (0.06)
from baseline (SE)	-0.33	-0.36	
Difference vs. PBO (95% CI)	(-0.49, -0.17)	(-0.53, -0.20)	—
Total body weight	.	.	.
Week 52 adjusted mean percent change	-2.80 (0.32)	-4.39 (0.31)	0.15 (0.33)
from baseline (SE)	-2.95	-4.54	
Difference vs. PBO (95% CI)	(-3.83, -2.06)	(-5.40, -3.66)	—
Safety outcomes at Week 52, n (%)	**n=277†**	**n=296†**	**n=260†**
≥1 AE	215 (77.6)	236 (79.7)	189 (72.7)
≥1 SAE	37 (13.4)	40 (13.5)	30 (11.5)
≥1 related SAE	8 (2.9)	13 (4.4)	2 (0.8)
≥1 event of any hypoglycaemia	227 (81.9)	241 (81.4)	212 (81.5)
≥1 event of severe hypoglycaemia	29 (10.5)	25 (8.4)	30 (11.5)
Events adjudicated as definite DKA	12 (4.3)	10 (3.4)	5 (1.9)
...Mild	...5 (1.8)	...2 (0.7)	...3 (1.2)
...Moderate	...3 (1.1)	...6 (2.0)	...1 (0.4)
...Severe	...4 (1.4)	...2 (0.7)	...1 (0.4)

AE, Adverse Event; CI, Confidence Interval; DAPA, Dapagliflozin; PBO, Placebo; INS, Insulin; SAE, Serious Adverse Event; SE, Standard Error. *n is the number of patients who received 52 weeks of treatment in the full analysis set (excludes the first 55 patients allocated to only DAPA groups due to an interactive voice response system randomization system error). †n is the number of patients who initiated the 24-week period in the safety analysis set (includes the first 55 patients incorrectly randomized to only DAPA groups). ‡Includes events monitored in both 24-week short-term period and 28-week extension.

Supported By: AstraZeneca

120-LB

Eldecalcitol, a Vitamin D Analog, for Diabetes Prevention in Impaired Glucose Tolerance (DPVD Study)

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Background: In cohort and observational studies, it was clear that vitamin D deficiency is associated with insulin resistance and risk of future diabetes. However, randomized controlled trials with vitamin D supplementation for improving glucose tolerance or prevention of type 2 diabetes is still controversial.

Methods: We conducted the Diabetes Prevention on Vitamin D (DPVD) study which was a large, randomized, double-blind, placebo-controlled study to examine whether eldecalcitol, an active form of vitamin D analog, can reduce the risk of type 2 diabetes in patients with impaired glucose tolerance. Participants were randomly assigned to receive eldecalcitol or placebo. The primary endpoint was the incidence of type 2 diabetes and the secondary endpoint was the conversion to normal glucose tolerance. The study duration was 3 years.

Results: The mean follow-up was 2.6 years. A total of 1256 participants were enrolled in the study. 57 of 630 (9.0%) participants in the eldecalcitol and 64 of 626 (10.2%) in the placebo group developed type 2 diabetes (hazard ratio, 0.87; 95% confidence interval, 0.68 to 1.09; p=0.37). In the subgroup participants with vitamin D deficiency (serum 25-hydroxyvitamin D<20 ng/ml), the difference of the incidence of type 2 diabetes between the two groups was greater; however, there was no statistical significance. Two hundred ninety-five of 630 (46.8%) participants in the eldecalcitol and 267 of 626 (42.7%) in the placebo group achieved normal glucose tolerance (hazard ratio, 1.10; 95% confidence interval, 0.93 to 1.31; p=0.45). No serious adverse events related to the intervention were recorded.

Conclusion: Our study showed that treatment with eldecalcitol was not associated with a reduction in the incidence of type 2 diabetes or an increase in the conversion to normal glucose tolerance among patients with impaired glucose tolerance.

Supported By: Chugai Pharmaceutical Co., Ltd.; Taisho Toyama Pharmaceutical Co., Ltd.

121-LB

Recombinant Protease Inhibitor Enhances Oral Insulin Pharmacodynamics in Pigs

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Oral insulin delivery is projected to provide both physiologic and technical benefits, and has been the focus of rigorous research efforts in recent years. The ORMD-0801 oral insulin formulation relies on the activities of both protease inhibitors and an absorption enhancer to ensure insulin integrity and bioavailability. In efforts to further improve its efficacy, a recombinant protease inhibitor (rPI), identical in sequence to its naturally sourced (nsPI) counterpart, was cloned and expressed in Pichia pastoris. The enzymatic activity of the isolated and purified protein was then tested in vitro. In addition, the glucose-lowering effect of ORMD-0801 formulated with various doses of rPI was assessed in 8 healthy, fasting pigs administered the preparation directly to the duodenum. rPI effectively inhibited its standard substrate in a dose-dependent manner and demonstrated >2.5-fold higher activity as compared to nsPI. When integrated in the ORMD-0801 formulation, pigs treated with the formulation containing 25 mg rPI experienced a 20% greater change from baseline serum glucose concentrations as compared to those treated with the PI-free formulation (AUC: -6369 mg/dL vs. -2201 mg/dL, respectively). In parallel, the duration of its effect (140±33 minutes) was 75% longer than the duration of the effect of the PI-free formulation (80±37 minutes). Further calibrations of the rPI-supplemented ORMD-0801 formulation promise to enhance oral insulin bioavailability and its salutary effects, subsequently improving its clinical potential and value.

122-LB

WITHDRAWN

123-LB

Effect of a Controlled-Release Mitochondrial Protonophore (CRMP) on Healthspan and Lifespan in Mice

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Caloric restriction without malnutrition (CR) is the most robust and reproducible way to extend lifespan and delay the onset of age-related diseases,

such as hepatic steatosis, insulin resistance and type 2 diabetes (T2D). Unfortunately, the strict dietary regime necessary to achieve the beneficial effects of CR limits the use of this treatment to retard aging and disease in humans and new therapies are required. In this regard, our lab has recently developed a new class of therapeutic agents that are designed to safely promote liver-targeted mitochondrial uncoupling with a wide-therapeutic index. Our second-generation compound in this class is controlled-release mitochondrial protonophore (CRMP) that is functionally liver-targeted and promotes oxidation of hepatic triglycerides by promoting a subtle sustained increase in hepatic mitochondrial inefficiency. While we have previously demonstrated that this agent safely reverses hypertriglyceridemia, fatty liver, and hepatic inflammation/fibrosis in young-adult diet-induced rodent models of obesity, its effects on healthspan and lifespan remain to be determined. Here, we evaluated the impact of CRMP on hepatic steatosis and insulin action in aged 74-week-old male C57BL/6J mice fed a high-fat diet (HFD; 45% fat) for 12 weeks. Specifically, we demonstrate that CRMP treatment significantly reduced liver triglycerides, diacylglycerols, and transaminase levels independently of changes in body weight, whole-body energy expenditure or food intake. Additionally, long-term CRMP treatment reduced fasting plasma glucose concentrations ($P < 0.05$) and improved whole-body insulin responsiveness, as reflected by a marked increase in the glucose infusion rate required to maintain euglycemia during a hyperinsulinemic-euglycemic clamp. Taken together, these studies provide important proof-of-concept data to support the use of liver-targeted mitochondrial uncouplers to promote healthy aging.

Supported By: National Institutes of Health (F32DK114954)

124-LB

Lower Risk of CV Events and Death Associated with Initiation of SGLT2 vs. DPP-4 Inhibitors—Analysis from the CVD-REAL 2 Study

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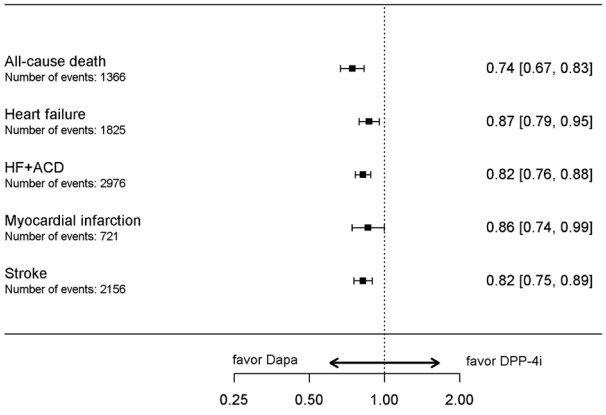
DPP-4 inhibitors and SGLT2 inhibitors are widely used in T2D. Clinical trials demonstrated lower risk of CV events with SGLT2i, and a neutral effect on CV events with DPP-4i. However, large comparative studies are lacking. We compared the risk of death, hospitalization for heart failure (HHF), MI and stroke in patients starting the SGLT2i dapagliflozin (DAPA) vs. any DPP-4i, using real world data from S. Korea, Japan, Israel, and Canada. Patients initiating DAPA or DPP-4i were identified via national registries, claims, and medical records. Propensity scores for SGLT2i initiation were developed in each country, with 1:1 matching. Hazard ratios were assessed by country and pooled using weighted meta-analysis, with an intent-to-treat approach. In total, 128,066 patients were included (mean age 55 years, 46% women, 25% with history of CVD). Post-match, baseline characteristics were balanced across matched groups. Initiation of DAPA vs. DPP-4i was associated with significantly lower risk of death, HHF, MI and stroke (Figure 1). In a large cohort of T2D patients seen in clinical practice across 4 countries, 75% without established CVD, initiation of DAPA was associated with lower risk of CV events (including stroke) and death compared with DPP-4i.

Figure 1. Pooled hazard ratios for the outcomes of all-cause death, hospitalization for heart failure, composite of all-cause death or hospitalization for heart failure, myocardial infarction, and stroke in patients initiated on dapagliflozin vs DPP-4i



Supported By: AstraZeneca

125-LB

Glucose Variables in T1D Studies with Dapagliflozin—Pooled Analysis of Continuous Glucose Monitoring Data from DEPICT-1 and 2

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Improved glycemic control and weight loss, without increased hypoglycemia, were demonstrated in two short-term, 24-week, Phase 3 studies of the SGLT2 inhibitor dapagliflozin (DAPA) as adjunct to adjustable insulin in patients with inadequately controlled T1D (DEPICT-1 and 2). In this post-hoc analysis we pooled continuous glucose monitoring (CGM) data at baseline and week 24 from both studies. In total, 1591 patients were included (DAPA 5 mg N=530; DAPA 10 mg N=529; placebo N=532). Baseline characteristics were comparable between the study groups. DAPA treatment significantly reduced mean interstitial glucose, mean amplitude of glucose excursions (MAGE), and postprandial glucose, while expanding the time in glycemic target range (>70 mg/dL to ≤180 mg/dL) (Table). In addition, DAPA treatment did not increase the percent of glucose readings ≤70 mg/dL or ≤54 mg/dL, or the percent of readings ≤70 mg/dL in the nocturnal period (00:00 to 05:59). These results demonstrate that DAPA as adjunct to insulin in patients with T1D reduced glycemic variability without increasing time in the hypoglycemia range.

Table. Pooled CGM Parameters.

CGM parameter	Treatment arm	Mean baseline value (SD)	Mean week 24 value (SD)	Adjusted mean change from baseline (SE)	Difference vs. placebo (95% CI)
Mean 24-hour glucose readings (mg/dL)	DAPA 5 mg	193.00 (28.78)	179.93 (32.41)	-8.40 (1.30)	–15.48 (–18.82, –12.13)
	DAPA 10 mg	191.00 (28.11)	174.87 (26.59)	–11.82 (1.32)	–18.90 (–22.25, – 15.54)
	Placebo	191.64 (29.04)	194.34 (32.62)	7.07 (1.33)	
MAGE (mg/dL)	DAPA 5 mg	170.53 (30.55)	154.67 (34.21)	–12.48 (1.37)	–13.36 (–16.89, –9.83)
	DAPA 10 mg	171.01 (31.59)	154.52 (34.52)	–13.06 (1.39)	–13.94 (–17.48, –10.40)
	Placebo	168.99 (31.46)	166.94 (31.62)	0.88 (1.40)	
Percent of 24-hour glucose values within >70 – ≤180 mg/dL (%)	DAPA 5 mg	43.38 (12.22)	51.69 (14.49)	6.48 (0.60)	9.07 (7.55, 10.59)
	DAPA 10 mg	43.98 (12.32)	53.89 (13.26)	8.08 (0.60)	10.67 (9.15, 12.20)
	Placebo	43.66 (12.64)	43.10 (13.97)	–2.59 (0.61)	
Percent of glucose readings ≤70 mg/dL over 24-hours (%)	DAPA 5 mg	4.96 (4.64)	4.85 (4.89)	–0.43 (0.21)	0.06 (–0.47, 0.59)
	DAPA 10 mg	5.30 (4.90)	5.10 (4.44)	–0.33 (0.21)	0.16 (–0.38, 0.69)
	Placebo	5.14 (5.56)	4.83 (4.72)	–0.49 (0.21)	
Percent of glucose readings ≤54 mg/dL (%)	DAPA 5 mg	2.22 (2.87)	2.02 (2.83)	–0.32 (0.13)	–0.14 (–0.47, 0.19)
	DAPA 10 mg	2.34 (3.13)	2.05 (2.63)	–0.34 (0.13)	–0.16 (–0.48, 0.17)
	Placebo	2.28 (3.82)	2.15 (3.15)	–0.19 (0.13)	
Postprandial glucose readings by CGM (mg/dL)	DAPA 5 mg	199.42 (40.51)	192.97 (43.90)	–0.85 (1.99)	–8.55 (–13.70, –3.41)
	DAPA 10 mg	196.61 (38.57)	186.93 (36.21)	–5.05 (2.02)	–12.76 (–17.93, –7.58)
	Placebo	197.35 (42.32)	199.68 (44.36)	7.70 (2.03)	
Percent of nocturnal (00:00–05:59) glucose values ≤70 mg/dL (%)	DAPA 5 mg	5.94 (7.64)	5.95 (8.26)	–0.38 (0.36)	–0.15 (–1.07, 0.78)
	DAPA 10 mg	5.52 (7.22)	6.00 (7.60)	–0.18 (0.37)	0.06 (–0.87, 0.99)
	Placebo	5.83 (7.74)	5.85 (7.64)	–0.24 (0.37)	

Supported By: AstraZeneca

126-LB

Simplici-T1—First Clinical Trial to Test Activation of Glucokinase as an Adjunctive Treatment for Type 1 Diabetes

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TTP399 is an oral liver selective Glucokinase Activator (GKA). Because it exhibits an insulin-independent mechanism of action, it may be suitable as an adjunctive treatment for type 1 diabetes (T1DM).

In clinical trials in type 2 diabetes (T2DM), TTP399 has shown significant reduction in postprandial glucose, increased percentage time in range and decreased percentage time in hypo or hyperglycemia. Moreover, TTP399 significantly reduced HbA1c without significant hypoglycemia, dyslipidemia, or ketoacidosis.

The Simplici-T1 trial (NCT03335371) is an adaptive three-part (sentinel, learning phase and confirming phase) Phase 1b/2 Proof of Concept study designed to explore the effect of TTP399 as adjunctive therapy for the treatment of T1DM. The aims of the study are to: 1.) evaluate the safety of TTP399

and 2.) evaluate whether TTP399 can replace or reduce mealtime insulin bolus and improve A1c in patients with T1DM.

The sentinel phase, an open label, dose escalation study in 5 adults with T1DM on insulin pump therapy and continuous glucose monitoring (CGM), showed that TTP399 was well tolerated. No incidents of severe hypoglycemia or diabetic ketoacidosis were observed. When compared to baseline, trends toward improved glycemic control while reducing insulin dose (Table) were observed with TTP399 treatment, supporting continuing to the randomized, placebo controlled phase of the study.

Table.

Parameter	Median Change from Baseline (% of BL)		
	400mg dose for 7days	800mg dose for 7days	1200mg dose for 7days
Time in Range (80-180mg/dL)	12	28	7
Time in Level 2 hypoglycemia (<54 mg/dL)	-79	-100	-90
Time in Hyperglycemia (>180 mg/dL)	-12	-1	5
Insulin (Bolus+correction)	-15	-33	-10
Basal Insulin	4	-4	-14

Supported By: JDRF

127-LB

Old but (Unfortunately) Not Forgotten—The Alarming Use of Outdated Sulfonylureas (InHypo-DM Study)

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While sulfonylureas (SUs) are known to induce hypoglycemia, their low cost and ease-of-use has made them a mainstay therapy for T2DM. Second-generation SUs (SGSUs), compared to first-generation SUs (FGSUs), have been successful at reducing these events. Pragmatic evidence substantiating this association remains limited; this study leverages data from the population-based InHypo-DM study to describe the real-world patterns of SU use and impact on hypoglycemia incidence in Canada. A validated questionnaire (InHypo-DMPQ) was administered online to a nationwide panel consisting of adults with SU-treated T2DM. Questions related to respondents' past hypoglycemia events, as well as socio-demographic and clinical traits. Negative binomial regression (NBR) was used to test the effect of SU type (FGSUs (chlorpropamide/tolbutamide) vs. SGSUs (glyburide/gliclazide/glimepiride)) on the annual rate of any hypoglycemia. A directed acyclic graph was constructed to identify the adjustment set. Of the 255 adults with SU-treated T2DM (56% male, mean age: 53.1 (SD: 14.4) years), 10.6% were on FGSUs (chlorpropamide: 7.5%, tolbutamide: 3.1%) and 89.5% on SGSUs (glyburide: 27.5%, gliclazide: 54.9%, glimepiride: 7.1%). Annualized crude event frequencies revealed that those on FGSUs, vs. SGSUs, were 1.57 times as likely to have ≥1 event; this group also experienced an average of 2.70 more events/person-year. Based on the NBR, FGSUs vs. SGSUs was associated with a 2.76 (95% CI: 1.07-7.11, p=0.035) factor increase in the rate of hypoglycemia, adjusting for drug coverage, T2DM duration, income, and clinician type. These results confirm that FGSUs induce a dangerous, real-world risk for hypoglycemia. It exposes a worrying trend for the continued use of outdated SUs for T2DM, despite the availability of safer alternatives in Canada. Our study serves as a pressing call-to-action to ensure that clinicians provide the safest and most effective therapeutic management for patients with T2DM.

Supported By: Sanofi Canada

128-LB

Effects of Ileo-Colonic Delivery of Conjugated Bile Acids on Glucose Metabolism, GLP-1, and Body Weight in Patients with Obesity and Type 2 Diabetes Mellitus—A Randomized Controlled Trial

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Bile acid secretion increases significantly after Roux-in-Y gastric bypass and may play a role in weight loss after bariatric surgery. The acute intrajejunal-delivery or intra-rectal delivery of bile acids improves glucose metabolism. We aimed to study the effect of conjugated bile acids released on the ileo-colonic region (IC-CBAS) on glucose metabolism and body weight. In a placebo-controlled, double-blinded, randomized, 28-days trial, we studied the effect of IC-CBAS 500 mg BID on glucose metabolism, incretin hormones (GLP-1 and FGF-19), gastric emptying (scintigraphy) and weight loss in obese type 2 diabetic subjects (n=24 white patients, age=57±2 years, BMI=38.6±1.3 kg/m^2, HbA1c=8.5±0.2%, fasting glucose 9.9±0.4 mmol/L). Participants were taking stable doses of DPP-4 inhibitors and metformin and were instructed to continue their current diet and exercise routine. Subjects underwent a meal challenge at baseline and at the end of the treatment period. The primary analyses compared treatment groups at the end of 28 days' treatment using analysis of covariance models incorporating the corresponding baseline study value as a covariate. IC-CBAS significantly increases postprandial GLP-1 (mean p=0.04, AAB p=0.04), postprandial insulin (AAB p=0.04) and postprandial c-peptide (AAB p=0.01); and decreases fasting insulin (p=0.04) when compared to placebo. IC-CBAS also induced a numerically (but not statistically significantly) improvement in fasting glucose (delta -16 mg/dl), postprandial glucose (delta mean -14 mg/dl) and weight (delta -0.45±.4 kg) compared to placebo. There were no reported side effects, or dropouts; and no difference in FGF-19, gastric emptying or number of bowel movements. IC-CBAS 28-day treatment results in significant increase in GLP-1 and postprandial insulin, suggesting a beneficial role in incretins, insulin and glucose homeostasis.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—PHARMACOLOGIC TREATMENT OF COMPLICATIONS

129-LB

Optimization of Blood Pressure Control, Metabolic Parameters, and Target Organs Protection with Perindopril + Indapamide Fixed Combination in Hypertensive Patients with Obesity and Prediabetes

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The study objective was to evaluate the ability of the Fixed Combination (FC) of Perindopril + Indapamide (P+I) to reduce insulin resistance and low intensive noninfectious inflammation as well as to improve arterial elasticity in patients with hypertension, obesity and prediabetes on previous successful antihypertensive therapy with losartan + Hydrochlorothiazide (L+HTZ) 100/12.5 mg. A 12-week open-label study included 50 patients (age 54.8 ± 6.6 years, Body Mass Index (BMI) 32.5 ± 3.2 kg/m2). All patients underwent a 24-hour ambulatory blood pressure monitoring, applanation tonometry (assessment of Augmentation Index (AI), Central Blood Pressure (CBP)), Pulse Wave Velocity (PWV) measurement and laboratory investigations (lipid profile, fasting glucose, the Homeostatic Model Assessment (HOMA) index, homocysteine, leptin, adiponectin, high-sensitive C-Reactive Protein (hsCRP)).

Results: The switch of patients from L+HTZ to a FC of P+I resulted in an additional decrease in systolic BP and diastolic BP by 3.9% and 5.4%, respectively (p <0.05). Significant decrease in the BP load and variability was observed. PWV, AI, central SBP, vascular age decreased by 2.2%, 9.4%, 2.1% and 6.0% (p <0.05 for all). Fasting glycemia, insulinemia, and HOMA index decreased by 4.9%, 6.0% and 10.3% (p <0.05 for all). Triglycerides (TG) decreased by 13.5% (p<0.05) and high density lipoproteins (HDL) increased by 9.6% (p <0.05). Leptin and hsCRP levels decreased by 14.4% and 11.0%, adiponectin increased by 9.9% (p <0.05 for all). Clinically significant results were obtained in weight and BMI reduction on 6,0% and 1,2%.

Conclusions: FC of P+I is superior to the L+HTZ in BP control, improvement of arterial elasticity and promotes a decrease in BMI, suppression of insulin-resistance and low intensive noninfectious inflammation in patients with hypertension, associated obesity and prediabetes.

130-LB

Impact of SGLT2 Inhibitors (SGLT2i) on Cardiovascular (CV) Risk and Estimated Glomerular Filtration Rate (eGFR) in the EXSCEL Placebo Group

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SGLT2i, empagliflozin and canagliflozin, have been shown to reduce the incidence of major adverse CV events (MACE), all-cause mortality (ACM) and renal events in CV outcomes trials (CVOTs), with robust real-world evidence (RWE) suggesting class effect benefits. In the exenatide CVOT EXSCEL, ~10% of patients took an SGLT2i with ~5% use of dapagliflozin (DAPA). Effects of all SGLT2i, and DAPA alone, on MACE, ACM, and eGFR were analyzed in EXSCEL participants randomized to placebo.

Propensity-matched cohorts (including by study visit) of SGLT2i users and non-users (n=709 per group) were generated, based on their last measured characteristics before SGLT2i initiation. Subsequent time-to-first adjudicated MACE and ACM were compared using a Cox regression. Decline in

eGFR over time (slope) was quantified in the matched cohorts using a mixed model repeated measurement (MMRM) analysis.

SGLT2i overall, and DAPA alone, numerically decreased the MACE hazard ratio, and SGLT2i significantly reduced the ACM risk (Table). The eGFR slope was improved significantly for SGLT2i overall and DAPA alone (Table).

This post-hoc EXSCEL analysis supports a beneficial class effect for SGLT2i on MACE, ACM, and renal function, consistent with published CVOTs, Real-World data, and for DAPA alone. DECLARE, the ongoing DAPA CVOT, will complete in 2018.

Table.

Time-to-First Adjudicated Event	Propensity-matched cohort	n	Events	Subject-years of follow-up	Crude rate (events/100 subject-years)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
MACE[a]	No SGLT2i	709	44	990	4.45		
	SGLT2i	709	28	822	3.41	0.78 (0.48–1.27)	0.79 (0.49–1.28)
	No DAPA	354	22	484	4.54		
	DAPA	354	11	408	2.69	0.59 (0.28–1.24)	0.55 (0.26–1.15)
All-cause mortality	No SGLT2i	709	37	1108	3.34		
	SGLT2i	709	14	871	1.61	0.48 (0.26–0.89)	0.50 (0.27–0.95)
	No DAPA	354	13	538	2.42		
	DAPA	354	7	432	1.62	0.66 (0.25–1.69)	0.66 (0.25–1.72)

MMRM analysis	Propensity matched cohort	eGFR slope (standard error)	Treatment effect (95% CI)	p-value
eGFR slope (mL/min/1.73m^2/year)	No SGLT2i	–0.91 (0.26)		
	SGLT2i	+0.87 (0.37)	+1.78 (0.87–2.69)	0.00013
	No DAPA	–1.04 (0.37)		
	DAPA	+1.24 (0.54)	+2.28 (1.01–3.54)	0.0004

[a]MACE: a composite endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke.

131-LB

Diabetogenic Potential of Dexamethasone and Effect of Annona Muricata Methanolic Bark Extract as Post-exposure Therapy in Albino Rats

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Background: Diabetes mellitus has been identified as the leading cause of death from non-infectious diseases. The use of dexamethasone is on the increase due to wide array of its therapeutic effects. Therefore, the potential of dexamethasone to induce DM and ability of Annona muricata methanolic bark extract (AMMBE) to treat DM were studied.

Methods: The research was carried in Federal College of Animal Health and Production Technology, Ibadan and lasted for twenty eight (28) days. Rats were allotted into four groups. Group B, C and D were induced with Dexamethasone (2mgkg^{-1}) daily for 7 days i.p, while A was positive control group. B was induced without AMMBE administered, C was induced and treated with AMMBE at 400mgkg^{-1} and D induced and treated with glibenclamide (2.5mgkg^{-1}b/w) for 14 days. Liver, kidney and pancreas were collected for histopathology.

Results: Dexamethasone induced diabetes after 7 days. Average blood sugar in induced groups (B, C and D) were 132.0±4.05^a,129.0±1.41^{a}and130.0±2.93^a respectively. After administration of AMMBE, average blood sugar for C and D were 91.0±1.72^b and 87.0±2.97^c respectively. Clinical signs of alopecia, dehydration, paw-licking etc was seen. Massive loss of pancreatic cell mass after induction was seen. Liver lesions ranges from no visible lesion, accentuation and marked vacuolar degeneration of hepatocytes in periportal areas. Kidney degeneration and multifocal coagulation necrosis of tubular epithelium were observed. Blood sugar post exposure to AMMBE and Glibenclamide were drastically reduced.

Conclusions: It could be concluded that prolonged use of dexamethasone has potential of inducing diabetes and AMMBE has antidiabetic effect which could be fully explored.

132-LB

Probabilistic Prognosis of Different Treatment for the Diabetic Kidney Disease Course in Overweight and Obese T2DM Patients with Microalbuminuria

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Introduction: Diabetic kidney disease (DKD) is one of the most enabling microvascular complications. Comparison of different treatment is problematic, as there are no clinical trials comparing different managements and patients' characteristics vary between the studies.

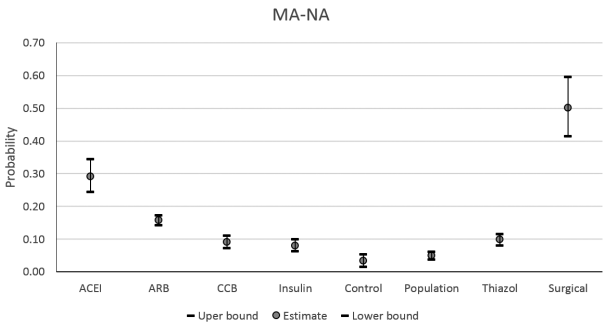
Aim: To create probabilistic model, which allows predict DKD course according to the different treatment.

Methods: A systematic literature review was performed, which allowed to estimate transition probabilities between the states of DKD - normoalbuminuria (NA), microalbuminuria (MA), diabetic nephropathy (NP), end stage renal disease. Due to the high complexity of dependence between transition rates and probabilities, Markov Chain Monte Carlo scheme was applied.

Results: Of 1,812 articles identified after initial search, 95 publications had relevant data to estimate transition probabilities between DKD states. The lowest transition probabilities from MA to NP and the highest probability of remission from MA to NA was found in surgery group, followed by ACEI and ARB medications group (Fig. 1).

Conclusions: According to the model data bariatric surgery presents the highest probability of regression to NA state and the lowest probability of progression to NP state among the overweight and obese patients with type 2 diabetes mellitus and MA.

Fig.1 Transition probabilities from MA to NA between different treatment modalities



Supported By: Lithuanian University of Health Sciences; Kaunas University of Technology

HEALTH CARE DELIVERY—ECONOMICS/QUALITY IMPROVEMENT

133-LB

Hypertension-Associated Medical Expenditures by Diabetes Status among Adult Female Medicaid Enrollees in Alabama

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Little information is available on how diabetes status affects medical expenditures associated with hypertension among Medicaid enrollees. In 2013, Alabama had the highest proportion of Medicaid enrollees who were women and the highest hypertension prevalence in the U.S. We estimated hypertension-associated medical expenditures among adult female Medicaid enrollees by diabetes status in Alabama. We used data for 15,885 female Medicaid enrollees aged 19-64 years from the 2012 Medicaid Analytic extract files. We identified persons with hypertension and diabetes using ICD-9 codes. We used General Linear Models to estimate per person total annual medical expenditures associated with hypertension by diabetes status and hypertension-related conditions including myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, renal disease, and stroke. Overall hypertension prevalence was 20.8%, with 60.0% and 17.5% among those with and without diabetes, respectively. Annual medical expenditure per enrollee with hypertension was $7,722. After controlling for age, race, and Charlson comorbidity index, hypertension-associated excess annual medical expenditures were $2,540 and $2,926 for persons with and without diabetes (all p<0.01). For persons without hypertension-related conditions, the excess expenditures were $1,931 and $2,533 for those with and without diabetes (all p<0.01). For persons with at least one hypertension-related condition, these excess expen-

ditures increased to $4,217 and $3,264, respectively (all p<0.01). Having hypertension increased medical expenditures greatly regardless of diabetes status. Having a hypertension-related condition further increased hypertension-associated medical expenditures among enrollees, especially in those with diabetes. These results can inform the development and evaluation of strategies to improve management of hypertension by diabetes status.

134-LB

Effectiveness and Applicability of Self-Management Peer Coaching in the Continuity of Diabetes Care

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The goal of this 2-year research project was to investigate the feasibility and effectiveness of telephone peer coaching for persons with type 2 diabetes. It involved a partnership between a university and 11 diabetes centers. One hundred nine persons with type 2 diabetes or who were familiar with type 2 diabetes (e.g., family members) were trained as coaches and learned how to use self-management behavioral change strategies and to navigate the healthcare system. Diabetes educators recruited 115 adults with type 2 diabetes who were experiencing difficulty managing.

Coaches and subjects were paired, and over a 6-month period, coaches telephoned subjects once each week and engaged in a 30 minute conversation focusing on managing their condition, their medications and on their family and work life. Both coaches and subjects completed questionnaires at baseline, and at 6 and 12 months. A one-way repeated-measures analysis of variance was used to investigate change with 14 measures. To investigate the peer coaching process, a grounded theory qualitative analysis was conducted to obtain information on the coaching process.

The analysis showed statistically significant improvements between baseline and 12 months, namely: A1c (-9%), patient activation (+15%), depression (-24%), self-efficacy (+23%), communication with health care professionals (+23%), and diabetes empowerment (+10%). Further analysis found that these results were not influenced by covariates of age, gender, number of chronic health conditions and education level. The main themes found in the qualitative study which contributed to participant improvements were: learning self-management skills, personal accountability, encouragement, finding resources, and the boundary between the coach and participant.

This pilot "pragmatic" study demonstrated that peer coaches are acceptable to clinicians and clients and have an important role in the continuity of care for persons experiencing diabetes.

Supported By: Lawson Foundation

135-LB

Development of a National Minimal Set of Patient-Important Outcome Domains for Value-Based Diabetes Care in Denmark

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Aim: To identify a minimal set of patient-reported (PRO) domains for use in value-based diabetes care in Denmark.

Methodology: A structured mixed-methods research protocol was applied to ensure an evidence-based approach to involvement of people with diabetes in the identification of patient-centered outcome domains. 20 people with diabetes and 4 caregivers of people with diabetes selected for representativeness in age, gender, type of therapy, duration of diabetes, type of diabetes, and disease burden were recruited for qualitative research and co-creation to examine 1.) psychological, physical and social impacts of diabetes and desired outcomes of treatment, 2.) dis-utilities of therapy and 3.) factors enabling sustainability in line with the value based care model. Qualitative research based on interviews, structured focus group and co-creation workshop sessions together with desk research on patient, clinical, health economic, and societal relevance of identified domains informed the final identification of domains by a multi-disciplinary and multi-sector working group using strict criteria of patient importance, clinical relevance and applicability, measurability and mutability.

Results: The following PRO domains were selected to complement the clinical outcome domains: Self-reported health, psychological well-being, symptom burden (e.g., sleep, sexual dysfunction, complications), multi-faceted impact of diabetes on life including diabetes distress, treatment burden and impacts of hypoglycemia, and specific indicators of care confidence, quality and diabetes self-care ability.

Conclusions: The assessment of patient-important outcomes for value based diabetes care in Denmark require the implementation of PRO questionnaires in standard diabetes care.

Supported By: Danish Regions; North Denmark Region

136-LB

Cost-Effectiveness of Once-Weekly Semaglutide 1.0 mg vs. Dulaglutide 1.5 mg as Add-On to Metformin in the Treatment of Type 2 Diabetes in Canada

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Semaglutide is a novel GLP-1R agonist with prolonged half-life due to enhanced binding to albumin and inhibition of degradation by dipeptidyl peptidase-4. SUSTAIN 7, an open-label, parallel-group, phase 3b trial of 1,201 individuals with type 2 diabetes inadequately controlled on metformin monotherapy compared semaglutide to dulaglutide over 40 weeks. Semaglutide 1.0 mg demonstrated statistical superiority to dulaglutide 1.5 mg in HbA1c lowering (-1.8% vs. -1.4% [ETD -0.41%; 95% CI -0.57 to -0.25]) and reductions in body weight (-6.5 kg vs. -3.0 kg [ETD -3.55 kg; -4.32 to -2.78]).

We used a validated non-product specific cost-effectiveness cohort model (the IHE Cohort Model of Type 2 Diabetes) to extrapolate outcomes and costs associated with semaglutide 1.0 mg vs. dulaglutide 1.5 mg over a 40-year time horizon. Treatment effects (e.g., HbA1c, BMI, and systolic blood pressure) as well as cohort characteristics were sourced from SUSTAIN 7. Treatment with semaglutide 1.0 mg and dulaglutide 1.5 mg were assumed to continue for three years, after which the cohort discontinued the initial treatments, and started insulin therapy. Costs and health-related quality of life impact associated with developing macro- and microvascular complications were sourced from a Canadian perspective where possible.

In the base case, semaglutide 1.0 mg was associated with fewer micro- and macrovascular complications (driven by observed differences in risk factors). For example, for every 1,000 individuals, four fewer patients in the semaglutide 1.0 mg arm were simulated to experience a stroke. Fewer events led to an increase in quality-adjusted life years of 0.05 at lower total costs for patients in the semaglutide 1.0 mg arm compared to the dulaglutide 1.5 mg arm. Results were tested in sensitivity analyses and found to be robust, suggesting that semaglutide 1.0 mg provides better health outcomes at a lower cost, compared to dulaglutide 1.5 mg.

Supported By: Novo Nordisk A/S

137-LB

Comparison of E-Consults and Face-to-Face Care on Costs and Glycemic Control among Veterans with Type 2 Diabetes Mellitus

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Electronic Consults (EC) offer enhanced access to endocrinologists for patients with type 2 diabetes mellitus (T2DM). The effects of EC on costs of care and glycemic control compared to Face-to-Face (F2F) visits are unknown. A retrospective chart review was conducted for Veterans who received EC (n=440) or F2F (n=397) care for T2DM through the VA Pittsburgh Healthcare System (VAPHS) from 2010 to 2015. Data on demographics, rurality, days to consult completion, and percent (%) A1C at baseline and post-consult at 3-6, and 12 months were collected. A web-based tool calculated the average round-trip distance in miles and travel time in hours from patient's residential zip code to VAPHS. Annual travel costs for recommended 3 visits per year were estimated at a reimbursement rate of $0.415 per mile. Continuous measures (mean ± standard deviation) were compared using Wilcoxon rank-sum tests. Categorical measures (sex, rurality) were presented as percentages and compared between groups by time point using chi-square tests. Veterans who received EC were predominantly male (98.4%), younger (64.2±8.5 years) and rural (15.8%) than those who received F2F care (95.3% male, p=0.01; 68.1±8.7 years, p<0.0001; 3.7% rural, p<0.0001). The EC cohort had shorter consult completion time than the F2F cohort (EC: 10±10 days, F2F: 37±33; p<0.0001). Mean annual travel-related savings per Veteran in the EC cohort were 431±297 miles, 9.4±7 hours, and $179±123. Mean annual travel burden per Veteran in the F2F cohort were 159±171 miles, 3.5±4 hours and $66±71. EC and F2F cohorts had similar baseline A1C values (10%±1.6). Both cohorts had decline in baseline percent A1C to 3- 6 months (EC: 8.98%±1.54, F2F: 8.75%±1.77, p=0.03) and from baseline percent A1C to 12 months (EC: 8.80%±1.61, F2F: 8.57%±1.72, p=0.002). Electronic consults deliver effective and expedient care by saving money and travel time, and offer long-term, sustainable glycemic control comparable to F2F care for patients in remote areas with T2DM.

138-LB

Nasal Glucagon Budget-Impact Model Shows Reduced Health Care Payer Costs for Severe Hypoglycemia Due to Emergency Services Costs Savings

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Background: Nasal glucagon [NG] is a compact, portable, ready-to-use nasal spray for the treatment of severe hypoglycemic events [SHE] via intranasal absorption. Current treatment with intramuscular glucagon [IMG] requires multiple steps to administer, including reconstitution, and is difficult to administer for caregivers or passersby. Due to its mode of administration, NG has been demonstrated to result more often in successful (full-dose) administration of glucagon than IMG. The advantage of NG is expected to reduce payer costs due to less use of emergency services, including more treat and release, fewer ambulance trips and fewer emergency department visits.

Objective: Model 2-year budget impact of different scenarios of current (IMG, no kit) vs. future intervention mix (NG, IMG, no kit).

Methods: Populations defined by diabetes type, age and treatment were assessed using population-specific SHE incidence and mortality data. Budget impact was calculated from the U.S. Medicare perspective, with cost data sourced from literature and fee schedules. For adults with type 1 diabetes, an incidence of 366 SHEs per 1,000 person-years and a kit ownership proportion of 60% were assumed. Of patients with kits, 20% and 30% were assumed to own NG kits in the first and second year, respectively. Both NG and IMG kits were modeled using current glucagon list price. All model inputs were varied in sensitivity analyses.

Results: Reduced spending on SHE with the new mix was observed in all modeled populations with higher cost-savings in populations at higher risk of SHE. For 10,000 adults with type 1 diabetes, Medicare pays USD 11.7 million with the current mix and would pay USD 10.6 million for the new mix over 2 years. Savings with NG resulted from reductions in emergency services due to a higher probability of successful SHE treatment by caregivers or passersby.

Conclusions: NG as a treatment option for SHE is associated with substantial cost savings for U.S. payers.

139-LB

Improvements in Patient Care by an Integrated Personalized Diabetes Management (iPDM) Approach May Be Driven by the Structured Process and How Physicians Use Data Sources

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Aim: The PDM-ProValue study program showed the benefit of iPDM for people with type 2 diabetes mellitus (T2D) on insulin therapy. Here, we analyze which treatment process conditions may be key for this success.

Methods: The study program was conducted over 12 months in a prospective, controlled, cluster-randomized setting. 101 medical practices were randomized to the iPDM arm (n=53) or the control (CNL) arm (n=48). In addition to medical and patient related outcomes, parameters of process quality and data sources for therapy decisions were monitored e.g., by means of Likert-scaled requests.

Results: After 12 months, HbA1c reduction vs. baseline was higher for patients in iPDM (0.5%, p<0.0001) compared to those in CNL (0.3%, p<0.0001; between-group difference=0.2%, p<0.05). The degree of using both patient reports and SMBG data to assess glycemic status increased: after 12 months, 94% of physicians in the iPDM group stated to use a combination of data sources vs. 75% in CNL (Baseline: 56% iPDM, 59% CNL). Similarly, doctors' appreciation of the combined information of SMBG and HbA1c (iPDM group only) increased in the course of the study. (Baseline: 43%, 12 months: 61%). After 12 months, 82% of physicians rated the usefulness of all information sources high or very high in the iPDM group compared to 49% in CNL (baseline: 28% vs. 28%). Physicians rated the iPDM process as more structured and better adaptable to the individual situation of the patient compared to before iPDM implementation.

Discussion: A more holistic and beneficial use of data sources by implementing iPDM may be key for the improvements observed in this difficult to treat patient group. A more structured treatment process applied by the physicians and better personalization of therapy seem to enhance physician-patient interaction. Physicians' positive perception of iPDM may facilitate more focused treatment decisions, thereby overcoming clinical inertia.

140-LB

Racial Disparities in Cost of Diabetes for U.S. Medicare Beneficiaries

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Diabetes disproportionately impacts U.S. minority populations, with Hispanics almost twice as likely as non-Hispanic whites (nHW) to be diagnosed. We analyzed data from the Medicare 5% sample file by race/ethnicity for both type 1 (T1D) and type 2 diabetes (T2D). We identified 1,397,933 enrollees in fee-for-service without Medicare Advantage coverage during 2012-13.

Although nHW accounted for the majority of this population (81.3%), the prevalence of T1D and T2D was higher for Hispanics than nHW (3.4% vs. 1.8%, p=.0006 for T1D and 33.4% vs. 21.9%, p<.0001 for T2D). Hispanics also had more acute hospital admissions (p=.0235 for T1D and p=.0009 for T2D) and longer length of stay (7.5 vs. 6.9 days for T1D, p=.0105 and 6.7 vs. 6.2 for T2D, p<.0001). Allowed and paid costs per member per month adjusted for confounding were higher for nHW compared to Hispanics with T1D (both p<.0001), and higher for Hispanics compared to nHW for T2D (both p<.0001).

The burden of chronic disease was significantly higher in Hispanics than nHW (both T1D and T2D, p<.0001). Hispanics with T1D were also more likely to have A1c and lipid tests (p=.0014 and p=.0011 respectively), although retinopathy and nephropathy screening rates were similar. For T2D, Hispanics were more likely to have A1c and lipid testing as well as retinopathy and nephropathy screening (all p<.0001).

This highlights important racial disparities in the burden and cost of diabetes for Medicare recipients in the U.S.

Table. Adjusted Costs Per Member Per Month by Race and Type of Diabetes.

Race/Diabetes Type	Allowed	Paid
Nondiabetes Hispanic	$626	$548
Nondiabetes nHW	$572	$490
Hispanic T1D	$2214	$1933
nHW T1D	$2320*	$2010*
Hispanic T2D	$1320	$1158
nHW T2D	$1300**	$1127**

*p<.0001 vs. Hispanics with T1D, ** p<.0001 vs. Hispanics with T2D.

141-LB

Storage Conditions of Insulin in Domestic Refrigerators and Carried by Patients—Insulin Is Often Stored Outside Recommended Temperature Range

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Objective: Not much is known about how patients with diabetes store their insulin in daily life. Objective of our study was to monitor temperature of refrigerated and carried insulin in industrialized countries to investigate how often storage conditions do not meet the manufacturers' recommendations.

Method: Patients (n=338; 46% in the U.S., 41% in the EU) put a total number of 400 temperature loggers (MedAngel ONE, NL) next to their insulin into their refrigerator or diabetes bag. Temperature was measured every 3 minutes (up to 480 times/day). Measurements were sent to an app and stored in a protected online database. Whenever temperature exceeded the recommended range (2-8°C for refrigerated insulin, 2-30°C when opened/carried), the user was notified by an alarm. Data was collected from November 2016 to February 2018 with an average protocol length of 49 days.

Results: Temperature logs from individual sensors were analyzed (230 for refrigerated, 170 for carried insulin). Deviations were found in 315 (78.8%) logs (230 (100%) refrigerated, 85 (50%) carried). For refrigerated insulin, temperature recorded by an average sensor was out of the 2-8°C range 11.31% of the time (10.10%-13.10%; 2 hours 43 minutes/day) with an average deviation of 3.68K (SD 5.02K). For carried insulin, temperatures were out of 2-30°C range 0.54% of the time (0.48%-0.64%; 8 minutes/day) with an average deviation of 1.11K (SD 1.24K). 17% of sensors measured temperatures <0°C (57 refrigerated, 9 carried).

Conclusion: Long-term storage conditions of insulin are known to have an impact on its blood-glucose lowering effect. These observational data showed that in a significant number of cases insulin was exposed to temperatures outside the recommended range, especially when refrigerated. Thus, domestic refrigerators may pose an underestimated risk for insulin quality. The extent of how temperature deviations in storage affect insulin efficacy and patient outcomes needs further systematic investigation.

142-LB

Budget Impact Analysis of Self-Monitoring of Blood Glucose vs. Flash-Continuous Glucose Monitoring in Intensive Insulin Users with Diabetes Type 2 Covered by Medicare and Medicaid

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Introduction: Self-Monitoring of Blood Glucose (SMBG) uses capillary blood glucose to measure glycemia in diabetic patients. Recently FDA-approved Flash Continuous Glucose Monitoring (F-CGM) reveals glucose levels when scanned by the reading device. The Centers for Medicare and Medicaid Services (CMS) have announced to reimburse F-CGM at the same level as CGM devices.

Aim: This analysis' objective was to quantify the CMS budget impact (BI) of F-CGM reimbursement in patients with type 2 diabetes (T2DM) on intensified insulin therapy (IIT), and compare it to the BI of conventional SMBG via cost-related break-even metrics. These were chosen because - in the absence of RCT-based, primary endpoint-driven clinical superiority evidence of F-CGM over SMBG for this population (REPLACE study) - they are well-suited to inform budget allocation decisions.

Methods: An economic model was developed in Excel. CMS reimbursement/patient co-insurance levels for SMBG and F-CGM were used; data on morbidity, treatment and usage patterns were sourced from the literature and official websites. Different scenarios were simulated to elicit break-even points between F-CGM and SMBG.

Results: The annual cost of SMBG with 3.7 tests per day (see REPLACE) is $180 per patient, compared to $2,156 incurred per F-CGM patient, representing a cost difference of $1,976/year or $5.41/day. This implies a budget break-even ratio of 1:12 patients (F-CGM:SMBG). Both technologies would break even at a consumption of 44 test strips per day. A year's SMBG budget would last only 30 days if spent on F-CGM.

Conclusion: With diabetes budgets under pressure, thoughtful spending policies are needed. It is recommended to analyze in detail which T2DM subgroups will benefit most from F-CGM, focusing reimbursement to the latter. SMBG, being an established technology, represents - at current reimbursement levels - an attractive spending option to budget holders.

143-LB

Glycemic Control in Patients with Diabetes across Primary and Tertiary Government Health Sectors in the Emirate of Dubai, United Arab Emirates—A Five-Year Pattern

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Background: In the United Arab Emirates (UAE) the comparative prevalence of diabetes is reported as 18.98%, but there are very few studies evaluating glycemic control.

Aims: Our primary aim was to assess the level of glycemic control across Dubai Health Authority (DHA) points of care over the past five years (2012-2016).

Methods: This audit is a retrospective analysis of the electronic medical records of all patients who attended the Dubai Health authority between 2012-2016.

Results and Discussion: A total of 26447 patients were included in the study making it the largest cohort of patients to be evaluated for diabetes control in the UAE. Out of those patients, UAE nationals were 73.8% (n=19508), while the other nationalities accounted for 26.2% (n=6939). The overall mean HbA1c from 2012 to 2016 was 7.76%. Patients attending primary care clinics had a mean HbA1c of 7.64%, compared to 7.68% for the tertiary care cohort. Out of the total population, 37.7% of them achieved HbA1c <7%, while the majority (42.0%) had HbA1c of 7-9%, and only 20.3% of the total patient had an HbA1c >9%. Upon comparing primary vs. tertiary patients who had HbA1c <7, there were 40.79% and 34.87%, respectively. Moreover, the total percentage of patients with HbA1c <9% were 80.53% and 79.24% in primary and tertiary setup, respectively.

Table (1): Mean of hbA1c and percentage of patients with HbA1c control <7%, 7-9%, and >9% representing controlled, uncontrolled and very uncontrolled categories. The difference in HbA1c between nationalities and across the years of the audit.

Category (Mean HbA1c)	A1c-2016	A1c-2015	A1c-2014	A1c-2013	A1c-2012	
Mean Total	7.653	7.803	7.723	7.769	7.899	
Mean primary	7.639	7.780	7.714	7.609	7.775	
Mean tertiary	7.671	7.831	7.732	7.968	8.093	
P Value	0.37	0.17	0.66	0.00	0.00	
Category (Percentages of HbA1c over years)	A1c-2016	A1c-2015	A1c-2014	A1c-2013	A1c-2012	P for trend
Percentage <7%	39.2%	35.9%	40%	38%	35.2%	0.000
Percentage 7-9%	42.9%	44%	40.3%	41.2%	41.5%	0.000
Percentage >9%	17.9%	20.1%	19.8%	20.8%	23.4%	0.000
Category (HbA1c based grouping)	Mean HbcA1c	<7%	7-9%	>9%		
Total	7.76	37.7%	42.0%	20.3%		
Tertiary	7.68	34.87%	44.37%	20.75%		
Primary	7.64	40.79%	39.74%	19.50%		
Nationality	Mean HbA1c	<7%	7-9%	>9%		
UAE	7.84	25.9%	57.20%	16.82%		
Non-UAE	7.65	27.00%	59.34%	13.50%		
P value	P<0.01			P=0.00		
Type of DM		<7%	7-9%	>9%		
T1DM		16.0%	45.3%	38.7%		
T2DM		40.7%	41.4%	17.9%		
P value		0.00	0.01	0.00		

144-LB

Software Price Modeling of Semaglutide

BRADLEY EILERMAN, LEONARD J. TESTA, *Covington, KY, Celebration, FL*

GlucosePATH is a clinically validated decision support system which creates drug regimens for patients with type 2 diabetes. Regimens are optimized for HbA1c, weight, side effect and benefit impact, adherence and cost using a composite score from 0 to 100. Used on a population level, GlucosePATH can model drug distribution for sets of clinical values, showing drug prescription frequency to that population. As new agents such as semaglutide become available, projected distribution of these options can be described at various prices. Among other things, this shows the maximum and optimal price for a new agent, given the cost and performance of existing agents.

A data set of 191 patients with HbA1c >7 was drawn from a distribution of patients cared for by PCPs in a large health system. Total monthly cost of care was computed based on the mean retail cost drawn from the GoodRX API. Using scores drawn from GlucosePATH, drugs were redistributed to find the lowest total cost at which the population's score was >70 out of 100. Total retail cost of care averaged $475.03 per month per patient for the 191 patients. Redistributed medication at this price generated a mean composite score of 71.5 at a projected mean HbA1c of 6.9.

Two price points were established for semaglutide. The "maximal price" (MP) is the highest price at which use of the agent in the population does not exceed the control group's retail cost of care and the composite score threshold is met. (That is, introducing the new agent does not increase cost or worsen results for the population.) The "maximal revenue" (MR) is the price at which the agent's manufacturer maximizes their gross revenue for the agent in the population.

Price optimization for semaglutide showed a MP between $800 and $825 (retail price: $808). At its MP, semaglutide would be prescribed to approximately 17% of the population with mean composite score of 76.1 and mean HbA1c of 6.9. At semaglutide's MR of $450 per month, it would be prescribed to approximately 49% of the population and generate a mean composite score of 77.8 with a mean HbA1c of 6.9.

145-LB

Software Price Modeling of Ertugliflozin

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GlucosePATH is a clinically validated decision support system which creates drug regimens for patients with type 2 diabetes. Regimens are optimized for HbA1c, weight, side effect and benefit impact, adherence and cost using a composite score from 0 to 100. Used on a population level, GlucosePATH can model drug distribution for sets of clinical values, showing drug prescription frequency to that population. As new agents such as semaglutide become available, projected distribution of these options can be described at various prices. Among other things, this shows the maximum and optimal price for a new agent, given the cost and performance of existing agents.

A data set of 191 patients with HbA1c >7 was drawn from a distribution of patients cared for by PCPs in a large health system. Total monthly cost of care was computed based on the mean retail cost from the GoodRX API. Using scores drawn from GlucosePATH, drugs were redistributed to find the lowest total cost at which the population's score was >70 of 100. Total retail cost of care averaged $475 per month per patient for the 191 patients. Redistributed medication at this price generated a mean composite score of 71.5 at a projected mean HbA1c of 6.9.

Two price points were established for ertugliflozin. The "maximal price" (MP) is the highest price at which use of the agent in the population does

not exceed the control group's retail cost of care and the composite score threshold is met. (That is, introducing the new agent does not increase cost or worsen results for the population.) The "maximal revenue" (MR) is the price at which the manufacturer maximizes their gross revenue for the agent in the population.

Price optimization for ertugliflozin showed a MP of approximately $300 (retail price: $270). At its MP, ertugliflozin would be prescribed to approximately 10% of the population with mean composite score of 76.8 and mean HbA1c 6.9. At ertugliflozin's MR of approximately $175 per month, it would be prescribed to approximately 39% of the population and generate a mean composite score of 77.6 with a mean HbA1c of 6.9.

146-LB

Sweet Transitions—Improving Outcomes for Hospitalized Patients with Diabetes

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Effective diabetes care after hospitalization is commonly limited by poor care coordination. Key information from hospitalization is often not communicated to outpatient clinicians as diabetes is rarely the reason for admission. Published interventions to address this problem are limited or lack sustainable benefit. We studied the effectiveness of Sweet Transitions (ST), a program providing and coordinating diabetes care after hospitalization. Sweet Transitions enrolled patients at a 750-bed hospital with poorly controlled diabetes (A1C ≥ 9%) for visits and phone communication with a nurse practitioner and diabetes educator. The ST dyad provided education, identified barriers, adjusted medication, and coordinated care within the organization and community. An individualized plan was transferred to the clinician responsible for diabetes care. Readmissions for ST patients were compared to matched controls, and A1C was assessed before and after ST intervention. For a median of 43 days, 197 patients participated in the program (64% male, age 52 ± 0.9). In 160 patients with repeat A1C at 131 ± 7 days, A1C decreased from 12.0 ± 0.1 to 9.1 ± 0.2% ($p < 0.0001$), and A1c decreased to ≤ 8.5% in 52%. A1C reduction was sustained in 94 patients with repeat A1C at 378 ± 5 days (12.0 ± 0.1 to 9.0 ± 0.3%, $p<0.0001$). There was a trend toward lower 30-day readmission rates in ST patients (11% vs. 17%, p=0.08). Readmissions were commonly elective among cardiovascular (CV) admissions (46 vs. 11%). Further analysis by admission diagnosis showed lower readmission rates in ST patients admitted for non-CV reasons vs. matched controls (8 vs. 17% p=0.02). Sweet Transitions was associated with improved glycemic control that persisted at 1 year as well as lower readmission rates. Sustained improvements at 1 year suggest effective engagement and communication at the level of patient, organization, primary care, and community. Scalability of ST's effectiveness relies on identifying factors and processes contributing to improved outcomes.

147-LB

Readmission and Comprehension of Diabetes Education at Discharge (ReCoDED Study)

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Diabetes (DM) is a major contributor to risk for hospital readmission. The Diabetes Early Readmission Risk Indicator (DERRI) is a predictor of 30-day readmission in patients with DM that may allow early identification and intervention for high-risk patients. A limitation to DERRI is the absence of DM-specific factors as contributors to this risk. To address this, we investigated HbA1c, glycemic measures and variability (GV), changes in DM therapy at discharge, and patient responses to a novel post-discharge questionnaire directed at Patient Comprehension (PC) of instructions provided for home DM management. Non-critically ill adult patients with DM were contacted by phone within 48 hours of hospital discharge to complete the PC Questionnaire. To date, 70 subjects (type 1 n=9, type 2 n=53, pancreatogenic DM n=8) (mean age 57.2 ± 12.8 years, BMI 31 ± 8.8 kg/m2, 56% men, 71% Caucasian, HbA1c 8.6 ± 2.0%, DM duration 19 ± 12 years, mean BG prior to discharge (210 ± 49 mg/dL), GV (66 ± 35 mg/dl) have been recruited. Of 41 subjects completing the PC questionnaire, those reporting that discharge instructions for home DM management were not provided had lower PC scores (70.6% vs. 81.5%, p=0.025) and more readmissions (OR 5.6, p=0.04) than those reporting that instructions were given. Among the 60 subjects with one-month post-discharge data, 22 patients (37%) reporting ≥1 readmission had higher DERRI scores than those without readmissions (26% vs. 20%, p=0.023). HbA1c, GV and changes in DM treatment regimens were not associated with readmission.

In summary, these results demonstrate that PC of discharge instructions may be a novel mediator of readmission risk and may add an additional measure of risk for hospital readmission.

148-LB

High Performance Two-Step Model for Early Detection and Management of Type 2 Diabetes Risk in the Workplace

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Background: Identification of T2D high risk individuals is key for early implementation of prevention interventions. Employers could be instrumental in reversing T2D risk for a majority of its population via improved predictive power risk detection tools.

Objective: To test the feasibility of a two-step screening model, based on the combination of a risk test score and Hb1Ac, for early detection and management of risk in an employee population.

Methodology: The model was tested in nondiabetic employees of a large employer in Mexico. As a first step, a T2D risk score was computed for each participant via a multivariate logistic regression model that integrates 16 T2D genetic variants, T2D parental history and BMI. Subjects with a risk score above certain cut points were considered medium and high-risk individuals. As a second step, medium and high-risk individuals identified in the first step were tested for levels of Hb1Ac. Subjects with Hb1Ac of ≥5.7% were recommended to join the employer's diabetes prevention program.

Results: 5,201 of 7,480 (69.5%) employees (46% women, 54% men) aged 18-60 years and free of diabetes agreed to participate in the screening program. 5,201 samples (buccal swabs) for genotyping and corresponding data (demographics, personal and family medical history) were collected on-site at 36 branch offices from 10/2017 to 12/2017 in Mexico City, Monterrey and Guadalajara. Participants risk scores stratified as low (52%), medium (34%) or high risk (14%). Of the medium and high-risk individuals, 31% showed elevated Hb1Ac (≥5.7%), and were suggested to join the employer's diabetes prevention program.

Conclusions: Our study initiates a data-driven discussion of how employers can radically support employee diabetes prevention and lower healthcare costs via improved predictive power tools. A two-step system, based on the combination of a risk test score and Hb1Ac, may be a useful tool for an effective identification of high risk individuals in a workplace setting.

149-LB

Cost-Related Barriers to New Diabetes Medications—A National Physician Survey

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Background: In recent clinical trials, some SGLT2is and GLP-1 receptor agonists have been shown to reduce cardiovascular events, leading to their prioritization for patients with cardiovascular disease in diabetes care guidelines. However, because these medications are costly, oftentimes medication access is limited by insurance companies.

Objectives: To determine the frequency that physicians encounter cost-related barriers to prescribing new diabetes medications.

Methods: We mailed a survey to a national sample of 720 primary care physicians (PCPs) and 480 endocrinologists in 2016 (adjusted response rate, 41%). Physicians were asked how often their patients were unable to start a new diabetes medication in general, and, specifically, an SGLT2i, because it was too expensive. Physicians also reported the frequency of completing a prior authorization (PA) for a new diabetes medication.

Results: In 2016, 28% (N=101) and 37% (N=129) of physicians reported that their patients were unable to start medications in general, and specifically, SGLT2is, due to costs "most of the time"/"always." More PCPs (45%, N=86) than endocrinologists (26%, N=43) were unable to start SGLT2is due to costs. Daily PA were reported by 43% of physicians (N=151); 62% (N=101) endocrinologists completed PAs daily. Adjusting for specialty and panel size, physicians with >50% of patients age >65 were more likely to report that patients were unable to start a new medication or SGLT2i due to costs (OR=2.25, 95% CI=1.38-3.67; p=0.001 and OR=1.63, CI=1.02-2.60, p=0.04). Endocrinologists (OR=5.03, CI=3.09-8.18; p<0.001) and physicians with >1000 patients in their panel (OR=2.69, CI=1.61-4.49; p<0.001) were more likely to complete PAs daily.

Conclusions: U.S. physicians experience significant cost-related barriers to prescribing new diabetes medication classes. Pharmacy benefit management strategies will need to be updated to facilitate access to glucose-lowering medications with clear cardiovascular benefit.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (K23DK092783 to N.L.), (K24DK105340 to E.H.); University of Chicago (P30 DK092949); University of Chicago Biological Sciences Division

150-LB

Understanding the Relationship between Primary Care Provider (PCP) Encounter Cadence, Medication Adherence, and Diabetes Control

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Introduction: Regular PCP encounters are associated with wellbeing; there is limited evidence to support the ideal PCP encounter cadence to optimize patient outcomes. The aim of this study was to measure the association between PCP encounter cadence and medication adherence and diabetes control, among those newly diagnosed with T2DM.

Methods: A cohort of 7,106 persons enrolled in a Medicare Advantage health plan and newly diagnosed with T2DM between 7/1/12-6/30/13, was identified and followed for 36 months. Two methods measured PCP encounter cadence: total PCP encounters (frequency) and quarters with PCP encounter (regularity). Proportion of days covered (PDC) assessed noninsulin diabetes medication (NIDM) adherence (PDC ≥80.0%). Diabetes control was defined as A1c ≤ 8.0%. Logistic regression was used to measure the relationship between PCP encounter cadence and outcomes (NIDM adherence, diabetes control). Covariates included patient demographics, Charlson Comorbidity Index score, chronic conditions, healthcare utilization, insulin use, and prior NIDM adherence and diabetes control.

Results: Overall, 5,212 and 326 people met inclusion criteria for the NIDM adherence and diabetes control analyses, respectively. Adjusted models indicated that each additional PCP encounter was associated with a 12.3% increase in the likelihood of NIDM adherence (95% CI 1.10, 1.15), and each additional quarter with a PCP encounter was associated with a 27.4% increase in the likelihood of NIDM adherence (95% CI 1.22, 1.33). PCP encounters (OR 1.06; 95% CI 1.00, 1.12) and quarters with a PCP encounter (OR 1.13; 95% CI 0.98, 1.30) were directionally associated with diabetes control.

Conclusion: Our findings suggest that frequency and regularity of PCP encounters were associated with medication adherence. This study contributes to the data needed to establish evidence-based guidelines for PCP encounter cadence, for those newly diagnosed with T2DM.

PEDIATRICS—OBESITY AND TYPE 2 DIABETES

151-LB

Clinical Characteristics and Antibody Persistence over Time in Youth in the Pediatric Diabetes Consortium (PDC) Type 2 Diabetes (T2D) Cohort

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Objective: To describe the characteristics of youth diagnosed with T2D who have tested positive for ≥1 islet autoantibody (IA) and to examine the persistence of IA over time.

Methods: Youth enrolled in the PDC T2D Registry with ≥2 years follow-up after diagnosis and ≥1 positive IA at any time were identified. T2D was determined using ADA guidelines. IAs were measured at each PDC site according to local practice and included IAA, GADA, IA-2A, ZnT8A, and ICA. Positive IAA tests were excluded if measured after insulin initiation. Clinical characteristics, clinical presentation, and treatment over time were analyzed.

Results: Positive IA is an exclusion for enrollment in the PDC T2D Registry; however, on review of the ~1,300 youth in the PDC, 38 were found to have IA. A single IA was found in 35 and >1 IA in 3 participants. GADA was most common (N=32); 3 were persistently positive, 13 converted to negative, 8 became positive after a negative GADA, and 8 had only 1 IA determination. Positive IAA (N=5), IA-2A (N=4) and ZnT8 (N=1) were uncommon or rare, no positive ICA were found. At diagnosis, those IA positive were more likely to be treated with insulin (95% vs. 73%) but with similar HbA1c (10.4% vs. 10.0%). At last visit, those IA positive had longer diabetes duration (5.7 years. vs. 4.8 years.) and higher insulin use (71% vs. 59%) compared to the IA negative cohort, but HbA1c levels were similar (8.7% vs. 9.0%). Age at diagnosis, race/ethnicity, percent male, and BMI were not different between those with and without IA.

Conclusion: Most IA positive youth with a T2D phenotype require insulin at diagnosis and more IA positive than IA negative youth require insulin during follow-up treatment. These findings suggest the importance of IA ascertainment at diagnosis and in those failing oral therapy. In T2D youth GADA is the most common IA; yield from ZnT8 and ICA determinations is low; fluctuations in IA positivity are not uncommon. Additional study of youth with T2D phenotype and IA is needed.

Supported By: Novo Nordisk; Boehringer Ingelheim; Takeda Pharmaceutical Company Limited

152-LB

Effect of Obesity and Exercise on Amino Acid Metabolites in American-Indian Adolescents at Risk for Diabetes

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Circulating amino acids (AA) and their metabolites are biomarkers for insulin resistance and future diabetes in adults, but there are few, and conflicting findings in studies of adolescents. We performed amino acid metabolomic profiling in American Indian adolescents to determine whether specific analytes would vary with body composition and insulin sensitivity, and/or be altered in response to exercise training. Boys and girls, 11-18 years who were normal weight (NW, n=36) or obese (Ob, n=58) completed tests of fitness, body composition, and a fasting blood draw. Forty-two of the Ob group were retested after completing 16 weeks of aerobic exercise training. A panel of 42 plasma amino acids and metabolites were measured by UPLC/MS/MS. The Ob group had several risk factors for future diabetes, including higher body fat, lower aerobic fitness, and lower insulin sensitivity (iHOMA2). The Ob group had 16 analytes that were higher and 8 lower than the NW group. Among those that were higher in the Ob group were branched chain AAs (Val, Leu, Ile, +13-17%) and aromatic AAs (His, Phe, Tyr, +15-34%); those AAs were also correlated with body fat (r=0.32 to 0.53) and insulin sensitivity (r=-0.32 to -0.60). The Lys metabolite, α-aminoadipic acid, a predictor of diabetes in adults, was 46% higher in the Ob group and correlated with insulin sensitivity (r=-0.43). β-aminoisobutyric acid, a myokine related to insulin resistance in adults, was 29% lower in the Ob vs. the NW group and correlated with insulin sensitivity (r=0.32). Exercise training resulted in a 10% increase in aerobic fitness, but body composition and insulin sensitivity were unchanged. Only two AAs were changed (His, Cys) after training. These novel findings in adolescents demonstrate that several plasma AAs are altered by obesity and serve as biomarkers of insulin action, but are not altered with this exercise intervention.

Supported By: National Institutes of Health

153-LB

Differential Effects of Birth Weight on Early-Onset Type 2 Diabetes in Adolescents and Young Adults

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Background: Type 2 diabetes mellitus (T2DM) is increasingly diagnosed in adolescents and young adults. However, the impact of birth weight (BW) on this early onset T2DM is not well quantified.

Methods: A longitudinal study of Southwestern American Indians, aged ≥ 5 years, was conducted from 1965-2007. Subjects who had a recorded BW and at least one research exam that included an OGTT were followed until they developed T2DM or their last exam before the age of 40 years, whichever came first. Age-sex-adjusted incidence rate of T2DM was computed and Poisson regression models were used to estimate the effect of BW on the incidence of T2DM, adjusted for sex, BMI z-score (fitted as time-varying), and maternal variables, such as the presence of diabetes during pregnancy. The effect of BW on T2DM was non-proportional over time, and in some regression models, the effect was non-linear (quadratic). Therefore, all analyses were stratified by decade of age at follow-up and BW was analyzed as quintiles.

Results: Among 4,275 subjects (52% females, median BW 3.45 kg), there were 728 incident cases of T2DM over a median follow-up of 20.6 years (7.5 cases per 1000 person-years). Incidence rates, stratified by decade of age at follow-up, were greater in females and in older age groups. In multivariable regression analyses, the effect of BW on T2DM risk varied by age group, showing a quadratic (U-shaped) effect at 10-19 years ($P<0.05$) and a negative linear effect at older age intervals (20-29 years, $P=0.015$; 30-39 years, $P<0.001$). We could not reliably estimate risk at 0-9 years because of few cases. Female sex, greater BMI z-score, and the presence of maternal diabetes in pregnancy added to the effect of BW on T2DM risk in all age groups.

Conclusions: Both low and high BWs increased the risk of T2DM in adolescence, but only the effect of low BW persisted into young adulthood. Effects of female sex, accelerated growth, or being the offspring of a diabetic pregnancy added to the effect of BW on the risk of early onset T2DM.

Supported By: National Institutes of Health

154-LB

Self-Monitoring of Blood Glucose (SMBG) in Youth with Poorly Controlled Type 2 Diabetes (T2D) in the TODAY Study

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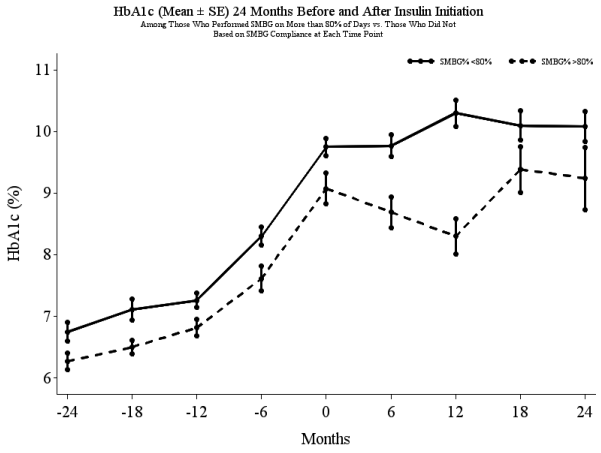
Objective: Determine if SMBG increased after starting insulin in T2D youth with poor glycemic control in the TODAY study.

Methods: Youth with recent onset T2D (n=699) were randomized to receive metformin ± rosiglitazone (rosi) or intensive lifestyle. They were asked to perform SMBG daily (supplies provided). When they reached primary outcome (PO; A1c ≥8% over 6 mon or inability to wean from temporary insulin due to metabolic decompensation), metformin (not rosi) was continued, daily insulin glargine started; dosing was intensified as needed. A1c and SMBG data for 2 year before and after PO were analyzed. SMBG% was defined as percent of days between visits when the meter was used ≥1 time.

Results: Of 319 youth who reached PO, 298 started insulin and 282 had SMBG data. At PO, mean (SD) age was 15.8±2.3 year, 65.3% female, 38.3% non-Hispanic black, 16.3% Hispanic, 7.1% non-Hispanic white, BMI 35.5±7.9 kg/m^2, and A1c 9.6±2.0%. Median SMBG% was 40% at PO which increased to 49% at 6 mo and fell to 41% at 1 year; 22% of youth tested ≥80% of days at PO, which increased to 25% at 6 mo and fell to 19% at 1 year. Compared with those who tested <80% at PO, youth who tested ≥80% were younger, with lower BMI and A1c. Use of SMBG was associated with ≥1% reduction in A1c at 6 and 1 year after insulin initiation (Figure).

Conclusion: Adherence to SMBG was poor but associated with lower A1c. Research is needed on interventions to help youth with T2D reach A1c goals.

Figure.



Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (U01DK61212, U01DK61230, U01DK61239, U01DK61242, U01DK61254)

PEDIATRICS—TYPE 1 DIABETES

155-LB

The Flexible Lifestyles Empowering Change (FLEX) Intervention Trial for Adolescents with Type 1 Diabetes—Primary and Secondary Outcomes

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Youth with T1D often have poor glycemic control and compromised health and well-being. Our aim was to test the efficacy of the FLEX adaptive behavioral intervention on the primary (HbA1c) and secondary (psychosocial and metabolic) outcomes at 18 months.

Youth (n=258) aged 13-16 years, diagnosed >1 year with T1D with HbA1c from 8.0-13.0%, were randomized at two sites to FLEX or usual care control. Mean (sd) duration of diabetes was 6.4 (3.8) years, 50% were girls, 78% non-Hispanic white, mean HbA1c was 9.6% (1.2) and 71% used insulin pump therapy. FLEX used motivational interviewing and problem-solving skills training to enhance self-management. Intervention fidelity was assessed via random selection of audiotaped sessions for counseling strategy and session content. Intent-to-treat analyses used mixed effects models, with fixed effects of site, timepoint, intervention group, intervention by timepoint and baseline level of primary or secondary outcomes, with a random intercept (alpha=0.05).

Retention was 97%, with intervention fidelity 4.6 out of 5 for counseling strategy and 97.4% complete for session content. HbA1c was not statistically significantly different between intervention and control at 18 months. Among secondary outcomes at 18 months, the intervention was associated with improved scores for symptoms of depression (p=0.04), quality of life (p=0.01), motivation (p=0.009), problem-solving (p=0.04), and diabetes self-management profile (p=0.01), as well as better total cholesterol (p=0.04), and better diastolic blood pressure (p=0.01).

The FLEX intervention did not change the primary outcome, but did positively effect psychosocial outcomes over the 18 months of the trial. Further analyses will reveal information regarding drivers of positive response to the intervention and will point to directions for improvement in the approach, perhaps incorporating more specific direction towards achievement of glycemic targets.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (1UC4DK101132)

156-LB

Depression Screening in Adolescents with Type 1 Diabetes Mellitus

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Background: Adolescents with type 1 diabetes mellitus (T1D) are at increased risk for depressive symptoms relative to youth without diabetes, which is associated with poor diabetes outcomes (Hood et al, 2014). As part of ongoing Quality Improvement initiatives at Texas Children's Hospital (TCH), we evaluated two validated depression screening measures, the PHQ-2 and PHQ-9: Modified for Teens, to standardize our depression screening process.

Objectives: We sought to 1.) review screening outcomes from youth with T1D who completed both the PHQ-2 and PHQ-9, 2.) determine which measure provided the greatest sensitivity to identifying depressive symptoms, and 3.) create a standardized process for implementation of the more sensitive screen.

Methods: Data was collected by a chart review of PHQ-2 and PHQ-9 scores for all patients with T1D age 12-17 seen at TCH Endocrine clinic sites between January 1-December 31, 2017. A positive screen was defined as PHQ-2 score ≥ 3 and PHQ-9 score ≥ 5. We then created an algorithm based on the more sensitive screen for referrals to mental health services.

Results: Of 961 eligible patients, 84% were screened using PHQ-2 and 15% using both the PHQ-2 and PHQ-9. Of the patients who completed both measures, the positive screening rate was 20% in PHQ-9 vs. 4% in PHQ-2. None of the patients with "moderate" PHQ-9 (≥5-9) screened positive on the PHQ-2, and only 1 patient with "severe" PHQ-9 (≥10) score screened positive on PHQ-2. Of the 3 patients who endorsed suicidality on the PHQ-9, none had a positive PHQ-2. 80% of patients who received both screens completed the screens within 2 months of each other.

Discussion: PHQ-2 depression screen may be less sensitive than PHQ-9 for capturing depressive symptoms in youth with T1D. We have created a standardized algorithm implementing PHQ-9 into the clinic flow and looking at optimizing mental health referrals.

Hood KK, Lawrence JM, Anderson A, Bell R, et al. Metabolic and inflammatory links to depression in youth with diabetes. Diabetes Care 2012;35:2443-2446.

157-LB

White Matter Differences and Neurodevelopment Outcomes in Patients with KATP Channel-Related Diabetes

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Background: Patients with KATP channel related diabetes (KATP-DM) experience improved glycemic control with sulfonylurea therapy, but the degree of improvement in their spectrum of neurological dysfunction remains unclear. We hypothesized that patients with KATP-DM have differences in brain white matter and associated neurodevelopmental impairments when compared to those with type 1 diabetes or sibling controls.

Methods: Subjects (8-20 years old) from the Monogenic Diabetes Registry at the University of Chicago included those with KATP-DM (n=8), type 1 or other non-KATP diabetes (n=7), and sibling controls (n=6). All participants had brain MRI with diffusion tensor imagining (DTI) on a 3T Philips Achieva Quasar scanner. Fractional anisotropy (FA) was used as an indirect measure-

ment of myelin in the brain. Subjects also participated in validated neurodevelopmental assessments.

Results: Nonparametric Kruskal-Willis testing of analyzable DTI data [4 KATP-DM, 5 T1DM, 3 siblings] revealed that FA values of the corpus callosum were not statistically different (p=0.58). However, DTI of the white matter tracks in the right hippocampus approached a significant difference among the three groups (p=0.07). Third ventricular volumes among all three groups [9 KATP-DM, 7 T1DM, 5 siblings] were significantly different (p=0.05). Significant differences between groups as determined by one-way ANOVA were found in Perceptual IQ (F (2,14)=4.862, p=.025); visual motor integration (F (2,14)=5.579, p=.017); and graphomotor coordination (F (2,14)=5.399, p=.018).

Conclusion: In this first study using quantitative MRI methods in patients with KATP-DM, DTI revealed no overall difference but possible regional variation in FA, while ventricular volume and neurodevelopmental function were different among this cohort. Larger studies are needed to assess the potential differences in brain white matter as well as the benefits of early sulfonylurea therapy on neurologic development.

Supported By: Endocrine Fellows Foundation

158-LB

FreeStyle Libre™ Use for Self-Management of Diabetes in Teenagers and Young Adults

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The challenges of caring for diabetes in teenagers and young adults are well known. We analyzed two research studies (IMPACT and SELFY) that evaluated FreeStyle Libre™ Flash Glucose Monitoring System as a replacement for self-monitoring of blood glucose (SMBG), looking specifically at outcomes in patients aged 13-24 years. IMPACT enrolled 241 patients with well controlled type 1 diabetes (T1DM), HbA1c 6.74±0.56% (50.1±6.1 mmol/mol), age 43.7±13.9 years (mean±SD) into a 6 month European RCT (23 sites). The control group (n=121) used SMBG and the intervention group used FreeStyle Libre for self-management. Of the 241 patients, 19 were aged 18-24 years. SELFY enrolled 76 young people aged 10.3±4.0 years (mean±SD), baseline HbA1c 7.9±1.0% (62.9±11.1 mmol/mol) into a 10 week single arm European study (10 sites). The study consisted of 2 weeks baseline masked (blinded) wear, followed by 8 weeks open use. Of the 76 patients, 25 were aged 13-17 years. IMPACT study results at 6 months showed no significant interaction of age with treatment group for the primary endpoint of time in hypoglycemia <70 mg/dL. For the younger adults, time in range (TIR) (70-180 mg/dL) significantly increased by 2.9±0.89 hours/day (mean±SE); p=0.0055. Time in hyperglycemia (>180 mg/dL) also significantly improved with a reduction of 2.40±0.834 hours/day (mean±SE); p=0.0113. Intervention group patients scanned the sensor on average 11.3 times daily. Teenagers in the SELFY study significantly improved the primary endpoint of TIR (70-180 mg/dL) by 1.2±2.5 hours/day (mean±SD), p=0.0254. HbA1c also significantly improved, -0.7±0.6%, p<0.0001. Time in hyperglycemia (>180 mg/dL) significantly reduced by -1.7±2.9 hours/day, p=0.0093, no statistically significant changes were observed in hypoglycemia (time<55 mg/dL, baseline 0.7±1.0 hours/day). Scan frequency of FreeStyle Libre was on average 9.7 times daily. The IMPACT and SELFY studies both demonstrated improvements in glycemic control in the teenager and young adult age groups.

159-LB

Association between Glycemic Control and Visits with Diabetes Care Team in Youth with Type 1 Diabetes

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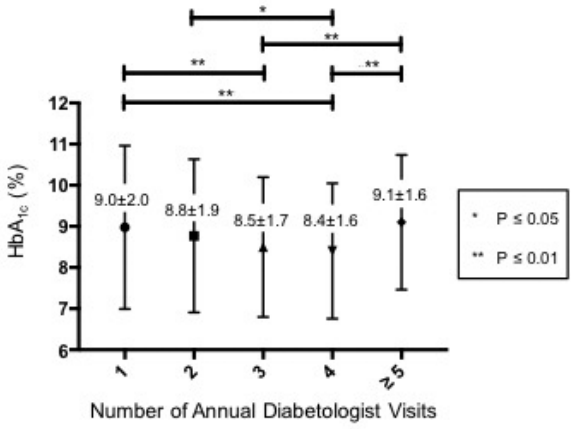
Clinical care of youth with type 1 diabetes (T1D) involves a multidisciplinary team including diabetes provider, registered dietitian (RD), certified diabetes educator (CDE), and social worker (SW) or psychologist. There is limited evidence to guide the ADA recommendations for visit frequency, so this study sought to evaluate the association between visit frequency and glycemic control. A cross-sectional analysis of demographic, clinical, and visit frequency data was performed from 1,995 T1D youth with diabetes duration ≥ 1 year, and ≥ 1 diabetes clinic visit during a 1-year period at a pediatric diabetes center. Patient demographics included 50.6% female, age 13.9±4.2 years, T1D duration 6.3±4 years, HbA_{1c} 8.6±1.8%, and race/ethnicity: 52.4% white, 23.4% Hispanic, 16.7% black, and 7.7% other. The cohort averaged 2.9±1.3 annual provider visits. Patients with 3 or 4 annual provider visits had statistically lower mean HbA_{1c} than those with 1, 2, or ≥ 5 visits (Figure 1). In total, 43.6% attended ≥1 CDE, 50.5% RD, and 71.8% SW/psychology visit. Seeing a CDE, RD, or SW/psychologist was not associated with lower HbA_{1c} among the overall cohort, but was associated with lower HbA_{1c} among privately insured patients. These findings reflect the complex, multidimensional nature of T1D management. Further investigation into clinical, psychosocial, and patient-reported outcomes beyond glycemic control is warranted.

Figure 1. Glycemic Control by Annual Diabetologist Visit Count



160-LB

HERV-W-Env Involvement in Human T1D Pathogenesis—New Insights from Two Mouse Models

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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 envelope protein of HERV-W family (HERV-W-Env), which has been involved in the pathogenesis of Multiple Sclerosis (MS), displays pro-inflammatory and autoimmune properties. This has initially been demonstrated in an MS context, but it subsequently turned out to be relevant for type 1 diabetes (T1D). We recently observed that HERV-W-Env protein and RNA are detected respectively in sera and PBMC of more than 50% of T1D patients. We demonstrated that this pathogenic protein is expressed by acinar cells in human T1D pancreas, and is associated with the recruitment of macrophages within the pancreas of these patients. HERV-W-Env also displays direct pathogenic properties, as it inhibits insulin secretion by human Langerhans islets. In this new report, we present data from two transgenic mouse models in which HERV-W-Env is expressed under the control of HERV-LTR and CAG promoter. In a first model, transgenic mice, generated in a C57Bl6/J background, were challenged by repeated STZ injections. We observed that transgenic mice are more susceptible to pancreatic damage than wild type mice, as they developed more severe insulitis (P<0.0001) and hyperglycemia (P<0.01). In a second model, transgenic mice are currently backcrossed in a NOD/ShiLtJ background. Preliminary results revealed that NOD transgenic males start to develop a hyperglycemia as soon as 4 weeks old compared to their controls littermates. Early results from these transgenic mice support a role for HERV-W-Env in human T1D pathogenesis, particularly in patients expressing this pathogenic protein. They provide additional justification for the ongoing phase IIa clinical trial which is designed to neutralize HERV-W-Env in T1D patients using a monoclonal antibody named GNbAC1 (NCT03179423). Six months interim results of this new therapeutic approach will be available 3rd quarter 2018.

161-LB

Text Message Responsiveness to BG Monitoring (BGM) Reminders Improves A1c in Teens with Type 1 Diabetes (T1D)

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Background: As teens with T1D become increasingly independent in self-care, adherence and glycemic control deteriorate. Teens need innovative ways to improve self-care and protect against glycemic decline. We evaluated a text messaging intervention in teens with T1D and assessed factors associated with text responsiveness and glycemic benefit over 18 months.

Methods: Teens with T1D (N=147), ages 13-17 years, received 2-way text reminders at self-selected times to check BG levels and reply by text with BG results. Teens received increasing numbers of text reminders, beginning with 1 and increasing to a maximum of 4/day.

Results: At baseline, teens (48% male, 78% white, 63% pump-treated) had mean±SD age 14.9±1.3 years, T1D duration 7.1±3.9 years, and A1c 8.5±1.1%. The mean proportion of days with 1+ BG response declined over time (months 0-6: 60±26% of days, months 6-12: 53±32%, months 12-18: 43±33%). Over the 18 month study, 50% of teens responded with 1+ BG result on ≥50% of days ("High Responders"). High Responders compared with "Low Responders" (<50% of days with 1+ BG response) were similar

regarding age, T1D duration, and sex distribution but High Responders had lower baseline A1c (8.2±1.0 vs. 8.7±1.1%, p=.005) and higher daily BGM frequency (5.2±2.3 vs. 4.3±1.6, p=.01). Regression analysis controlling for baseline A1c revealed no significant change in A1c from baseline to 18 months in High Responders (p=.42) compared with a significant A1c increase in Low Responders (+0.3%, p=.009). In teens with baseline A1c ≥8%, High Responders (n=39) were 2.6 (95% CI 1.03, 6.6) times more likely than Low Responders (n=52) to improve A1c by ≥0.5% from baseline to 18 months (p=.04).

Conclusions: Responding to text reminders on ≥50% of days over 18 months provided clinically significant glycemic benefit to teens with T1D, especially in those with high baseline A1c. There remains a need to tailor interventions for teens over time to maintain their engagement and optimize improvements.

Supported By: National Institutes of Health (R01DK095273, K12DK094721, P30DK036836); JDRF (2-SRA-2014-253-M-B)

162-LB

Quarterly HbA1c Surveillance in Children with Islet Antibodies (IA) Accurately Predicts Type 1 Diabetes (T1D) Timing

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IA sensitively predict future T1D, but onset often occurs many years after seroconversion. Early diagnosis results in less DKA and milder initial disease, especially in young children. Using the international TEDDY cohort, we asked if quarterly HbA1c testing could predict T1D among pre-pubertal subjects with ≥1 persistent IA (GADA, IA2A, IAA). Mean(SD) age at seroconversion and T1D onset was 43(29) and 73(22) months respectively. Of 8,504 HLA high risk children, 456 had persistent confirmed IA, had undergone at least 3 quarterly HbA1c tests in the prior 12 months, and were not on diabetes drugs or diets. Of these, 104 progressed to T1D and 352 did not. Subjects were split into training (292 total, 62 progressors) and test (164 total, 40 progressors) datasets with similar characteristics. The optimal maximum HbA1c cutpoint within 1 year pre-onset to predict T1D, by ROC analysis, was similar in training and test datasets (p=0.66). For both, HbA1c ≥5.6% gave the best Youden index. Other factors significant for T1D risk in the training dataset included age at HbA1c test, month of HbA1c test, continent and IA2A titer, but not gender, family history, HLA type, seroconversion age, IAA titer nor T1D-related SNP genotypes. Adjusted for significant factors, the optimal HbA1c cutpoint of ≥5.6% for quarterly testing was 91% sensitive, 91% specific, 73% PPV and 98% NPV to predict T1D within 1 year in children with HLA and IA risk. The final predictive model fit both training and test data similarly (p=0.28). Median(SD) time from first HbA1c ≥5.6% to diagnosis was 8.6(4.5) months, enabling monitoring and education for earlier treatment. Quarterly HbA1c surveillance is cost-effective and clinically accessible. A hierarchical plan for pediatric T1D prediction is proposed comprising initial genetic screening, then IA surveillance of those at genetic risk, then HbA1c surveillance of those with IA, and finally close glycemic surveillance of those with HbA1c ≥5.6% to ascertain metabolic onset.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (U01DK63829, U01DK63861, U01DK63821, U01DK63865, U01DK63863, U01DK63836, U01DK63790, UC4DK63829, UC4DK63861, UC4DK63821, UC4DK63865, UC4DK63863, UC4DK63836, UC4DK95300, UC4DK100238, UC4DK106955, HHSN267200700014C); National Institute of Allergy and Infectious Diseases; Eunice Kennedy Shriver National Institute of Child Health and Human Development; National Institute of Environmental Health Sciences; JDRF; Centers for Disease Control and Prevention

PREGNANCY—BASIC SCIENCE/TRANSLATIONAL

163-LB

Effect of Gestational Diabetes and Maternal Obesity on Fetal Programming—Are miRNAs Key Epigenetic Modifiers or Biomarkers of an Altered Intrauterine Milieu?

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Background: Pregnancies complicated by gestational diabetes (GDM) or maternal obesity (MOB) induce abnormal fetal development that can lead to diabetes and obesity later in life with sex specific manifestations. Alterations in miRNA expression in GDM and MOB exposed offspring and effects on development have not been fully described.

Hypothesis: Exposure to an aberrant intrauterine milieu complicated by GDM and MOB leads to changes in miRNA and target gene expression in human fetal liver.

Methods: Candidate miRNA expression was measured in second trimester AF from women diagnosed with GDM via multiplex miRNA assay (Firefly Bioworks, Abcam). Gene targets of differentially expressed miRNAs were determined from TargetScan and pathway enrichment determined via Ingenuity Pathway Analysis (IPA). MiRNA and target gene expression (mRNA and protein) were measured in a separate cohort of 2nd trimester primary human fetal hepatocytes (PHFH) exposed to MOB via QPCR and western blot. All studies were approved by UPENN and TEMPLE University IRBs.

Results: GDM exposed AF had significant increases in miRNAs 199a-3p, 503-5p, and 1268a (p<0.05) and sex specific analysis showed enrichment in miRNAs 378a-3p, 885-5p, and 7-1-3p in female offspring samples (p<0.05). IPA with gene targets of enriched miRNAs centered hepatic pathways. GDM exposed AF miRNA enrichment was confirmed in PHFH exposed to MOB for miRNAs 885-5p, 199-3p, 503-5p, and 7-1-3p (p<0.05). Female PHFH exposed to MOB were enriched for miRNAs 885-5p, 199-3p, 503-5p, and 7-1-3p (p<0.05) and corresponded to decreased expression of target genes ABCA1, PAK4. In male PHFHs, no miRNA expression changes were measured but there was increased expression of ABCA1 and PAK4 (p<0.05).

Conclusion: Our data suggest sex specific changes in miRNA and target gene expression in PHFH may be one mechanism responsible for sex specific metabolic changes in offspring exposed to GDM and obesity in utero.

Supported By: National Institutes of Health (UL1TR001878)

164-LB

Circulating Exosomal miRNA Signature in Gestational Diabetes Mellitus Influences Glucose Metabolism in Placental Cells

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There is increasing evidence that miRNA, which are enriched in small nanovesicles called exosomes, are important regulators of gene expression. In this study, we tested the hypothesis that circulating exosomes from women with Gestational Diabetes Mellitus (GDM) carry a specific set of miRNAs which regulate genes associated with placental glucose metabolism. Exosomes were isolated from plasma obtained from normal glucose tolerant women (NGT; n=12) and women with GDM (n=12) pregnancies at delivery by differential and buoyant density centrifugation. Exosomal RNA was extracted and an Illumina TrueSeq Small RNA kit was used to construct a small RNA library. Gene target identification and gene ontology analysis for miRNAs was performed using the Ingenuity pathway analysis (IPA). The effect of exosomes on glucose metabolism in placental cells was assessed using a human glucose metabolism array. In plasma, a total of 44 miRNAs were upregulated in exosomes from women with GDM compared to NGT pregnant women (p<0.005). IPA showed that exosomal miRNAs isolated from women with GDM regulates the expression of placental genes associated with the glycolytic pathway including 6-phosphofructokinase and phosphopyruvate hydratase. Interestingly, exosomes from women with GDM increases the expression of placental genes associated with glycolysis and decrease the expression of genes associated with pentose phosphate pathway. After integration of the miRNA and mRNA data, we identified 74 differentially expressed exosomal miRNAs associated with the modulation of 10 potential target mRNAs in placental cells, which are associated with glucose metabolism. This data suggests that circulating exosomes under diabetic conditions might modulate the placental metabolic state to enhance glycogen metabolism in GDM.

Supported By: Diabetes Australia; National Health and Medical Research Council of Australia (1114013); Fondo Nacional de Desarrollo Científico y Tecnológico (1170809)

165-LB

Proteomic Profile of Adipose Tissue-Derived Exosomes and Their Potential Role on Placental Glucose Metabolism in Gestational Diabetes Mellitus

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Emerging studies suggest that adipose tissue derived exosomes involves in regulating insulin action and glucose homeostasis. In this study, we hypothesised the protein content of adipose tissue derived exosomes (exo-AT) differs in Normal Glucose Tolerant (NGT) and Gestational Diabetes Mellitus (GDM) pregnancies which lead to changes in placental glucose metabolism. Human omental adipose tissue was obtained from GDM (n=60) and BMI-matched NGT (n=48) pregnancies at the time of term Caesarean section. Exosomes were isolated from tissue-conditioned media by differential centrifugation and characterised using nanoparticle tracking analysis and SWATH mass spectrometry. The effect of exosomes on human placental cells was evaluated using a Human Glucose Metabolism RT² Profiler PCR

Array. The total number of exosomes (number of vesicles/mg adipose tissue/24 hour) were significantly higher in GDM compared to NGT. The number of exosomes positively correlated with maternal BMI and fetal weight. We identified 122 proteins upregulated in the exo-AT from GDM compared to NGT. Ingenuity pathway analysis revealed the upregulated proteins are associated with mitochondrial dysfunction and oxidative phosphorylation (OXPHOS). When compared to NGT exo-AT, GDM exo-AT increased ALDOB, PGK2 and GCK in placental cells. The data obtained in this study suggest that exosomes secreted from adipose tissue regulates placental glucose metabolism in GDM. Improving the communication of exo-AT to placental tissues may serve as an effective intervention strategy to prevent the consequences of GDM such as fetal overgrowth.

Supported By: Diabetes Australia; National Health and Medical Research Council of Australia (1114013); Fondo Nacional de Desarrollo Científico y Tecnológico (1170809)

166-LB

Circulating Exosomal miRNA Signature in Pregnancies with Gestational Diabetes Mellitus across Gestation

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Exosomes are small nanovesicles that carry bioactive molecules (e.g., miRNAs) which can be delivered to other cells and modify their phenotype. Recently, we have established that the number of circulating exosomes is higher in women with Gestational Diabetes Mellitus (GDM); however, the exosomal miRNA profile in GDM across gestation has not been established yet.

The aim of this study was to establish the circulating exosomal miRNA profile in women with normal glucose tolerance (NGT) and GDM women (BMI-matched) in a prospective cohort of patients at three time points during pregnancy. Exosomal RNA was sequenced using an Illumina NextSeq 500 platform. Linear mixed modelling was performed on the normalized miRNAs across gestation for normal and GDM pregnancies, using the lme4 package in R. Statistically significant differences in miRNA expression between NGT and GDM women was determined using likelihood ratio tests. In the first trimester of pregnancy, 92% (84 out of 92) of exosomal miRNAs were significantly elevated in plasma of women with GDM when compared to NGT women. Interestingly, in the second trimester of pregnancy the expression of these miRNA decreased in the GDM women with no significance difference observed in the exosomal miRNA profile between GDM and NGT women. Gene ontology analysis revealed that miRNAs which changed expression across gestation for GDM pregnancies are involved in the regulation of insulin.

In summary, we have identified a range of exosomal miRNAs which change expression across gestation for GDM and normal pregnancies. Gene ontology analysis revealed that these miRNAs are involved in the regulation of insulin, playing significant role in the pathophysiology of GDM.

Supported By: Diabetes Australia; National Health and Medical Research Council of Australia (1114013); Fondo Nacional de Desarrollo Científico y Tecnológico (1170809)

PREGNANCY—CLINICAL/EPIDEMIOLOGY

167-LB

Prospective Association between Gestational Diabetes and Subsequent Abnormal Liver Function Scores 9 to 16 Years after Pregnancy

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Chronic hyperglycemia is a risk factor for liver dysfunction. Women with Gestational Diabetes Mellitus (GDM), glucose intolerance first recognized in pregnancy, may identify a population of individuals at an increased risk for liver complications. However, large prospective studies examining liver function following a GDM pregnancy are lacking. The Diabetes & Women's Health (DWH) Study (2012-2014) followed women with and without GDM in the Danish National Birth Cohort (DNBC). DNBC was a population-based cohort study of pregnant Danish women (1996-2002). At 9-16 years postpartum, the DWH Study conducted a clinical exam and collected bio-specimens on 607 of 1,274 women with GDM and 619 of a random sample of 1,457 women without GDM during the index DNBC pregnancy. Markers of liver function measured at follow-up included: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT). Liver function scoring indices were used to assess liver capacity including: nonalcoholic fatty liver disease liver fat score (NAFLD-LFS), fatty liver index (FLI), hepatic steatosis index (HSI), and liver fat percentage. The mean (standard deviation) age (years) at follow-up for women without and with prior GDM was 43.4 (4.5) and 43.8 (4.6), respectively. Women with prior GDM had an increased risk at follow-up of elevated NAFLD-LFS (Adjusted Relative risk [RR], 2.34; 95% CI, 1.68-3.27), FLI (RR, 1.59; 95% CI, 1.27-1.99), and HSI (RR, 1.44; 95% CI, 1.21-1.71) adjusted for pre-pregnancy BMI and other relevant risk factors compared to women without prior GDM. Women with prior GDM also had a significantly higher fatty liver percentage (Adjusted difference (%), 1.93; 95% CI, 1.10-2.77). Women with GDM during pregnancy were at an increased risk for subsequent abnormal liver function 9-16 years postpartum. GDM may serve as another risk indicator for the early identification and prevention of liver dysfunction.

Supported By: Eunice Kennedy Shriver National Institute of Child Health and Human Development (HHSN275201000020C, HHSN275201500003C, HHSN275201300026I, HSN275201100002I); National Institutes of Health (UM1CA176726); March of Dimes Birth Defects Foundation (6-FY-96-0240, 6-FY97-0553, 6-FY97-0521, 6-FY00-407); Innovation Fund Denmark (09-067124, 11-115923); Health Foundation (11/263-96); Heart Foundation (96-2-4-83-22450); European Union (FP7-289346); Novo Nordisk Foundation

168-LB

Maternal Exposure to Perfluorooctane Sulfonate (PFOS) Is Associated with Maternal Hyperglycaemia and Adverse Neonatal and Childhood Outcomes

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Perfluorooctane sulfonate (PFOS) belongs to a class of endocrine-disrupting chemicals, perfluoroalkyl chemicals (PFCs), implicated in adiposity. Although supposedly phased out since 2002, its use remains widespread in Asia. We aim to examine the relationship between exposure to PFOS and maternal hyperglycaemia and metabolic outcomes in the offspring. We measured blood PFOS and other PFCs in archived samples taken at 24-32 weeks gestation from mothers in the Hong Kong centre of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study between 2002-2004. All mothers underwent 75g OGTT and GDM was diagnosed according to the IADPSG/WHO 2013 criteria. Pregnancy outcomes, neonatal anthropometrics and childhood outcomes at 7 years were documented. PFCs were measured using high performance LC-MS-MS. We completed analysis of PFCs in 1,601 maternal samples, a subset of 99 cord blood samples, and 970 offspring at 7 years follow-up. There is strong correlation among PFOS and other PFCs in cord blood (ρ=0.51-0.74, $p<0.001$), as well as correlation with maternal levels (ρ=0.60, $p<0.001$). Ratio of cord blood to maternal PFOS was 0.60. Using regression analysis with adjustment for maternal age, BMI, and offspring gender, maternal PFOS showed association with maternal 1 hour glucose, 2 hour glucose, HbA1c, AUC during OGTT and GDM, though only the association with HbA1c remained significant using log-transformed PFOS (beta 0.0746 ± 0.0132, $p=1.7x10^{-8}$). Log-transformed maternal PFOS was associated with higher birthweight, lower birth length, higher ponderal index and lower neonatal sum of skin fold thickness (beta -0.337 ± 0.085, $p=7.1x\ 10^{-5}$), after adjustment for all covariates. Maternal PFOS during pregnancy was associated with lower height in offspring at age 7, but not offspring glycaemic parameters. Exposure to PFOS may be an important contributing factor to the epidemic of hyperglycaemia in pregnancy and childhood metabolic disorders in Asia.

Supported By: Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01HD34242); National Institute of Diabetes and Digestive and Kidney Diseases (R01HD34243); Research Grants Council of Hong Kong, China (CUHK473408, CUHK471713); Health and Medical Research Fund of Hong Kong (13140761)

169-LB

Differential Effect of Nativity on Type 2 Diabetes Diagnosis Post-Gestational Diabetes, by Race/Ethnicity

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Background: Women with GDM have seven times higher risk of T2D compared to women with normoglycaemic pregnancies, with black women having the highest risk. Immigrants are a growing share of the U.S. population, with approximately 9% of the black population and 34% of Hispanic population being foreign-born. Due to differences in acculturation and assimilation, for-

eign-born U.S. women experience different pregnancy-related outcomes and subsequent chronic disease development, depending on their race/ethnicity.

Objective: To examine the association between nativity and T2D diagnosis following a prior GDM pregnancy and whether this association differs by racial/ethnic group.

Methods: We conducted a cross-sectional analysis of data from the 2007-2014 National Health and Nutrition Examination Survey, a nationally representative survey of non-institutionalized Americans. The analytic population included women with at least one prior GDM pregnancy. Logistic regression (OR, 95% CI) was used to examine the association.

Results: Our final sample included 433 women. The population was predominantly non-Hispanic white (62%), followed by Hispanic (18%) and black (12%). T2D was found in 29% of the population. After controlling for confounders, foreign-born black women had 0.14 (0.02-0.82) times the odds of developing T2D post GDM compared to black U.S. born women. Nativity was not significantly associated with cumulative incidence of T2D among Hispanics (1.45, 0.48-4.41) or non-Hispanic whites (1.53, 0.04,-6.07).

Conclusion: We found differential effects of nativity across racial/ethnic groups consistent with prior literature. Among black women, being foreign-born significantly decreases the odds of developing T2D following a GDM pregnancy but not among other groups. This observed effect may be due to U.S. born black women experiencing higher levels of racialized and gendered stress, both associated with higher levels of inflammation that can lead to higher risk of T2D.

170-LB

Initial Diastolic Blood Pressure and Risk of Pregnancy Hypertensive Disorders in Pregestational Diabetes—Can We Set a Number?

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Background: In pregestational diabetes (PGD) pregnancies, blood pressure (BP) close to normal is warranted to prevent pregnancy hypertensive disorders (PHD); targets are not well defined. Diastolic BP (DBP) was recently described as a modifiable factor.

Aim: To evaluate distinct levels of DBP as risk factors to PHD in a retrospective cohort of PGD women.

Methods: Women were cared for at a specialized prenatal care facility. DBP measured at the first antenatal appointment was categorized. Poisson regression with robust estimates was used.

Results: Baseline characteristics of women are in Table 1, and multivariable analysis, in Table 2.

Conclusion: In this PGD cohort, a DBP >80 mmHg at booking was associated to increased risk of PHD, suggesting that levels above this value should be prevented.

Table 1. Characteristics of Pregestational Women.

	Type 1 diabetes (n=84)			Type 2 diabetes (n=129)		
	PHD 32 (38.1)	No PHD 52 (61.9)	p	PHD 32 (24.8)	No PHD 97 (75.2)	p
Age (years)	26.8 (5.5)	27.7 (5.9)	0.515	34.1 (4.3)	33.1 (5.8)	0.385
Self-declared white	93.8	84.6	0.364	96.9	70.1	0.004
Years since diagnosis	15.4 (7.3)	11.9 (8.7)	0.058	6.8 (6.2)	3.5 (4.2)	0.008
Previous PHD	4 (12.5)	3 (5.8)	0.498	6 (18.8)	22 (22.7)	0.826
Chronic hypertension	8 (25.0)	4 (7.7)	0.050	16 (50.0)	24 (24.7)	0.014
Systolic BP (mmHg)	120 (14)	116 (14)	0.214	128 (16)	119 (14)	0.003
Diastolic BP (mmHg)	77 (13)	72 (10)	0.042	82 (13)	76 (11)	0.025
DBP>70 mmHg	56.2	48.1	0.615	62.1	61.5	>0.999
DBP>75 mmHg	56.2	46.2	0.500	62.1	60.4	>0.999
DBP>80 mmHg	21.9	5.8	0.062	37.9	23.1	0.182

Table 2. Risk of Pregnancy Hypertensive Disorders (n=178).

Risk factor	Relative risk	95% CI	p
Type 1 diabetes	1.91	1.20-3.02	0.006
Self-declared white skin	3.71	1.22-11.27	0.021
Primigravid	1.13	0.76-1.68	0.558
Diastolic blood pressure >80 mmHg	1.64	1.05-2.56	0.031
Initial A1c test ≥7.0%	0.678	0.44-1.05	0.083
Excessive GWG	1.55	1.04-2.30	0.030

Supported By: Fundo de Incentivo à Pesquisa e Eventos-Hospital de Clínicas de Porto Alegre

171-LB

Low Vitamin B12 Levels in Early Pregnancy Are Associated with Fasting Glycemia—A Prospective Cohort Study

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Background: The pathogenesis of gestational diabetes mellitus (GDM) is not fully understood and combining novel biomarkers with established risk factors could improve early prediction of GDM. Low vitamin B12 (B12) levels have been linked to obesity, insulin resistance and GDM but its predictive ability in early pregnancy as a risk factor for later GDM has not been proven.

Methods: Micronutrients in Pregnancy as a Risk factor for gestational diabetes and Effects on mother and baby (PRiDE) is a cohort study of pregnant women at high risk of developing GDM (n=4751 recruited). GDM was diagnosed by a 2-hour 75g OGTT according to UK NICE criteria (fasting blood glucose, FBG ≥5.6mmol/l or 2-hour BG ≥7.8mmol/l). B12 and folate were measured by electrochemiluminescence and deficiency defined as ≤200pg/ml and ≤3ng/ml respectively. Multiple linear and logistic regression models were done with covariates including age, BMI, ethnicity, parity, smoking status, gestational weight gain and folate levels.

Results: The data from the first 3412 women with complete B12/folate and OGTT results were analysed (median (range) gestational age $12^{+5}(4^{+3}, 16^{+0})$ and 26^{+4} (15^{+0}, 32^{+1}) weeks respectively). Mean (±SD) age was 30.7±5.2 years, BMI 30.8±7.3 kg/m^2 and 56.0% were obese. 11.5% had GDM and B12 and folate deficiency rates were 10.2% and 0% respectively (p>0.05 in GDM vs. no-GDM). GDM women had similar B12 and folate values to no-GDM (346±151 vs. 357 ± 155 pg/ml and 19.8±12.6 vs. 18.8±12.1 ng/ml respectively, adjusted p>0.05). B12 was negatively correlated with BMI (Pearson's r=-0.24, p<0.001) and inversely related to FBG, after adjustment for covariates including BMI (β=-0.03, p=0.003). There was no association with 2-hour BG. Low B12 values were more predictive of GDM among obese women (mean 314±119 vs. 328±134 pg/ml, adjusted p=0.06).

Conclusions: Early pregnancy B12 values were predictive of high FBG in late gestation. Low B12 levels may be an independent risk factor for GDM, particularly in obese women.

Supported By: UK Medical Research Council (MR/J000094/1)

172-LB

Sleep Disturbances and Daytime Sleepiness in Pregnant Women with Diabetes

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Sleep disturbances in pregnancy are associated with depression, preterm delivery, hypertension, hyperglycemic disorders, and higher rate of cesarean as well as adverse perinatal outcomes. Diabetes is other prevalent condition in pregnancy related to these adverse outcomes, and insulin resistance is a common disruptor. As such, it is important to evaluate the quality of sleep and daytime somnolence in diabetic pregnancy.

Aim: Evaluate sleep quality and excessive daytime sleepiness in pregnancy complicated by diabetes mellitus. This is a cross-sectional study involving 115 pregnant women with diabetes (PWD), gestational age from 10 to 39 weeks. Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI-BR) and daytime sleepiness by the Epworth Sleepiness Scale (ESS). The study was approved by IPADE ethic board (1.801.860). Statistical analysis was performed using the software IBM SPSS.

Results: Poor sleep quality (PSQI>5) was observed in 60,4% of PWD, which is higher them most reported rates for normal pregnancy (60,4% vs. 45% p: 0.01, CI99%. SEDOV, 2017) but similar to reported data on Brazilian overweight pregnant women (65,9%; RIBEIRO 2015). The mean PSQI score was 6.91. Short sleep duration was present in 35,8% (mean sleep duration: 7,2 hours/night). Sleep was disturbed by frequent urination in 66,1% of PWD. Daytime somnolence reported in 20.8% of PWD, and was not related with the quality of sleep. The higher number of parity was independently associated with poor sleep quality [p=0.03; OR=1.74; CI=1.03-2.97]. The presence of obesity, hypertension, educational level, type of diabetes or treatment were non-influential to sleep quality or daytime sleepiness.

Conclusion: Poor sleep quality and excessive daytime sleepiness are frequent in PWD and a higher number of parity is independently associated with poor sleep quality. Given that sleep disturbances are related to adverse outcomes in PWD, we suggest that this group of patients should be the focus of therapeutic measures to improve sleep.

173-LB

Central Obesity in Early Pregnancy Increased Risk for Gestational Diabetes

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Central obesity has been linked to type 2 diabetes but prospective data are limited among pregnant women. We examined the associations of central obesity measures, waist-to-hip ratio (WHR) and waist circumference (WC), in early pregnancy with subsequent gestational diabetes (GDM) risk; and evaluated the potential for insulin resistance markers to mediate the central obesity and GDM association. Within the Pregnancy Environment and Lifestyle Study prospective cohort of 1,750 women, waist and hip circumferences were measured at 10-13 weeks of gestation. In a nested case-control study within the cohort, 115 GDM cases ascertained by Carpenter-Coustan criteria and 230 non-GDM controls had fasting serum insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and adiponectin measurements at weeks 16-19. Multivariable Poisson and conditional logistic regression models were used, adjusting for established risk factors including age ≥35 years, minority race/ethnicity, pre-pregnancy overweight/obesity, family history of diabetes, previous GDM, and preexisting hypertension. Compared to women with WHR <0.85 and no established risk factors, women with WHR ≥0.85 and no risk factors had a 3.74-fold (95% CI 1.92-7.27) increased risk of GDM, and women with WHR ≥0.85 and at least one risk factor had a 6.63-fold (3.48-12.63) increased risk. In the receiver-operating-characteristic curve analysis, WHR significantly improved GDM risk prediction beyond established risk factors (C-statistics 0.796 vs. 0.744, P-for-difference <0.0001). Similar but attenuated results were observed for WC ≥88cm. Insulin, HOMA-IR, and adiponectin levels mediated the WHR-GDM association by 9.0%, 9.6%, and 11.1%, respectively; corresponding mediation proportions for WC-GDM were 40.0%, 41.1%, and 35.4% (all P-values <0.04). Our findings suggest that central obesity in early pregnancy represented a high-risk phenotype for GDM and may help identify at-risk women for early screening, prevention, and treatment.

Supported By: National Institute of Environmental Health Sciences; Eunice Kennedy Shriver National Institute of Child Health and Human Development

174-LB

Plasma Lipidomics and Gestational Diabetes—A Longitudinal Study in a Multiracial Cohort

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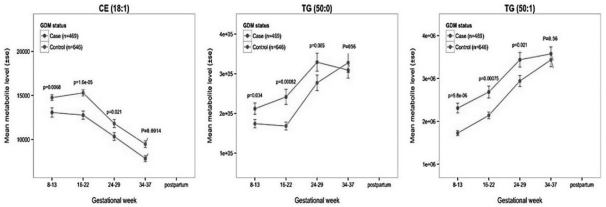
Dyslipidemia is implicated in glucose intolerance. Study of lipidomics in pregnancy may identify novel metabolites that may provide new insights to the etiology of gestational diabetes (GDM). Such studies, however, are sparse. We prospectively investigated lipidomics and GDM risk in a matched case-control study of 107 GDM and 214 non-GDM women nested in the NICHD Fetal Growth Studies. GDM diagnosis was based on Carpenter and Coustan Criteria. We measured plasma lipidome of 420 metabolites at gestational weeks (GW) 8-13, 16-22, 24-29 and 34-37 by gas chromatography mass spectrometry. Associations between individual lipids and GDM were assessed using linear mixed effect models at GW 8-13 and GW 16-22. At GW 8-13, 48 metabolites were significantly related to GDM risk (FDR <0.05). Specifically, the mid-to-long carbon-chain (C) glycerolipids (34-38C diglycerides [DGs]; 48-58C triglycerides [TGs]) were positively related to GDM, while long carbon-chain cholesteryl esters (18-22C CEs) were inversely related. At GW 16-22, 87 metabolites (34-36 C DGs, 48-58C TGs, 18-22C CEs, glycerophospholipids) were significantly related to GDM. Mean levels of top-identified metabolites between cases and controls are presented (Figure). We identified novel metabolites related to GDM with relations differed by lipid structure and the timing of pregnancy. Future studies are warranted to evaluate their roles in GDM early prediction.

Figure.



Mean levels of top identified lipid metabolites between cases and controls by gestational weeks. Standard error of the mean and P-values for two sample t-test to assess the difference in lipid metabolite levels between cases and controls at each specific time point are also shown.

EPIDEMIOLOGY—AGING

175-LB

Gender and Age Variations in Obesity in the Jackson Heart Study

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In 2013-2014 in the U.S., the prevalence of obesity (body mass index (BMI)≥30 kg/m2) among African Americans was 38.2% in men and 57.2% in women, decreasing after age 60 in men but not in women. We used data from the Jackson Heart Study (JHS) to examine gender- and age-variations in prevalence of obesity as defined by BMI, waist circumference (WC), and waist-to-height ratio (WHtR). Based on data from JHS Visit 3 (2009-2013), we conducted a cross-sectional analysis of prevalence of obesity defined by BMI (≥30), WC (>88 cm among women and >102 cm among men), and WHtR (>0.5) by age and gender. We used logistic regression to evaluate associations of obesity defined by BMI (ref: BMI<25), WC (ref: ≤88 cm for women and ≤102 cm for men) and WHtR (ref: ≤ 0.5) with gender and age, adjusted for physical activity. JHS Visit 3 participants (n=3680) were 64% female and had a mean age of 62.2 years. Prevalence of obesity defined by BMI for age groups 20-49, 50-59, and ≥60 years was 67%, 67%, and 59%, respectively (p=0.005) among women; and 58%, 48%, and 40% respectively (p<0.001) among men. For the same age groups, the prevalence of obesity defined by WC was 82%, 83%, and 83%, respectively (p=0.732) for women, and 48%, 51% and 47%, respectively (p=0.540) for men; and by WHtR was 91%, 94%, and 94%, respectively (p=0.127) for women, and 87%, 87%, and 89%, respectively (p<0.001) for men. Age- and physical activity-adjusted odds ratio (aORs) for obesity among women compared to men were 2.2 (95% CI: 1.8-2.7) when based on BMI, 5.2 (95% CI: 4.5-6.1) when based on WC, and 2.0 (95% CI: 1.5-2.5) when based on WHtR. For women, physical activity-aOR for obesity per 1-year increment in age was 0.96 (95% CI: 0.95-0.97) when based on BMI but did not differ from the null when based on WC or WHtR. For men, similar physical activity-aORs for obesity per 1-year increment were observed. For both women and men, prevalence of obesity defined by BMI decreased with age but not when defined by WC or WHtR. Age-related decreases in obesity defined by BMI may not reflect decreases in obesity defined by WHtR.

Supported By: National Institutes of Health

176-LB

National Trends in Type 2 Diabetes Treatment—Comparing Older and Younger Adults

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With expanding therapeutic options for type 2 diabetes, the treatment of older adults requires special care to balance safety and complexity with glucose control. We compared national trends in type 2 diabetes treatment among older (≥65 years) and younger adults (30-64 years) using the 2006-2015 National Ambulatory Medical Care Survey (NAMCS), an annual probability sample of visits to U.S. outpatient providers. We included all visits of patients with type 2 diabetes using ≥1 diabetes medication. Analyses were weighted to yield nationally-representative estimates. In the most recently available data, 2014-2015, there were 23.3 million and 20.1 million annual treated diabetes visits for older and younger adults, respectively. The most frequently used medications in older and younger adult visits were metformin (50.4% vs. 62.3% respectively, p<0.001), sulfonylureas (31.1% vs. 26.7%, p=0.301), and long-acting insulins (30.2% vs. 22.4%, p=0.017). GLP-1 receptor agonists were used in fewer older than younger adult visits (2.9% vs. 6.2%, p=0.004); DPP-4 inhibitor use was similar (12.9% vs. 11.1%). In the past decade, mean diabetes medication counts increased in both older and

younger adult visits (1.47 to 1.54, p-trend=0.046; and 1.53 to 1.67, p-trend 0.052, respectively). Between 2006 and 2015, the proportion of visits with metformin, DPP-4 inhibitors, and insulin increased for both older and younger adults; sulfonylurea and thiazolidinedione use decreased (p<0.05 for all trends). Long-acting insulin use increased markedly in older adults, particularly between 2010-2015 where it rose from 12.5% to 30.2% of older adult visits. In younger adult visits, the increase was modest, from 17.2% to 22.4%, a slower rate of increase than in older adults (p-interaction <0.001).

In conclusion, the outpatient treatment of type 2 diabetes differs between older and younger adults driven in part by a marked increase in the use of long-acting insulin among older adults, which may have implications for risk of hypoglycemia.

Supported By: National Institutes of Health (5T32HL00718040)

177-LB

Incidence and Evolution of Prediabetes among Older Adults—A Population-Based Cohort Study

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Objective: The incidence and evolution of prediabetes in older adults is still unclear. We aimed to estimate the incidence of prediabetes, the rates of prediabetes reverting to normoglycemia or progressing to type 2 diabetes, and to identify possible prognostic factors among older adults with prediabetes.

Methods: In the Swedish National Study on Aging and Care-Kungsholmen Project, 3049 diabetes-free participants aged ≥60 years were examined at baseline (2001-2004), and were followed-up to 12 years (2013-2016). At each wave, type 2 diabetes was ascertained based on self-report, antidiabetic drug use, medical records, or glycated haemoglobin (HbA1c) ≥6.5% (48 mmol/mol). In diabetes-free participants, prediabetes was assessed as HbA1c ≥5.7% (39 mmol/mol), and normoglycemia was defined as HbA1c <5.7%. Data were analysed with Poisson regression and multinomial logistic regression.

Results: During 12 years follow-up, among 1972 (64.7%) participants with normoglycemia, 505 (25.6%) developed prediabetes (incidence=4.3/100 person-years, 95% CI 3.9-4.8). Of the 1077 (35.3%) participants with prediabetes at baseline, 204 (18.9%) reverted to normoglycemia (reversion rate=3.1/100 person-years, 95% CI: 2.6-3.6) and 119 (11.0%) progressed to type 2 diabetes (progression rate=1.7/100 person-years, 95% CI: 1.3-2.1). The reversal to normoglycemia was significantly associated with lower systolic blood pressure and weight loss, while, obesity and weight gain were risk factors for progression to type 2 diabetes.

Conclusions: The incidence of prediabetes is high (about 26%) among older adults. Around 19% of people with prediabetes may revert to normoglycemia and 11% progress to type 2 diabetes. Weight change and systolic blood pressure may play a role in such evolution.

Supported By: Swedish Ministry of Health and Social Affairs; Participating County Councils and Municipalities of Sweden; Swedish Research Council; China Scholarship Council; Emil och Wera Cornells Stiftelse

178-LB

One-Year Follow-Up of Medicare Advantage Enrollees with Type 2 Diabetes and an Initial Elevated HbA1c Value

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Introduction: Blood glucose control is critical to slowing the onset of T2DM complications for individuals. National guidelines encourage clinicians and payers to ensure patient HbA1c lab results are less than 8.0%. Understanding the longitudinal patterns of HbA1c control among individuals with lab results over 8.0% is therefore an important undertaking. This study aims to characterize the proportion of individuals returning to HbA1c control within a one year period after an uncontrolled result.

Population and Study Design: Medicare Advantage (MA) patients with a large, national health and wellness company residing in Florida with a diagnosis of type 2 diabetes were included if they had an HbA1c lab value greater than or equal to 8.0% in 2016. Patients had at least one year of continuous coverage prior to the uncontrolled result and were followed until disenrollment, death, or a controlled HbA1c lab value, up to a maximum of one year. Cox regression stratified by initial HbA1c value (8.0-8.9%, 9.0-9.9%, 10.0-10.9%, 11.0-11.9%, 12.0%+) was used to assess the adjusted proportion of persons returning to control over the one year follow-up period. Confounders in the model included: demographic factors, supply of insulin, and comorbidities.

Results: The study cohort consisted of 28,026 persons who met the inclusion criteria (50.7% female, 57.4% white, mean age 71.9 years). Overall, 50.5% (95% CI: 50.0%, 51.1%) of persons achieved HbA1c control within the 1 year follow-up. Inability to return to control was driven by higher initial Hba1c [8.0-8.9% return rate: 61.6% (60.9%, 62.4%) vs. 9.0-9.9%: 39.4% (38.1%, 40.7%) vs. 12.0+%: 27.7% (25.1%, 30.2%)].

Implications: MA patients with HbA1c results greater than 9.0% experienced challenges resuming controlled status suggesting increased attention to this population may be warranted.

EPIDEMIOLOGY—CARDIOVASCULAR DISEASE

179-LB

Incident Silent Myocardial Infarction among People with Prediabetes—Results from Four Longitudinal Cohort Studies

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Approximately 45% of first of myocardial infarctions (MI) are silent. People with diabetes are more likely to have MIs than those without diabetes. Little is known, however, about silent MIs (SMIs) among those with prediabetes. The prognosis of SMIs is similar to clinical MIs making timely detection imperative. We aimed to assess the association between prediabetes and incident SMI in four long duration cohort studies. We pooled data from the following studies: Cardiovascular Health, Atherosclerotic Risk in Communities, Health Aging and Body Composition, and Multi-Ethnic Study of Atherosclerosis (n=30,898). Population characteristics were: mean age 61.3 years, 45% male, 66.4% white, 40.0% had hypertension and 35.3% had hyperlipidemia. Diabetes status was based on fasting glucose (100-125mg/dL=prediabetes and >=126mg/dL=diabetes). Participants were also defined as having diabetes if they were taking medications for diabetes or reported a previous diagnosis. At baseline, 36% did not have diabetes, 50% had prediabetes and 14% had diabetes. Among participants with prediabetes, 3% experienced SMI over a mean follow-up of 9.6 years compared with 2% among those without diabetes. In Cox Proportional Hazards Models, we found an increased risk of incident SMI among those with prediabetes compared to those without diabetes (Hazard Ratio=1.25; 95% CI: 1.04-1.5, p=0.02), adjusting for age, sex, race, smoking status, hypertension, and high cholesterol. Significant baseline predictors of SMI in addition to having prediabetes included being male, older age, current smoking, and hypertension. People with prediabetes, comprising 50% of these cohort study populations, may be at increased risk for SMI, and could benefit from increased focus on prevention and treatment of cardiovascular risk factors.

180-LB

Current Smoking—An Independent Predictor of Elevated A1C in Adults with Type 2 Diabetes

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While the cardiovascular risk of smoking is well documented in persons with type 2 diabetes (T2D), less is known about the impact of smoking on glycemic control in this population. The purpose of this study was to determine predictors, including smoking status, of elevated A1C in a sample of adults with T2D. This secondary analysis used baseline data from adults (N=256; 48% male) recruited for the Diabetes Sleep Treatment Trial. Participants were queried on demographics, diabetes-related distress (Problem Areas in Diabetes), diabetes knowledge (Diabetes Knowledge Test), and smoking behavior (never/former/current). A clinical assessment obtained height and weight to calculate BMI (kg/m^2) and A1C. Non-smokers (53%; n=136) and former smokers (28%; n=72) were similar (p ≥.05) in terms of age, A1C, BMI, diabetes-related distress and knowledge; however, current smokers (19%; n=48) were less obese (BMI 33.3 [SD 6.5] vs. 36.1 [SD 6.9] kg/m^2, p=.016), more likely to be non-Caucasian, have lower education, more financial difficulty, higher diabetes-related distress, and lower diabetes knowledge than non-smokers (all p-values <.05). Using hierarchical regression diabetes duration, diabetes distress, and current smoking status were identified as predictors of higher A1C. We conclude smoking is associated with lower BMI and higher A1C, providing further support for counseling for smoking cessation in adults with T2D.

Table. Final Model of Regression to Predict Glucose Control (A1C).

Variable	Unstandardized b	Std. Error	Beta	Sig.	95% CI for b	
					Lower	Upper
Duration of diabetes	-.458	.220	-.126	.038	-.890	-.026
Diabetes-related distress	.020	.005	.230	<.001	.009	.030
Current Smoker	.686	.283	.150	.010	.182	1.305

N=256; Duration of diabetes=<10 years vs.10 or more years; Diabetes-related distress=scores on Problem Areas in Diabetes (PAID) questionnaire; Current smoker compared with non-smoker or former smoker. Sex, race, financial difficulty, education, and former smoking status not significant; removed from final model. Model Summary: Adj. R^2=.098; p<.001.

Supported By: National Institutes of Health

181-LB

Blood Pressure and Mortality in U.S. Adults with Diabetes

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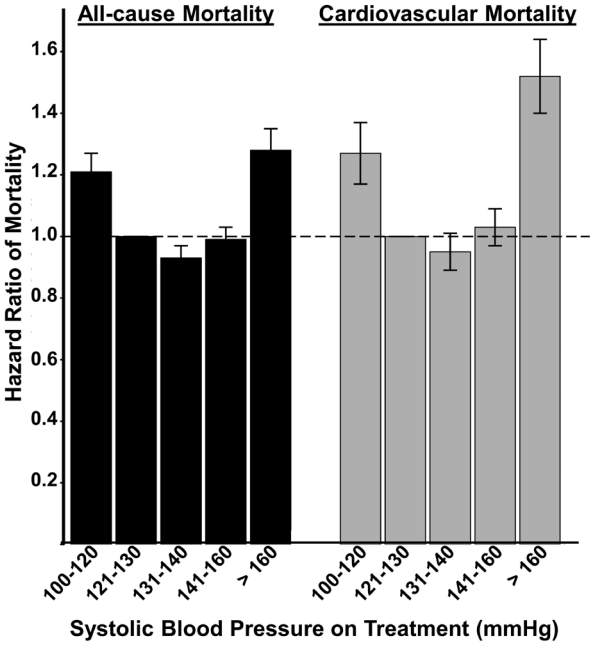
Recent clinical trials have led to revised hypertension guidelines, but the relationship between blood pressure (BP) control and mortality in diabetes patients receiving routine care has not been described in a contemporary national U.S. cohort. We studied 130,192 primary care patients in the Veterans Health Administration with diabetes (ICD-9 codes 250.xx + outpatient diabetes prescription), newly started on a BP medication in 2003-2005, and with a mean systolic BP (SBP) >130 mmHg in the year prior to BP drug initiation. Mean on-treatment outpatient SBP in the 2nd year after BP drug initiation was the primary exposure. All-cause and cardiovascular (CV) mortality through 2014 were the primary outcomes; mean follow-up was 9 years. We estimated associations between SBP and mortality using multivariable Cox proportional hazards regression, adjusting for age, sex, race, comorbidities, HbA1c, number of BP drugs, and CV risk factors. Relative to SBP 121-130 mmHg, all-cause and CV mortality were significantly higher in those with an SBP of 100-120 mmHg or >160 mmHg on treatment. All-cause mortality was lowest in those with an SBP of 131-140 mmHg; CV mortality did not differ significantly between those with an SBP between 121 and 160 mmHg.

Conclusions: There was only minor variation in mortality rates for BPs from 121 to 160 mmHg in patients with diabetes and hypertension in routine clinical care, but mortality was higher in those with treated BP <120 mmHg or >160 mmHg.

Figure.



Supported By: American Heart Association; U.S. Department of Veterans Affairs; National Institutes of Health

EPIDEMIOLOGY—CLINICAL—DIAGNOSIS AND SCREENING

182-LB

Characteristics of Adult vs. Childhood-Onset Type 1 Diabetes (T1D) in the T1D Exchange Registry

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We aimed to compare diagnosis characteristics, diabetes management, and comorbidities to identify differences between childhood and adult onset T1D. This analysis was performed in the T1D Exchange registry across the following age at diagnosis groups: <10, 10-17, 18-24, 25-39, and ≥40 years. Diagnosis characteristics were compared using a regression model adjusting for possible confounders. Current characteristics came from the participant's most recent clinic exam and were restricted to those with current age ≥25 years and T1D duration ≥1 year. For each outcome, two models were fit, one including adjustment for current age and one including adjustment for T1D duration. Age at diagnosis was associated with an outcome if an association was present and the direction of effect was consistent across models. DKA at diagnosis was more common at childhood onset. The use of oral agents preceding diagnosis was higher in participants diagnosed as adults, likely due to initial misdiagnosis as type 2 (Table). Current pump use and celiac disease were more frequent in participants diagnosed at younger ages; however, HbA1c, CGM use, insulin requirements, and other comorbidities were not significantly different across age at diagnosis groups. A better understanding of differences in persons diagnosed with T1D as children vs. adults is needed to understand prognosis and subtype-specific therapeutic approaches.

Table: Diagnosis Characteristics, Diabetes Management, and Comorbidities by Age at Diagnosis

Diagnosis Characteristics (N=20,148)					
	Age at Diagnosis				
	<10 yrs	10-17 yrs	18-24 yrs	25-39 yrs	≥40 yrs
N	11474	5253	1126	1499	796
DKA at Diagnosis[a] %	40%	40%	30%	24%	19%
Oral Agent Use Preceding Diagnosis[a] %	-	1%	15%	37%	58%
Current Characteristics (N=6,749) (Cohort restricted to current age ≥25 years and diabetes duration ≥1 year)					
	Age at Diagnosis				
	<10 yrs	10-17 yrs	18-24 yrs	25-39 yrs	≥40 yrs
N	1535	1862	1065	1495	792
Current Age *Mean ± SD*	40 ± 12	43 ± 14	47 ± 14	54 ± 12	65 ± 9
T1D Duration *Mean ± SD*	35 ± 12	30 ± 14	27 ± 14	23 ± 12	16 ± 8
HbA1c *Mean ± SD*	7.8 ± 1.3	7.7 ± 1.3	7.7 ± 1.3	7.8 ± 1.3	7.8 ± 1.3
Pump Use[b] %	70%	68%	64%	61%	54%
CGM Use %	36%	36%	34%	33%	25%
Total Daily Dose U/Kg *Mean ± SD*	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3
Comorbidities %					
Thyroid Disease	32%	29%	30%	31%	36%
Celiac Disease[b]	6%	3%	3%	2%	2%
CVD	10%	10%	12%	13%	14%
Hypertension	38%	41%	41%	49%	59%
Nephropathy	14%	12%	10%	8%	9%
Retinopathy	24%	19%	17%	16%	8%

a. P-value for age at diagnosis group <0.01
b. P-value for age at diagnosis group <0.01 in both models (one adjusting for age and one adjusting for duration) and the direction of the effect is consistent

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

183-LB

Hemoglobin A1c (A1c) Genetics Contributes to A1c/Glucose Mismatches in the Multiethnic VA Million Veteran Program (MVP)

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A1c accuracy is important for diabetes management but mismatches in A1c relative to underlying glucose can impede care. Since the basis for mismatches is poorly understood, we assessed the contributions of 22 A1c variants identified in GWAS that were associated with erythrocytic traits but not glycemia. 73,128 MVP patients had continuity of care and monitoring: >1 PCP visit, >1 outpatient random plasma glucose (RPG) and >1 A1c within each of 3 consecutive two-year periods. They had mean age 67 years

and BMI 31 kgm^{-2}; 71% were white and 21% were black; 51% had diabetes (ICD 9 codes and diabetes Rx). Mismatches were defined by the hemoglobin glycation index (HGI) calculated from regression residuals of mean A1c on mean RPG within each period, averaged over the 3 periods. We evaluated the associations with HGI of each A1c variant and a genetic risk score (GRS; sum of alleles weighted by their reported A1c effect sizes) by race. Mean HGI was -0.07% A1c units in whites and 0.2% in blacks. Of the 22 variants, 15 at 13 loci were associated with HGI ($P<5 \times 10^{-8}$, ANK1, CNTN5, ERAL1, G6PD, HBS1L/MYB, HK1, HIST1H4A/HFE, MYO9B, SENP1, SPTA1, SYN2, TMPRSS6 and PEIZO1). GRS was associated with HGI (whites $P=2 \times 10^{-189}$, blacks $P=1 \times 10^{-233}$) and explained HGI variance (whites 1.7%, blacks 5.1%), especially in those without diabetes (whites 3.5%, blacks 11.4%). People in the lowest 10% of GRS had a glucose-independent fall in A1c (mean HGI, whites -0.19%, blacks -0.31% A1c units) while those in the highest 10% of GRS had the opposite (mean HGI, whites 0.06%, blacks 0.29%). The variants with the largest effects on HGI were rs1800562/HIST1H4A/HFE [mean HGI, AA: -0.37%, GG: -0.06% A1c units] in whites and rs1050828/G6PD [mean HGI, T: -0.31%; C: 0.29% A1c units] in black men.

Conclusions: HGI is higher in blacks than whites - a glucose-independent higher A1c. Common genetic variation explains 2-11% of the variance in HGI. Accounting for genetic variation in A1c may improve its accuracy in guiding diabetes care.

184-LB

The Association of Impaired Fasting Glucose and Serum Fibroblast Growth Factor-21 (FGF-21)

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Prediabetes includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) and there is a strong probability that prediabetes will lead to diabetes mellitus (DM). Serum fibroblast growth factor 21 (FGF-21) is known to increase as a compensatory response to metabolic imbalance under conditions such as obesity, metabolic syndrome, and DM. This study aimed to identify the relationship of serum FGF-21 to prediabetes and to biomarkers of related metabolic diseases. Three hundred five Korean adult patients participated in a cohort study from June 2012 to December 2015. Study subjects comprised of those with normal glucose tolerance(n=165), prediabetes(IFG, IGT, n=87) and type 2 diabetes(n=54). The biochemical parameters were analyzed using auto-analyzer, and the level of FGF-21 was estimated using an ELISA kit. The analysis revealed that FGF-21 levels were significantly higher in the Prediabetes group compared to those in the normal group(193.94±10.62, 343.49±60.94)(P=0.004). One-way ANCOVA was conducted on the correlations between serum FGF-21 levels and other parameters, dyslipidemia(F=7.428, P=0.007), HbA1c(F=11.874, P=0.001) was show statistical significance.

In conclusion, our results revealed that serum FGF-21 level serves as a marker predicting IFG.

185-LB

The Association between Inpatient Hyperglycemia and Thirty-Day Mortality Is Modified by Type 2 Diabetes History

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Background: There is a well-established association between inpatient hyperglycemia (HG) and mortality. However, evidence is inconsistent regarding whether this association is differential among those with and without type 2 diabetes mellitus (T2DM). Most studies results are limited by selected patient populations and many did not adjust for comorbidities. We aimed to examine if the association between inpatient HG and 30-day mortality is modified by T2DM status among a population-based cohort with over 15 years of medical history.

Methods: A retrospective cohort study of individuals who were first hospitalized between 2012-2015. Thirty-day mortality was assessed during the inpatient stay up to 30 days post discharge. The adjusted association between inpatient HG and mortality was first assessed with logistic regression models. Then, four interaction terms were entered into the model to assess if the association of HG with mortality significantly differed by pre-hospital glycemic status (T2DM, prediabetes, unscreened and non-T2DM).

Results: The multivariate model demonstrated a 2.18-fold risk of mortality associated with HG (OR [95% CI]: 2.18 [2.07-2.29]). After including the interaction terms between HG and pre-hospital glycemic status the model yielded the following results: the odds of mortality, compared to T2DM group with HG, were 1.43 [1.27-1.62] in non-T2DM group, 1.32 [1.16-1.52] in prediabetes group, and 1.28 [1.02-1.60] in unscreened group. This relationship remained robust throughout all sensitivity analyses that we conducted.

Conclusion: The findings indicate that inpatient HG is positively associated with mortality and the group without T2DM is at highest risk. Glucose targets should be reconsidered for this group during their inpatient stay and their transition to the outpatient setting needs to be more closely monitored. Prospective research is needed to examine the efficacy of lowering their glucose targets on short-term mortality.

Supported By: D-Cure

186-LB

The Importance of Metabolic Syndrome in Patient Progression to Type 2 Diabetes Mellitus

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Introduction: Type 2 diabetes mellitus (T2DM) is a common chronic condition associated with significant risk of morbidity and mortality. Metabolic syndrome (MetS) is a chronic prevalent condition, but rarely documented in administrative data. A positive MetS finding comes from tracking five clinical dimensions, and employing a minimum three condition threshold. The aim of this study was to validate a new administrative data MetS algorithm by showing its relevance in tracking progression to T2DM.

Methods: A cohort of 1,321,314 persons enrolled for 3 years in a Medicare Advantage health and wellness company with no evidence of diabetes in the first year were tracked in the subsequent 2 years. Demographic information along with evidence of prediabetes from administrative claims and lab data were documented for the first year. Algorithms to detect MetS and Charlson Comorbidity Index (CCI) were applied to the first year data. For the subsequent 2 years, ICD-10 diagnostic information from administrative data was tracked to identify individuals who progressed into T2DM. Descriptive statistics and Poisson regression analysis were used to assess correlation between first year data and subsequent relative risk for T2DM.

Results: The study population was 87.3% white, 56.4% female, mean age of 70.6, and an overall T2DM progression rate of 8.63%. In the first year, 79.3% had no MetS and no prediabetes (NMNP), 6.9% had MetS but no prediabetes (MNP), 6.8% had no MetS but with prediabetes (NMP), and 7.1% had MetS with prediabetes (MP). Compared to NMNP, the MNP group had an elevated risk of progression to T2DM (RR 1.63 | 95% CL: 1.60, 1.67), as did NMP (1.73 | 1.70, 1.76), and MP (2.47 | 2.43, 2.51). Nonwhite races (1.31 to 1.52), male (1.21), and higher CCI scores (1.02 to 1.45) all were associated with elevated and significant relative risk of T2DM.

Conclusion: Our findings reveal that use of MetS diagnosis and consideration of patient demographics and CCI risk score yield valuable information regarding risk of T2DM.

EPIDEMIOLOGY—DIABETES COMPLICATIONS

187-LB

Risk Profiles for Microvascular and Macrovascular Disease at Baseline in the Glycemia Reduction Approaches in Diabetes—A Comparative Effectiveness (GRADE) Study

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Microvascular and macrovascular complications drive morbidity, mortality, and health care costs in type 2 diabetes (T2D). The GRADE trial enrolled 5047 participants with T2D <10 years and treated with metformin only, with creatinine <1.4 (women) <1.5 (men) mg/dL, and HbA1c 6.8-8.6% at enrollment. The enrolled population was 36% female, 57±10 years old (mean±SD), had T2D duration 4.2±2.8 years, and HbA1c 8.0±1.0%. Baseline prevalence was 1.0% for retinopathy (self-report), 15.8% for moderately increased albuminuria (albumin/creatinine ratio 31-300 mg/g), 2.4% for decreased eGFR (30-60 ml/minutes/1.73m^2), 41.8% for neuropathy (Michigan Neuropathy Screening Instrument clinical score >2), 5.1% for myocardial infarction (self-report); and 2.0% for stroke (self-report). The Table describes age- and sex-adjusted associations between individual risk factors and complications as odds ratios comparing the presence vs. absence of the complication. Notable features include associations of HbA1c, obesity and blood pressure with micro- but not macrovascular disease; association of triglycerides with microvascular disease only; and associations of smoking and HDL with both micro- and macrovascular disease. These data reveal unexpected patterns

in the clustering of risk factors with complications in GRADE patients with short T2D duration.

Table.

	ACR≥30		eGFR<60		Retinopathy		MNSI>2		MI		Stroke	
	OR	p	OR	p	OR	p	OR	p	OR	p	OR	p
HBA1C at screening (%)	1.038	0.3066	0.658	**0.0030**	0.837	0.2854	1.094	**0.0017**	0.996	0.9591	0.937	0.5605
BMI (kg/m2)	1.040	**<0.0001**	1.044	**0.0029**	0.980	0.3886	1.045	**<0.0001**	0.996	0.7193	0.996	0.8481
Waist Circumference (cm)	1.017	**<0.0001**	1.011	0.0757	0.991	0.3430	1.022	**<0.0001**	1.000	0.9365	1.001	0.7997
Smoking former*	1.036	0.6877	0.874	0.5251	0.426	**0.0293**	1.065	0.3473	1.546	**0.0043**	1.101	0.6799
Smoking current*	1.500	**0.0002**	1.154	0.6439	1.230	0.5770	1.238	**0.0156**	2.492	**<0.0001**	2.180	**0.0036**
Systolic BP (mm Hg)	1.021	**<0.0001**	0.995	0.4783	1.020	**0.0235**	1.002	0.1937	0.999	0.8298	1.010	0.0956
Diastolic BP (mm Hg)	1.022	**<0.0001**	0.994	0.5897	1.016	0.2746	0.998	0.6063	0.994	0.4131	1.011	0.2546
LDLc (mg/dl) **	1.001	0.2902	0.999	0.6803	1.009	**0.0437**	0.999	0.2662	0.996	0.1526	1.004	0.2398
HDLc (mg/dl)	0.989	**0.0021**	0.980	**0.0255**	1.019	0.0787	0.993	0.0174	0.976	**0.0003**	1.004	0.5854
(log) Triglycerides (mg/dl)	1.477	**<0.0001**	1.589	**0.0064**	0.798	0.3734	1.115	**0.0315**	1.152	0.2142	0.869	0.4324

OR=Odds Ratio per unit increase in a quantitative covariate or for the stated category versus the complement. *Versus never smoking. ** Further adjusted for statin exposure.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

Epidemiology/ Genetics **POSTERS**

188-LB

Serum Apolipoprotein C-III and Cardiovascular Events in Type 1 Diabetes

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Background: Apolipoproteins Apo-B, Apo-C-III, and Apo-E are atherogenic and are associated with diabetic dyslipidemia and cardiovascular disease (CVD). Apolipoprotein-defined lipoprotein subclasses (ADLS) also show associations with CVD, but prospective associations of these detailed metrics with CVD in people with type 1 diabetes (T1DM) have not been explored.

Objective: Prospective associations of serum apolipoproteins and ADLS with CVD and major atherosclerotic cardiovascular events (MACE: composite of CVD death, nonfatal myocardial infraction or nonfatal stroke) in T1DM.

Methods: Serum apolipoproteins and ADLS (14 biomarkers in total) measured in sera (1997-2000) in a subset (n=465) of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Prospective associations of CVD and MACE over 5942 and 6180 patient-years follow-up, respectively, were investigated using Cox proportional hazards models unadjusted and adjusted for risk factors.

Results: During 15 years follow-up, 50 CVD and 24 MACE events occurred. Significant positive univariate associations for CVD were: Lp-B, Apo-B, Apo-C-III (total, heparin precipitate (HP), i.e., Apo-C-III in VLDL, and heparin soluble (HS), i.e., Apo-C-III in HDL) and Lp-B:C; for MACE: Apo-C-III sub fractions (total, Apo-C-III-HP, and Apo-C-III-HS). Adjusting for sex, age, HbA1c, systolic blood pressure, pulse rate, LDL-cholesterol, and triglycerides: for CVD, Apo-C-III-HS remained significant (HR (95% CI): 1.18 (1.03, 1.35); P=0.01). For MACE, total Apo-C-III and Apo-C-III-HS persisted when adjusted for age, HbA1c and LDL [1.11 (1.01, 1.22); P=0.02, and 1.22 (1.02, 1.45); P=0.02, respectively], but not for age, HbA1c and (log) triglycerides. No significant associations of other ADLS, Apo-A-I, A-II and Apo-E with CVD/MACE were observed.

Conclusions: Total serum Apo-C-III and Apo-C-III in HDL and Apo-B-containing lipoproteins may serve as predictive biomarkers for CVD events in T1DM adults.

189-LB

Uric Acid and Cardiovascular Disease in Type 1 Diabetes

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Background: Serum uric acid (UA) is associated with the pathogenesis of diabetes complications, including cardiovascular disease (CVD) and kidney injury. Current epidemiological evidence is limited regarding the association between UA and the development of CVD in type 1 diabetes mellitus (T1DM).

Objective: To examine associations of serum UA with CVD and major atherosclerotic cardiovascular events (MACE) in T1DM.

Methods: UA was measured in sera (1997-2000) from a subset of participants (n=973; males=540, females=433) in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Subsequent CVD events were adjudicated by a review committee masked to DCCT assignment and HbA1c levels, and defined as the time to the first of any of the following: non-fatal myocardial infarction (MI) or stroke, CVD death, silent MI on annual ECG, angina confirmed by ischemic changes with exercise tolerance testing, congestive heart failure, or revascularization; MACE were defined as a composite of CVD death, nonfatal MI, or stroke. Cox proportional hazards models were used to evaluate prospectively the effect of UA as a fixed covariate on CVD and MACE, separately by gender, and adjusted for age and HbA1c.

Results: Over 15 years follow-up, there were 201 adjudicated CVD events among 110 participants (HR=1.10 per 1 mg/dl change in UA, 95% CI 0.93-1.30); 61 males experienced 96 events (HR=1.15, 95% CI 0.90-1.46) and 49 females, 105 events (HR=1.17, 95% CI 0.88-1.56). There were 62 adjudicated MACE among 53 participants (HR=1.18, 95% CI 0.93-1.49); 29 males experienced 31 events (HR=1.10, 95% CI 0.77-1.58) and 24 females, 31 events (HR=1.47, 95% CI 1.01-2.14). No significant associations between quartiles of UA and either CVD or MACE were observed in either sex.

Conclusions: Our results show UA may not serve as a predictive biomarker for CVD events in T1DM adults. Sex-specific associations with MACE deserve further investigation.

190-LB

National Trends and Outcomes in Patients with Uncontrolled Diabetes and Related Complications

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Introduction: Patients with uncontrolled DM can present to the hospital with life threatening complications: DKA, hyperosmolar syndrome and coma. There is a paucity of data on the contemporary trends and outcomes of uncontrolled diabetes related hospitalizations (UDH).

Methods: We analyzed the 2003 to 2011 Nationwide Inpatient Sample database (https://www.hcup-us.ahrq.gov) to examine the trends and in-hospital outcomes in patients with UDH aged ≥18 years in the U.S. All patients with primary diagnosis of uncontrolled DM were identified using ICD-9 CM codes- 250.02-250.03, 250.10 -250.13, 250.20 -250.23 and 250.3.

Results: From 2003 to 2011; 1,690,457 patients had UDH. The yearly hospitalization increased from 171,408 (2003) to 216,965 (2011)(ptrend <0.001). Breakdown by sex, race, income and insurance status are in Table 1. The in-hospital mortality decreased from 0.8% to 0.4% (adjusted odds ratio [per year] 0.90; 95% confidence interval 0.89 to 0.91; ptrend <0.001). The average hospital charges increased from $14,370 to $22,897 (ptrend <0.001), whereas the average length of stay decreased from 3.9 to 3.4 days (ptrend <0.001).

Conclusion: Hospitalizations with UDH increased by ~25% in all U.S demographic groups between 2003 and 2011. However, outcomes improved during the same period, with decreases in length of stay and risk-adjusted in-hospital mortality.

Table 1. Demographic Pattern in Diabetes Related Hospitalizations

	2003	2011	p-value
Total admissions	171,408	216,965	<0.001
Age (y)	46.6+-18.5	45.1+17.8	<0.001
Females	51.4%	48.9%	<0.001
Race			<0.001
Whites	50.9%	52.8%	
Blacks	29.7%	29.6%	
Others	19.4%	17.6%	
Insurance			<0.001
Private	29.9%	25.2%	
Public	51.1%	51.5%	
Others	19.0%	23.3%	
Median household income			<0.001
0-50th percentile	62.7%	65.6%	
50th-100th percentile	37.3%	34.4%	

ADA-Supported Research

191-LB

The Rates of Overtreatment and Deintensification of Antidiabetic and Antihypertensive Medications in Patients with Diabetes Mellitus

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Background: Targeting better HbA1c and blood pressure (BP) goals may endanger older adults with type 2 diabetes mellitus (T2DM) for a number of risks. Overtreatment of T2DM and hypertension (HTN) is a trending issue but awareness and attitudes of physicians need to be explored.

Objective: To assess the rates and predictors of overtreatment and undertreatment of glycemia and blood pressure in older adults with T2DM. Treatment deintensification or intensification by the physicians were also investigated.

Method: Data from older adults (≥65 years) enrolled in a large nationwide T2DM survey in 2017 across Turkey were analyzed. Overtreatment was defined as HbA1c <6.5% plus use of ≥2 oral hypoglycemics or insulin, and systolic BP <120 mmHg or diastolic BP <65 mmHg plus use of ≥2 drugs). Undertreatment was defined as HbA1c >9% at all, and SBP >140 mmHg or DBP >90 mmHg plus use of <3 drugs. Deintensification or intensification rates were calculated according to treatment modification by the physicians.

Results: A total of 1276 patients were included. The overtreatment rates for glycemia and BP were 9.8% and 5.9%, whereas undertreatment rates were 14.2% and 17.7%, respectively. In the adjusted model, use of oral hypoglycemics only (OR:3.1, 95% CI:1.9-5.3) and follow-up at a private clinic (OR:2.2, 95% CI:1.2-3.9) were the predictors of glycemia overtreatment. Presence of microvascular complications (OR:2.0, 95% CI:1.1-3.5) was the only predictor of BP overtreatment. The deintensification and intensification rates for glycemia were 25% and 75.7% respectively, and for the BP 10.9% and 9.0% respectively.

Conclusion: The overtreatment rates of diabetes and BP in Turkish older adults with T2DM were consistent with the previous studies, while the undertreatment rates were much higher. Doctors seem to feel more comfortable to intensify glycemic management and largely ignore BP control. The results warrant enforced measures to improve care of older adults with T2DM.

Supported By: Society of Endocrinology and Metabolism of Turkey

EPIDEMIOLOGY—NUTRITION

192-LB

The Mediterranean Diet and Two-Year Changes in Cognitive Function in Puerto Rican Adults With vs. Without Type 2 Diabetes

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People with type 2 diabetes (T2D), especially uncontrolled T2D, have high risk of cognitive decline. The role of a Mediterranean diet on cognitive function has not been assessed for adults with vs. without T2D within the same population. We aimed to determine associations of a Mediterranean diet score (MeDS) with 2 year changes in cognitive function by T2D status and by glycemic control status. We used data from the Boston Puerto Rican Health Study (mean (SD) age= 57.2 (7.6) y; n=711 without T2D; n=465 with T2D defined as fasting plasma glucose ≥ 126 mg/dL or medication use). Glycemic control at baseline was categorized as uncontrolled (hemoglobin A1c ≥7%; 74% of T2D sample)) vs. controlled (26%). Two-y changes in glycemic control were defined as stable/improved (32%) vs. poor/declined (68%). Baseline MeDS ranged from 0-9 by scoring participants within the sex-specific healthy median intake of 9 foods and nutrients. The primary outcome was 2 year change in global cognitive function z-score, which included 7 cognitive tests. Adjusting for baseline sociodemographic and lifestyle factors, comorbidities, and baseline measure, MeDS was positively associated with 2 year change in global cognitive function in adults with T2D ($\beta \pm SE=0.027 \pm 0.011$; p=0.016) but not without T2D (-0.002 ± 0.008; p=0.80). Similar results were noted for single cognitive tests (i.e., mini-mental state examination, word recognition, digit span, clock drawing). Better global cognitive function over 2 years with higher MeDS was noted with glycemic control at baseline (0.062 ± 0.020; p=0.004) or stable/improved over 2 years (0.053 ± 0.019; p=0.007), but not for uncontrolled or poor/declined glycemic control. Adhering to a Mediterranean diet is associated with positive 2 year changes in cognitive function among adults with T2D. Glycemic control further sustains these benefits, suggesting that both a healthy Mediterranean diet and effective clinical management may help preserve optimal cognitive function in adults with T2D.

Supported By: National Heart, Lung, and Blood Institute (K01HL120951, P50-HL105185); National Institute on Aging (P01AG023394)

EPIDEMIOLOGY—OTHER

193-LB

Real-World Distribution of Hematocrit Values in the Netherlands and the Czech Republic—A Cross-Sectional Study

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Many self-monitoring of blood glucose (SMBG)-systems demonstrate positive glucose bias at lower and negative bias at higher hematocrit (HCT) levels. Variations can thus lead to measurement errors and possibly to over- or underdosage of insulin. ISO 15197:2013 demands that manufacturers publish HCT-ranges within which BG-meters perform within certain tolerance limits. But how wide should these ranges be? In this cross-sectional study, we collect real-world data from hospital outpatients to assess the frequency of out-of-range HCT-values compared to healthy individuals.

Data from more than 1 million patients were collected from hospitals in Leeuwarden (NL) and Prague (CZ) and stratified by outpatient status, sex and age. Data were compared to common HCT labelled range limits and data from 1780 healthy Czech subjects to assess differences in distribution.

Compared to healthy subjects, outpatients from Prague were distributed with significantly higher dispersion of values. Independent of the location, low HCT-values are common in age groups known to also have high prevalence of diabetes.

Real-world data indicate that BG-meters labelled to perform only within the frequently used 30-55% range would leave thousands of patients at risk of falsely high or low results. Adequate SMBG-systems should be chosen carefully, particularly for patients with increased and decreased HCT-values.

Table.

Age group	Location	Total number Female/Male	Number <30% HCT F/M	Percentage <30% HCT F/M	Prevalence of Diabetes (Eurostat) F/M
55-64	NL	27329/33546	1043/1324	3.8%/3.9%	6.2%/10.3%
55-64	CZ	22212/19035	748/970	3.4%/5.1%	10.9%/11.6%
65-74	NL	32004/44181	1958/2849	6.1%/6.4%	12.0%/15.0%
65-74	CZ	33598/31321	1987/1924	5.9%/6.1%	18.1%/19.5%
75+	NL	42435/45080	3431/4535	8.1%/10.1%	14.4%/19.7%
75+	CZ	26645/22706	1923/2041	7.2%/9.0%	27.3%/25.3%

194-LB

Impact of Longitudinal Changes in Metabolic Syndrome Status Over Two Years on 10-Year Incident Type 2 Diabetes Mellitus

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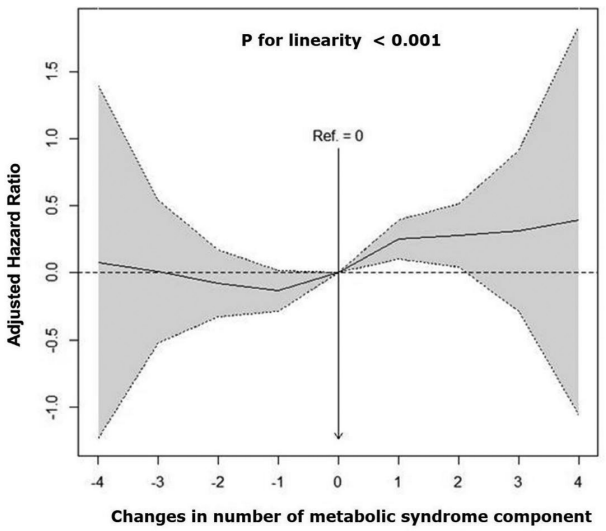
Aim: Metabolic syndrome (MetS) is a known predictor of diabetes mellitus (DM), but whether longitudinal changes in MetS status modify the risk for DM remains unclear. We investigated whether temporal changes in MetS status over two years modify the 10-year risk of incident DM.

Methods: A prospective cohort study was conducted in 7,317 adults aged 40-70 years without DM at baseline. Subjects were categorized into four groups based on repeated longitudinal assessment of MetS status over two years: non-MetS, resolved MetS, incident MetS, and persistent MetS. The hazard ratio (HR) of new-onset DM during 10 years was calculated in each group using Cox models.

Results: During the 10-year follow-up, 1,099 (15.0%) developed DM. Compared to the non-MetS group, the fully adjusted hazard ratios for new-onset DM were 1.27 (1.01-1.61) in the resolved MetS group, 1.78 (1.43-2.22) in the incident MetS group, and 1.85 (1.52-2.26) in the persistent MetS group (P for trend <0.001). The risk of DM in subjects with resolved MetS was attenuated compared to those with persistent MetS over two years (P<0.001). The adjusted hazard ratio for 10-year developing DM gradually increased as the number of MetS components increased two years later (Figure 1).

Conclusion: We found that discrete longitudinal changes pattern in MetS status over two years associated with 10-year risk of DM. These findings suggest that monitoring change of MetS status and controlling it may be important for risk prediction of DM.

Figure 1.



195-LB

Lower Risk of Dementia in Elderly Patients Initiated on Dipeptidyl Peptidase-4 Inhibitor vs. Sulfonylurea—A Population-Based Cohort Study

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Background: Type 2 diabetes is related with an increased risk of dementia. Dipeptidyl peptidase-4 inhibitors (DPP-4i) have shown promising results for its use in dementia in preclinical studies. Therefore, we investigated the risk of developing dementia in elderly patients initiated on DPP-4i vs. sulfonylurea (SU).

Methods: A population-based cohort study using claims database named the Korean National Health Insurance Service Senior cohort (ver. 3.0, 1 January 2002 to 31 December 2015) was performed. DPP-4i-treated patients and SU-treated patients were matched by 1:1 propensity score matching which was calculated with 49 confounding variables. Kaplan-Meier curves and Cox proportional hazards regression analysis were performed to estimate the risk of dementia among patients who were prescribed DPP-4i compared with patients who were prescribed SU.

Results: In total, 7,561 patients on each group were paired using propensity score matching. The risk of dementia was lower in the DPP-4i group compared to the DPP-4i group (hazard ratio [HR] 0.66; 95% confidence interval [CI] 0.56-0.79; P<0.001). Also, HR of Alzheimer's dementia, and vascular dementia were lower in DPP-4i-treated patients compared with SU-treated patients (HR 0.71; 95% CI 0.57-0.89); P=0.002 for Alzheimer's dementia, HR 0.50; 95% CI 0.30-0.85); P=0.01 for vascular dementia).

Conclusions: Our findings suggest that DPP-4i use decrease the risk of dementia compared with SU.

196-LB

Autoimmunity in Patients with Type 2 Diabetes in Newfoundland and Labrador

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Latent Autoimmune Diabetes of the Adult (LADA) is a slowly progressive form of diabetes associated with autoantibody positivity. LADA shares characteristics with type 1 and 2 diabetes (T1D, T2D) but is often misdiagnosed as T2D. Epidemiologic data shows patients with LADA may account for 2 to 12% of all cases of diabetes.

The aim of the study was to collect information on prevalence of autoimmunity in patients with T2D and describe their characteristics in Newfoundland and Labrador, Canada.

A cross- sectional study design was used to collect data in 140 patients. The frequency of GAD 65 antibody, ICA, Insulin and C-peptide levels was examined by radioimmunoassay and enzyme-linked immunosorbent assays. We collected data on height, weight, Body Mass Index (BMI) and tested for Thyroid Stimulating Hormone and Glycosylated Hemoglobin levels. Data collected included age at diagnosis, family history and number of co-morbidities. Adults 18 years and above with T2D were included. Pregnant and lactating females were excluded. SPSS version 24 was used to analyze data.

Results obtained showed 13 (8 males and 5 females, p 0.181) of the 132 patients tested were GAD 65 positive thus placing prevalence of LADA in NL at 9.7%. Baseline characteristics were similar in both GAD 65 positive and negative patients. None of the patients tested were positive for ICA antibodies thereby improving our confidence that the sample did not contain any patients with T1D. Prevalence of GAD 65 was higher in the patients requiring Insulin whereas the C-peptide levels were lower. BMI was high in both GAD 65 positive and negative group with data trending towards higher BMI in the GAD 65 positive group.

GAD 65 positivity was associated with older age group, higher BMI which is different from reported literature indicating that older age and obesity have a predictive value in diagnosis of T2D but not in LADA.

197-LB

Cross-Sectional Associations between Drinking Bottled Water and Prediabetes/Diabetes

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Dietary recommendations for healthy adults include adequate hydration (males: 125 ounces/day, females: 91 ounces/day) from drinking water, other beverages, and water contained in food. Bottled water sales in U.S. exceeded 11.7 billion gallons in 2015 (36.5 gallons per capita). Low water intake, as well as some chemicals in water sources, are associated with hyperglycemia. However, the association between drinking water sources and hyperglycemia/diabetes has not been studied. In a cohort of overweight/obese Puerto Ricans, we evaluated the association between water sources (bottled and filtered compared to tap water) and prediabetes/diabetes. In 2014-2016, 1023 participants reported their primary source of water as bottled (52%), filtered (25%) and tap (23%); diabetes status was assessed using ADA criteria for fasting and 2-hour post load glucose, and HbA1c. Logistic regression models controlled for age, gender, waist circumference, smoking, alcohol intake, physical activity, and hypertension. Bottled water consumers (compared to tap water) had higher prediabetes (OR=1.43; 95% CI: 1.02, 2.01), and diabetes (OR=1.93; 95% CI: 1.08, 3.46). Further controlling for amount of water, sugar sweetened beverages, or canned food and drinks did not change the associations, but controlling for education or income strengthened the association with diabetes. Results were stronger when restricted to San Juan city residents (43%): prediabetes (OR=1.68; 95% CI: 1.01, 2.79), and diabetes (OR=4.05; 95% CI: 1.48, 11.1). Filtered water users had somewhat higher prediabetes/diabetes (OR=1.38; 95% CI: 0.93, 2.04) compared to tap water users. Results suggest that drinking bottled water may be associated with higher prevalence of diabetes compared to tap water, potentially mediated by endocrine disruptors in plastic bottles. We cannot determine time sequence or causality, given the cross-sectional analyses. The impact of water sources on diabetes risk needs to be further evaluated longitudinally.

Supported By: National Institutes of Health

198-LB

Dietary Animal and Saturated Fat Predict Future Visceral Fat Accumulation in Japanese Americans

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Both diet and visceral adiposity play key roles in cardiometabolic disease. However, the association between dietary fat and subsequent visceral fat accumulation is not known. Thus, we prospectively examined future visceral fat accumulation in relation to dietary intake of animal and plant fats, or saturated and polyunsaturated fats in 312 nondiabetic Japanese-American men and women. Visceral adiposity was measured as intra-abdominal fat (IAF) area at the umbilicus by computed tomography at baseline and 10-11 years. Detailed dietary information was assessed at baseline using a food frequency questionnaire and 24-hour recall. Insulin sensitivity was evaluated by homeostasis model assessment for insulin resistance (HOMA-IR) and insulin response by the insulinogenic index (IGI) [Δinsulin/Δglucose (30-0 minutes)]. After adjustment for baseline IAF, age, sex, smoking habits (non-smokers, past-smokers, current smokers), physical activity, alcohol consumption, HOMA-IR, IGI, total protein intake, and total carbohydrate intake in multiple linear regression models, baseline log transformed animal fat intake [coefficient=15.319 (P=0.002)], but not plant fat intake [0.163 (P=0.270)], was associated with future IAF change. In the model that included saturated and polyunsaturated fat substituted for animal and plant fat intake, saturated fat was associated with future IAF change in both men [0.892 (P=0.030)]

and women [1.121 (P=0.022)], but a statistically significant interaction was present between sex and polyunsaturated fat, such that polyunsaturated fat intake was inversely associated with future IAF change in men [-1.290 (P=0.003)], but not women [-0.058 (P=0.905)].

In conclusion, in both men and women, higher intake of animal fat and saturated fat, not plant fat, precede more visceral fat accumulation, while in men only, higher polyunsaturated fat intake precedes less visceral fat accumulation.

Supported By: National Institutes of Health

199-LB

Mortality Risk in Adults With and Without Type 2 Diabetes after 18 Years of Follow-up in Northern Spain—The Asturias Study

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Objective: People who develop type 2 diabetes (T2D) have higher mortality risk. Regarding Asturias Study, after 18 years of follow-up, we have estimated all-cause, cardiovascular and cancer mortality-risks according to categories of impaired glucose metabolism.

Research Design and Methods: Asturias study (launched in 1998) included a mortality follow-up of 18 years of its regionwide sample representative of population aged 30-75 years. Age and sex- stratified hazard ratios (HR) were calculated for 48 participants with diagnosed T2D (self reported diagnosis or antidiabetic medication), 83 with undiagnosed T2D (no diagnosed T2D, glycated hemoglobin A1c ≥6,5%, fasting glycemia≥126 mg/dL or glycemia after 75g glucose load ≥200 mg/dL), 296 with prediabetes (glycated hemoglobin A1c 5,7-6,4%, fasting glycemia 100-125 mg/dL or glycemia after 75g glucose load 140-199 mg/dL) and 607 with normoglycemia.

Results: Over 18,612 person-years, 204 people died (32 with undiagnosed T2D, 30 with diagnosed T2D, 62 with prediabetes and 80 with normoglycemia). HR for all cause mortality, adjusted by previous cardiovascular disease, history of high blood pressure, LDL cholesterol level, age, sex, BMI and estimate glomerular filtration rate, was 2.22 (1.42-3.48) for diagnosed T2D, 1.57 (1.03-2.39) for undiagnosed diabetes. Adjusted hazard ratio for cardiovascular mortality was 3.12 (1.55-6.29) for diagnosed T2D and, for cancer mortality, was 1.83 (0.79-4.22) vs. normoglycemia. Women with T2D have higher age-standardized cardiovascular-mortality risk than men with T2D (7.36 (2,84-19.09) vs. 1.58 (1.45-5.56)). People with prediabetes have similar mortality risks as people with normoglycemia.

Conclusions: In Asturias, age and sex-standardized all-cause mortality is more than two times higher for adults with T2D than for adults without T2D. HR for cardiovascular mortality is highly increased in women with T2D comparing with men with the same condition.

200-LB

Over 22 kg/m^2 of BMI at Young Age Is a Risk Factor for Future Diabetes in Japanese Men

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Type 2 diabetes (T2DM) is easily developed in Asian adults with normal body mass index (BMI), compared with other ethnicities with similar BMI. For example, it has been shown that slightly increased BMI level (>23 kg/m^2) in middle age (around 50 years old) is a risk for development of T2DM in Asians. However, it is still unclear whether slightly elevated BMI at young age within normal BMI range (<25 kg/m^2) also increases the risk of T2DM later in life. To clarify this, we investigate the impacts of BMI at young age on development of T2DM later in life by historical cohort study. The study subjects are male alumni who were graduated physical education school in Japan from 1971 to 1991. From 2007 to 2017, a self-administered follow-up questionnaire was sent by mail to the subjects to ask their previous medical diagnosis of diabetes. This study analyzed 657 male alumni and covered 32-year follow-up period (interquartile range: IQR: 27-36) which included 20,607 person-years of observation. Subjects were 22 (22-22) years old at graduated college and 54 (50-59) years old at final follow-up investigation. Median BMI was 22.0 (21.1-23.0) kg/m^2 at college age and 23.9 (22.3-25.6) kg/m^2 at first follow-up investigation. During the period, 57 men developed diabetes. Then, the participants were categorized into four categories: BMI at college age of <21.0 kg/m^2 (n=155), 21.0-22.0kg/m^2 (n=172), 22.0-23.0kg/m^2 (n=170), and ≥23.0kg/m^2 (n=160), and the incidence of diabetes was compared. The prevalence rates of diabetes for lowest to highest BMI categories were 4.5%, 7.6%, 11.2%, and 11.3%, respectively (p=0.10), and their hazard ratios were 1.00 (reference), 1.65 (95% CI: 0.66-4.14), 2.45 (1.02-5.87), and 2.51 (1.05-6.03), respectively (p=0.02 for trend). This trend was similar after adjustment for age, year of graduation, smoking and participation in college sports club. These data suggested that over 22.0kg/m^2 of BMI at young age might be a risk factor for future T2DM in Japanese men.

201-LB

Metabolic Markers Predictive of Prediabetes in the Korean Population

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Background: Prediabetes (PD) is a high-risk state for type 2 diabetes (T2D), but the risk of progression from PD to T2D can be prevented by early diagnosis and intervention. Metabolomics studies suggest that metabolic biomarkers can shed insight into etiological mechanisms and improve the accuracy of prediction of disease onset.

Objectives: We aimed to identify serum metabolic biomarkers and verify their predictive performance for PD in the Korean population, as compared to the performance of known clinical risk factor (CRF) as well as previously reported metabolites (PRM) in other population studies.

Methods: A targeted metabolomics was carried out to quantify serum metabolites for 1,723 participants from the Korea Association REsource (KARE) cohort from which 500 individuals were followed-up to 6-years. PD-related metabolites were identified at baseline by statistical methods including multivariable regression analysis, and tested their association to incidence of PD during follow-up.

Results: The 12 metabolites were significantly altered in PD (adjusted P<4.07 E-04). These metabolites predicted incidence of PD with an area under curve (AUC) of 0.71. The AUC of the metabolic markers was significantly higher than that of the two PRM models (0.56 and 0.64, P<0.005) and the CRF (0.64, P<0.01). The performance of the metabolic markers compared to glucose model was significantly higher among the obese (BMI >= 25 kg/m^2, 0.79 vs. 0.58, P<0.001), significantly lower among the female (0.73 vs. 0.85, P<0.002) and the lean (BMI<25 kg/m^2, 0.68 vs. 0.78, P<0.01), and not significantly different among the age and the male. The full model with metabolic markers, CRF, glucose yielded the best prediction (AUC=0.84).

Conclusion: Our results revealed that the novel metabolic markers are not only associated with the risk of PD, but also improve the prediction performance in combination with classical approaches. These findings may help understanding causality of diabetes progression and developing preventive strategies for T2D.

202-LB

Global Prevalence of Type 2 Diabetes over the Next Ten Years (2018-2028)

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Objective: We aimed to estimate the global prevalence of type 2 diabetes over the next ten years, taking into account trends in obesity. Our analysis includes estimates for 45 countries representing almost 90% of the world population. We defined a prevalent case as anyone living with type 2 diabetes, irrespective of whether it has been formally diagnosed or not and excluded type 1 diabetes cases.

Methods: We performed a global systematic search of published studies and other data sources that reported the prevalence of type 2 diabetes, as well as any factors that may change its risk or prognosis over time or between countries. Our analysis is based on critically-appraised literature and database evidence that reports the total prevalence of type 2 diabetes. From the results of this search, we appraised and selected country-specific estimates to project up to national totals. These estimates were adjusted to account for historical or future trends in risk, as well as relevant differences between countries when extrapolations were made. Our model includes country-specific obesity prevalence to incorporate the impact of obesity on diabetes trends.

Results: We estimate that in 2018 there are more than 500 million prevalent cases of type 2 diabetes worldwide and the prevalence is comparable between high- and low-income countries. The prevalence will increase in all countries covered over the projection period, but the greatest growth will be experienced in lower-income countries.

EPIDEMIOLOGY—TYPE 1 DIABETES

203-LB

The Presence of Cerebral White Matter Lesions and Lower Skin Microvascular Perfusion Predict Decline in General Cognitive Ability in Type 1 Diabetes Patients but Not in Healthy Controls

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Objective: Cognitive impairments in type 1 diabetes may result from hyperglycemia-associated cerebral microangiopathy. In this study we aimed to identify cerebral microangiopathy and skin microvascular dysfunction - as surrogate marker for generalized microvascular function - as predictors of cognitive decline over time.

Research Design and Methods: Twenty-five type 1 diabetes patients and 25 matched healthy controls underwent neurocognitive testing at baseline and after follow-up (mean duration of 3.8±0.8 years). At baseline, 1.5 T cerebral magnetic resonance imaging was used to detect white matter lesions (WML) and cerebral microbleeds. In addition, skin capillary perfusion was assessed by means of capillary microscopy. Multiple linear regression analysis was performed to examine if cerebral microangiopathy and capillary perfusion were associated with changes in cognitive performance.

Results: In type 1 diabetes patients, but not in healthy controls, the presence of WML (ß=-0.419;p=0.037) as well as lower skin capillary perfusion (baseline: ß=0.753;p<0.001; peak hyperemia: ß=0.743;p=0.001; venous occlusion: ß=0.675;p=0.003; absolute capillary recruitment: ß=0.549;p=0.022) at baseline were associated with decline in general cognitive ability over time, independent of age and sex, HbA1c and severe hypoglycemic events. The relationship between WML and cognitive decline was significantly reduced to non-significant levels after adjusting for capillary perfusion.

Conclusions: In type 1 diabetes patients, presence of WML and lower skin capillary perfusion predict poorer general cognitive ability over time. The relationship between WML and cognitive decline was significantly reduced when adjusting for capillary perfusion, suggesting that generalized microvascular dysfunction at least partly underlies WML-associated cognitive decline.

Supported By: Dutch Diabetes Research Foundation; European Foundation for the Study of Diabetes

204-LB

A Systematic Review of Cases of Diabetes Mellitus following Immune Checkpoint Inhibitor Therapy for Cancer

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Introduction: Immune checkpoint inhibitors (ICI) [anti-PD-1, anti-PD-L1, and anti-CTLA-4] are novel drugs increasingly used to treat solid tumor malignancies. Immune-related adverse events (irAE) occur with such therapy. We conducted a systematic review of case reports on endocrine irAE following ICI therapy. Here, we focus on the diabetes mellitus (DM) irAE case reports.

Method: In July 2017 we searched Medline, Embase, Cochrane Central Register and Web of Science for articles related to endocrine irAE and ICI. From 815 citations retrieved, 241 mentioned DM. From these, 32 articles reported 43 cases (had close temporal relationship of immunotherapy and development of DM IrAEs and clinical, biochemical, and/or treatment data). A hand-search in Jan 2018 found 8 more papers with 8 cases. These 51 cases were reviewed independently by 2 co-authors for quality of data, using a standardized form.

Results: Thirty-five patients presented in DKA (21 with fulminant T1DM), 15 with hyperglycemia, and 1 with lab data not reported (NR). The median age of the 31 males and 20 females was 63 years. Median time to onset of DM was 7 weeks after treatment initiation. Anti-GAD65, IA2, or ZnT8 were positive in 53% and negative or NR in 47%. Top 2 cancer treated were melanoma (n=23) and non-small cell lung cancer (n=11). The ICIs used were anti-PD-l (n=34); anti-PD-L1 (n=4); anti-PD-1 + CTLA-4 (n=7); and anti-CTLA-4 then anti-PD-1 (n=6). When DM occurred, ICI was stopped in 16, continued in 12, and NR in 23. At onset, 3 cases with known T2DM continued with oral meds, but all were treated with insulin and fluids. All patients recovered - 38 remained on insulin, 1 stopped insulin 81 days after ICI was stopped; and 12 NR.

Conclusion: Reported cases of T1DM irAE are rising - 9 in 2015, 13 in 2016 and 28 in 2017. Most (69%) presented in DKA. All were treated with anti-PD-1/PD-L1 drugs with the majority on monotherapy. All recovered and 38 were insulin-dependent. Endocrinologists and oncologists should collaborate in managing such patients.

205-LB

Index60 Is More Strongly Associated with the Highest Type 1 Diabetes (T1D) Risk HLA DR3-DQ2/DR4-DQ8 (DQ2/DQ8) Genotype than Glucose Measures

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Dysglycemia (i.e., fasting glucose=110-125 mg/dl; 30, 60, or 90-minutes glucose ≥200 mg/dl; and/or 2-h glucose=140-199 mg/dl, from oral glucose tolerance test [OGTT]) is used both as a predictive marker and pre-diagnostic endpoint in T1D prevention trials. However, recent evidence suggests that Index60 (based on fasting C-peptide, 60-minutes glucose and 60-minutes C-peptide, from OGTT) at a 1.00 threshold may be superior to dysglycemia. We thus hypothesized that Index60 is more strongly associated with T1D-linked genetic factors than glucose measures alone. We compared autoantibody-positive TrialNet Pathway to Prevention Study participants (n=1,098) with or without DQ2/DQ8 for associations with Index60, fasting glucose, 2-h glucose and dysglycemia. Participants with DQ2/DQ8 (n=159) compared to those without it (n=912) had higher Index60 values (median [interquartile range, IQR]=0.6 [-5.6 to 2.6] vs. 0.25 (-4.4 to 2.9]; p=0.001). In contrast, neither fasting glucose (p=0.51) nor 2-hour glucose p=0.07) were significantly different between the groups. The percentage with Index60≥1.00 was significantly higher in participants with (37.6%) than without (22.8%) DQ2/DQ8 (p=0.0001), whereas the percentages with dysglycemia were not significantly different (32.7% vs. 26.1%; p=0.11). Among those with normal OGTTs, Index60≥1.00 was more frequent among participants with DQ2/DQ8 (23.8%) than without it (12.0%; p=0.001), while among participants with Index60<1.00, the frequency of dysglycemia was similar in those with and without DQ2/DQ8 (17.5% vs. 16.0%; p=0.70).

In conclusion, Index60, a metabolic marker based on glucose and C-peptide, is more strongly associated with the highest T1D risk HLA DQ2/DQ8 genotype than glucose measures, including dysglycemia. This suggests that Index60 has higher pathogenic specificity for T1D than glucose measures and should be considered for use in T1D prevention trials.

Supported By: National Institutes of Health

206-LB

Establishing Cost-Effectiveness of "Acceptable" T1D Care in Less-Resourced Countries

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Aim: Cost-effective arguments are needed to help convince less-resourced governments to provide essential T1D services. We developed two scenarios for Pakistan (Lower-Middle Income) (S1) and Azerbaijan (Upper-Middle Income) (S2).

Methods: We modelled the complications/costs/mortality/Disability Adjusted Life Years (DALYs) associated with achieving a mean HbA1c of 9.0% (75 mmol/mol) for S1 and 8.5% (69 mmol/mol) for S2 compared with those with a mean HbA1c level of 12.5% (113 mmol/mol). 'Acceptable care' S1 involved human insulin by multiple daily injections (MDI), two blood glucose tests/day, education and complications screening etc. S2 was S1 with analog rather than human insulin and four tests/day. 'Minimal care' was non-MDI insulin, syringes and routine clinic reviews. A discrete time Markov illness-death model with diabetes-duration-dependent transition probabilities was developed in R 3.3.1. Input parameters included 30 years (y) of University of Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort statistics for T1D diagnosed <17 y of age and DALYs and background mortality data from WHO. Eleven complications were included. Costs were determined from international and local estimations.

Results: Complications were markedly raised with HbA1c at 12.5% compared to 9.0% and 8.5%. For instance, blindness at 30 y was 49.4%, 11.6% and 9.5% respectively. For S1, 30 y total costs (maintenance and cost of acute and chronic complications) were $20,919/patient at 9.0% and $20,796 at 12.5%. For S2, costs were $61,429 at 8.5% and $60,826 at 12.5%. Thirty y survival rate for Pakistan was 87% at 9.0% and 64% at 12.5%, and for Azerbaijan 91% at 8.5% and 66% at 12.5%. Cumulative DALYs lost in 30 years in Pakistan were 2.6 y at 9.0% and 6.0 y (12.5%). Azerbaijan was 2.0 y (8.5%) and 5.8 y (12.5%).

Conclusion: 'Acceptable care' is of similar cost to 'Minimal care' in Pakistan and Azerbaijan, with improved survival and reduced DALYs. This model can be used in other less-resourced countries.

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

207-LB

Dysglycemia Is as Common in Autoantibody-Negative Relatives as in Single-Autoantibody-Positive Relatives of Type 1 Diabetes (T1D) Patients

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Autoantibody positive (Ab+) relatives of T1D patients have an increased risk for dysglycemia and progression to T1D. However, the occurrence of dysglycemia in Ab- relatives is not known. Thus, we compared the frequency and pattern of dysglycemia from oral glucose tolerance tests (OGTTs) between Ab- (n=101; mean age: 11.7± 3.6 years) and single Ab+ (n=977; mean age 10.4± 3.9 years) relatives in the TrialNet Pathway to Prevention study. Single Abs were ICA, GADA, IA-2A, mIAA, or ZnT8A. The glucose criteria for dysglycemia were: fasting 110-125 mg/dl; 30, 60, and/or 90-minutes glucose ≥ 200 mg/dl; and/or 120-minutes glucose 140-199 mg/dl. Of the Ab-'s, 29/101 (28.7%) had at least one dysglycemic OGTT at baseline or during follow-up, whereas 192/977 (19.7%) Ab+'s had a dysglycemic OGTT. At baseline, there were no significant differences in the proportions of dysglycemia [Ab-'s: 13/101 (12.9%) vs. Ab+'s: 114/977 (11.7%)]. Of those with normal OGTTs at baseline, the proportion progressing to dysglycemia was actually higher (p=0.007) in the Ab-'s (dysglycemia/total: [16/87 (18.4%) vs. 78/846 (9.2%)], but the hazard ratio for dysglycemia risk from a Cox regression analysis was not significant after adjustments for age, BMI%tile, relation to proband, and number of OGTTs performed. OGTT glucose and C-peptide at the first dysglycemic OGTT did not differ significantly between Ab-'s and Ab+'s after adjustments, except for a higher 90-minutes glucose in the Ab-'s (p=0.004). The early C-peptide response values (30-0 minutes C-peptide) did not differ significantly between the groups and were not indicative of overt insulin deficiency (Ab-'s: 5.6± 3.2 ng/ml vs. Ab+'s: 5.2± 3.3 ng/ml).

In summary, dysglycemia was as common in Ab- relatives as in single Ab+ relatives with similar dysglycemic OGTT patterns. These findings suggest that dysglycemia can precede Ab's during the progression to T1D and/or an appreciable proportion of single Ab+ dysglycemic individuals do not develop T1D.

GENETICS—TYPE 1 DIABETES

208-LB

WITHDRAWN

209-LB

Genetic Risk for Type 1 Diabetes Profoundly Influences the Core Gut Microbiome in Children

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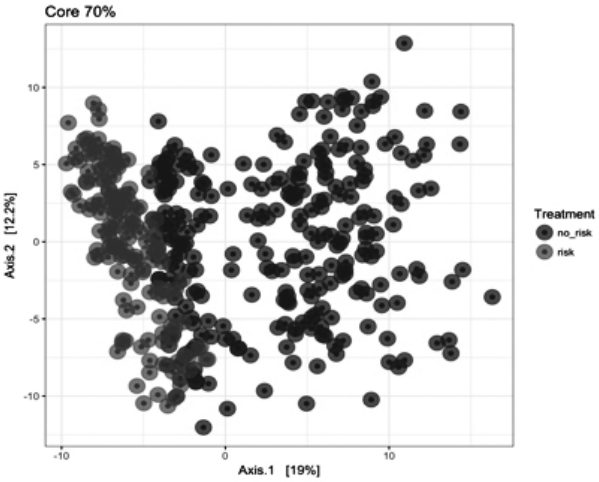
All of the gut microbiome associations with type 1 diabetes autoimmunity to date have been discovered in cohorts where all subjects are at high genetic risk for the disease. The design of such cohorts precludes an assessment of the influence HLA high risk alleles on gut microbiome composition. This question is addressed here by using stool samples from the general population All Babies in Southeast Sweden (ABIS) cohort where most children are at no genetic risk for type 1 diabetes. A proportion of ABIS children do possess high risk alleles including DR3/DQ2, DR4/DQ8, and DRB1. DNA from stool samples, collected at one year of age from 441 ABIS children (169 at high genetic risk), stored at -80°C, was extracted and 16S rRNA amplified, sequenced, and analyzed. The core microbiome for each category was computed by including only those reads from taxa found in at least 70% of all subjects within that group. The core microbiomes of the two groups were readily separated by PCoA (Figure 1) and were significantly different (p=0.001). Each core microbiome comprised about 65% of the reads collected. Bifidobacterium was significantly higher in the no-risk group while Veillonella was higher in the risk group. Thus, HLA risk alleles appear to influence the core gut microbiome and posit a novel mechanism whereby the microbiome may influence the pathogenesis of type 1 diabetes.

Figure 1. Principal coordinates analysis (PCoA) based on a binomial distance matrix showing the separation of core gut microbiomes between subjects at high risk for type 1 diabetes versus those with no genetic risk.



GENETICS—TYPE 2 DIABETES

210-LB

Polygenic Risk Testing at the Time of Diagnosis of Diabetes Could Help Prevent Its Micro- and Macrovascular Complications

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Cardiovascular and renal complications of T2D represent a human and societal burden. Early detection of susceptibility to complications could help their prevention. Clinical scores are useful to predict hard outcomes but genomic score can be applied earlier than a risk factor based score and thus save morbidity. We have constructed a polygenic risk score (PRS) based on genetic variants associated to risk factors and outcomes of T2D available from GWAS catalog and tested it on 5,000 genotyped Caucasian subjects with T2D of ADVANCE trial and its 5 year extension in ADVANCE-ON. We selected 620 SNPs which in combination with geo-ethnic principal component, age of onset and diabetes duration achieved a highly significant prediction of outcomes, including cardiovascular (AUC=0.80) and total mortality (AUC=0.77), equalling and surpassing such clinical scores as Framingham and UKPDS. The highest positive predictive values for micro- and macrovascular prevalent cases were 81% and 78%, respectively. Individuals within the highest tertile of genetic risk for total prevalence of both microvascular and macrovascular events, had significantly higher cardiovascular death than subjects with the lowest genetic score ($p=2.02x10^{-12}$). The number needed to treat to prevent one CV death over 5 years by ADVANCE therapies, was 12 in subjects with high PRS (p=0.0045) compared to 45 (p=0.14) in subjects with low PRS. Cox cumulative hazard plots demonstrated persistence of benefits for all cause and cardiovascular mortality in high PRS tertile over 10 years of intensive blood pressure control, while for glucose intensive therapy the benefit was restricted to the high PRS group for end-stage renal disease. We conclude that the use of a PRS that detects the risk of micro- and macrovascular complications at the time of T2D diagnosis could effectively assist in preventive and therapeutic measures to attenuate diabetes complications.

Supported By: Consortium Québécois sur la Découverte du Médicament; Le Ministère- inistère de l'Économie, de la Science et de l'Innovation; Quebec Government; Les Laboratoires Servier; Genome Quebec

211-LB

WITHDRAWN

212-LB

Discovery and Fine-Mapping of Type 2 Diabetes Susceptibility Loci in Diverse Populations Using More than a Million Individuals

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To discover type 2 diabetes (T2D) loci and enhance fine-mapping resolution, we conducted the largest meta-analysis of genome-wide association studies of the disease to date by aggregating 171,262 cases and 1,075,072 controls from diverse populations (45% non-European ancestry). We identified 250 loci at genome-wide significance ($p<5x10^{-8}$); 59 mapped outside regions previously implicated in T2D. Across these loci, conditional analyses revealed a total of 475 distinct signals of association (locus-wide significance, $p<10^{-5}$). We observed strong evidence of heterogeneity in allelic effects on T2D ($p_{HET}<1.4x10^{-4}$, Bonferroni correction) correlated with ancestry at 17% of signals, including LEP (rs35589574, $p_{HET}=4.8x10^{-25}$, East Asian specific) and multiple associations at/near KCNQ1 and TCF7L2 (representing ethnic-specific/-differentiated effects). T2D-associated variants showed significant enrichment (odds-ratio range 1.90-6.63; $p<0.05$) in coding exons, pancreatic islet enhancers and promoters, adipose enhancers, and binding sites for transcription factors, including NKX2.2 and FOXA2. Increased sample size, population diversity, and annotation-informed fine-mapping substantially improved localisation of potential causal variants compared with previous efforts, and highlighted 76 signals with a single variant accounting for >80% of the posterior probability of association (PPA); of these 35 signals had PPA of >99%. Clustering of signal-specific annotation enrichment highlighted distinct clades of T2D associations driven by different underlying molecular processes. These analyses represent the most comprehensive view of the genetic contribution to T2D to date and, through integration with expression quantitative trait loci in disease-relevant tissues, point to previously unreported effector genes (such as SKOR1, CLUAP1, and PEPD) and mediating molecular mechanisms at several loci.

213-LB

A Low-Frequency Amerindian Specific Variant in PALD1, a Negative Regulator of Insulin Signaling, Associates with Type 2 Diabetes

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We recently completed a genome wide association study for type 2 diabetes (T2D) in 7659 American Indians who are predominantly of Pima Indian heritage using a custom designed Axiom array. A novel intronic variant (hg19 chr10:72276664 G>C) in PALD1 was identified that associated with T2D (risk allele frequency (RAF)=0.01, OR=2.19[1.49-3.22] per risk allele [C], $P=6.6\times10^{-5}$ adjusted for age, sex, birthyear, PCs 1-5 and accounting for genetic relatedness). Further analysis in a dataset of Urban American Indians (N=3029) representing several tribal groups living in the Phoenix area, identified a directionally consistent association (OR=2.32, P=0.12), but this variant was rare among the entire Urban American Indian sample (RAF=0.003). A meta-analysis of both datasets resulted in a summary OR of 2.15[1.49-3.13], $P=4.9\times10^{-5}$. In Pima Indians, this variant is highly concordant (r2=0.92) with a novel missense variant (hg19 chr10:72298980 C>T, p.[P568S]) in PALD1. The missense variant also had a significant association with T2D in Pima Indians (RAF=0.02, OR=1.80[1.25-2.60], P=0.002) and in Urban American Indians (RAF=0.008, OR=2.29[1.03-5.12], P=0.04). However, after conditional analysis, only the intronic variant remains significant in the Pima Indian dataset. PALD1 is a predicted phosphatase and acts as a negative regulator of insulin signaling. Overexpression of PALD1 leads to lower insulin stimulated AKT phosphorylation and insulin receptor abundance. For preliminary functional studies, a short fragment (100bp) containing each allele of the PALD1 intronic variant (C or G) was cloned upstream of a SV40 promoter luciferase vector and transfected into C2C12 myoblasts. The T2D risk allele (C) fragment had significantly (P=0.004) higher SV40 promoter mediated luciferase activity as compared to the non-risk (G) allele. This result is consistent with the possible role of PALD1 in T2D pathogenesis. Further mechanistic studies are currently ongoing.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

214-LB

Conserved Haplotype in SGLT1 and Risk for Dietary Hyperglycemia

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Background: Loss of function mutations in SGLT1 lead to a rare, severe malabsorption disorder and neonatal death if untreated. The clinical consequence of SGLT1 variation in the general population is unknown.

Methods: Exome sequencing was performed in participants from 4 U.S. communities in the ARIC Study. Association of nonsynonymous substitutions (NS) in SGLT1 with impaired glucose tolerance (IGT) and other cardiometabolic outcomes were assessed.

Results: Among 5687 European Americans (mean age 54±6), those with at least two NS in SGLT1 had lower odds of IGT and obesity than non-carriers determined by a relatively common (6.7%) haplotype of 3 missense mutations: Asn51Ser, Ala411Thr, and His615Gln [IGT, OR=0.71 (0.59-0.86); obesity, OR=0.79 (0.66-0.96)]. Replication in African Americans n=2791 confirmed the association of reduced IGT [0.39 (0.17-0.91)] and obesity [0.60 (0.37-0.98)] in haplotype carriers. In combined ARIC samples, haplotype carriers had reduced DM and death or heart failure [HR=0.81 (0.69-0.94) and 0.80 (0.70-0.91)]. Association of the haplotype with lower IGT, obesity, and death persisted in meta-analysis with an external Finnish sample (n=27,294).

Conclusions: Missense variants in SGLT1 protect from diet induced hyperglycemia and may protect from obesity and additional disease outcomes in multiple populations, providing support for therapies that target SGLT1 to prevent and treat metabolic conditions.

Table. OGTT and Obesity According to the Asn51Ser/Ala411Thr/His615Gln Haplotype in SGLT1.

		Oral Glucose Tolerance Test			
		Fasting Glucose Value (mg/dL; beta-coefficients)	2-hour Glucose Value (mg/dL; beta-coefficients)	Impaired Glucose Tolerance OR (95% CI)	Prevalent Obesity OR (95% CI)
ARIC European-Americans		-2.7 (-5.1, -0.3)	-8.0 (-12.7, -3.3)	0.71 (0.59, 0.86)	0.79 (0.66, 0.96)
ARIC African-Americans		-4.3 (-19.7, 11.1)	-16.3 (-36.6, 4.1)	0.39 (0.17, 0.91)	0.60 (0.37, 0.98)
ARIC Combined		-5.9 (-9.1, -2.8)	-8.1 (-13.0, -3.2)	0.72 (0.59, 0.87)	0.66 (0.55, 0.79)
	P-value‡	2.2×10^{-4}	1.2×10^{-3}	8.3×10^{-4}	1.3×10^{-5}
FINRISK/DILGOM		-0.3 (-1.5, 1.1)	-3.2 (-4.8, -1.6)	0.81 (0.68, 0.98)	0.89 (0.71, 1.12)
Meta-Analysis		-1.1 (-2.3, 0.1)	-4.7 (-7.3, -2.0)	0.77 (0.67, 0.88)	0.74 (0.64, 0.85)
	P-value‡	0.08	6.5×10^{-4}	8.9×10^{-5}	$3.3x10^{-5}$

Supported By: National Institutes of Health (2T32HL094301-06)

215-LB

Replication of Previously Type 2 Diabetes Associated Loci in 35,000 Samples of Korean Population

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In the last decade, genome-wide association studies (GWAS) have revealed about hundreds of loci associated with type 2 diabetes(T2D) and related traits. However, most of loci have been discovered based on Europeans and a few GWAS conducted in populations with East Asian ancestry. To identify genetic variants responsible for complex traits such as T2D, obesity, and blood biochemical traits in Koreans, Korea Biobank Array(KBA) project was initiated in 2014. KBA is designed to contain about 830K tagging and functional variants optimized for Korean genome. In this study, quality controlled genotype data of about 35,000 samples was used. Among them, we conducted genome-wide association scan in 3,022 T2D case subjects and 27,195 control subjects. As a result, we replicated five previously known loci (CDKAL1, SLC30A8, CDKN2A, KCNQ1, and HNF1B) at genome-wide significance ($P <= 5x10-8$). We further compared genetic effects in Koreans with those of previously reported loci. As of March 2018, there were 373 unique variants of 50 T2D GWAS papers listed in GWAS catalogue. Among 373 variants, 359 variants were available after excluding variants with low imputation quality (<0.3). We compared odds ratios of 359 variants between KBA T2D GWAS and previously reported results. In overall, Pearson correlation coefficient of odds ratios was -0.04. For replicated results (130 variants with P<0.05 in KBA T2D GWAS), however, we observed high correlation (r=0.58).

Our study identified five known T2D loci and confirmed consistent genetic effects across populations for 130 previously reported T2D associated variants. Further study is warranted to examine genetic diversity and lack of statistical power due to insufficient sample size in non-replicated loci. These results will be valuable scientific evidence in T2D precision medicine considering genetic effects across populations.

Supported By: Korean National Institute of Health (2017-NI73001-00)

216-LB

Discovery and Replication of HDL-Associated Loci in the Korean Population Using 35,000 Individuals

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Low levels of HDL are known to be associated with increased risk of type 2 diabetes. It has been suggested as a new therapeutic approach that increase HDL levels in plasma. Previously, to identify lipids traits associated loci, we performed large-scale genome-wide meta-analyses comprising 25,923 East Asian individuals from 11 studies from Korea, Japan, Philippines, China, Singapore, and Taiwan in the discovery stage. With subsequent replication study, we have revealed seven novel loci associated with HDL including loci at CD163-APOBEC1, NCOA2, and NID2-PTGDR. However, previous study was limited in sample size in the discovery stage and low association mapping resolution due to HapMap based imputation analysis. In this study, we performed genome-wide association analyses (GWAS) on HDL using about 35,000 Korean samples and imputed based on 1,000 Genomes project phase 3 and Korean Reference Genome. We focused on imputed (imputation quality score >0.4) and genotyped common variants with minor allele frequency >= 1%. In this discovery study, 17 known loci were replicated at the genome-wide significance level (P<5x10-8). However, no novel association meet the genome-wide significance. We further examined associated loci at suggestive statistical significance (P<5x10-6). As a result, 11 known loci were additionally replicated and 10 possible novel candidate loci were identified including a variant near GATA4. It is noteworthy that the variant near GATA4 was previously reported to be associated with triglyceride level.

In summary, we performed a GWAS on HDL using about 35,000 Korean samples. The GWAS confirmed 28 known loci and discovered 10 possible novel candidate loci responsible for variation of HDL level. However, a replication study in an independent cohort is warranted for validating the results. Taken together, the possible novel candidates discovered from this study may provide potential novel therapeutic targets for diseases associated with HDL.

Supported By: Korean National Institute of Health (2016-NI73001-00)

217-LB

Increased Obesity Is Causal for Increased Inflammation—A Mendelian Randomisation Study

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Inflammation is endemic to obesity and type 2 diabetes (T2D) but it is unclear if it is a cause or a consequence. If the latter, then inflammation may increase the risk of obesity and diabetes complications. Large genome-wide association studies (GWAS) of inflammation and cardiometabolic traits can be used to investigate causal mechanisms. Summary statistics were assembled from GWAS of 49 cytokine (N=840-80,000) and 20 cardiometabolic traits (N=2,447-465,333). Shared genetic background was measured using LD score regression. Polygenic scores (PGS) were generated from GWAS data for 49 cytokines (representing inflammation) and 20 cardiometabolic traits and used in two-way Mendelian Randomisation (MR) analyses. Causal relationships were identified using summary statistics for all traits, and individual data (UK Biobank, N=465,333) to test the association of cytokine PGS with body mass index (BMI) and T2D. LD score regression analysis demonstrated that BMI and T2D shared a genetic background with acute phase cytokines. However, MR analyses showed that genetically-driven variation in cytokine levels were not associated with increased BMI or T2D risk. This argues against a causal role for inflammation (as represented by these cytokines) in the development of obesity and T2D. In contrast, genetically driven obesity was associated with increased inflammation: a PGS for increased BMI was associated with increased C-reactive protein (Beta [95% CI], 0.40 [0.34,0.46], $p=1.3\times10^{-36}$) and activated plasminogen inhibitor (Beta [95% CI], 0.39 [0.19, 0.59], $p=7.8\times10^{-5}$) levels. Genetically-driven variation in cytokine levels were causally linked with chronic kidney disease in subjects with T2D: fibroblast growth factor 2 (OR[95% CI], 0.58[0.46,0.72], $p=1.8\times10^{-6}$) and interleukin 13 (OR[95% CI], 1.28[1.15,1.43], $p=7.0\times10^{-6}$) We conclude that chronic inflammation is a consequence, rather than a cause, of T2D and obesity, and may contribute to some of their complications.

Supported By: Novo Nordisk Foundation; JDRF; Innovative Medicines Initiative

ADA-Supported Research

218-LB

Association of Maternal and Offspring Genetic Risk for Type 2 Diabetes with Offspring Birth Weight among African-Ancestry Populations

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Background: Mother's genetic risk for type 2 diabetes (T2D) may influence intra-uterine glycemia leading to increased birth weight. However, the U-shaped relation between offspring birthweight and later-life T2D risk suggests that relations of offspring's T2D genetic susceptibility with birthweight may be U-shaped.

Methods: We investigated the effects of maternal and offspring genetic risk for T2D on birthweight using genotype data from 949 mother-offspring pairs of African ancestry from the Hyperglycemia Adverse Pregnancy Outcome study. We generated a genetic risk score for T2D (dGRS) for mothers and offspring as the weighted sum of 90 T2D risk alleles. Offspring dGRS was separately calculated for birth weight-reducing and -increasing alleles based on the direction of correlation between a T2D-risk allele and birthweight in our data. We used linear regression adjusting for maternal and offspring covariates and the proportion of African ancestry to estimate the change in birthweight by quartiles of maternal and offspring dGRS.

Results: Changes in birthweight across increasing quartiles of mother's dGRS were 0 (reference), 83.3g (95% CI: 6.7, 160.0), 102g (95% CI: 25.1, 179.5), and 92.9g (95% CI: 12.7, 173.1) (P-trend=0.042). In contrast, changes in birthweight across increasing quartiles of offspring dGRS based on birthweight-reducing alleles were 0, –105.7g (95% CI: –180.9, –30.5), –105.5g (95% CI: –180.4, –30.5), and –143.2g (95% CI: –218.6, –67.8) (P-trend=0.001), whereas those of dGRS based on birthweight-increasing alleles were 0, 15.3g (95% CI: –60.7, 91.3), 113.3g (95% CI: 38.1, 188.6), and 142.4g (95% CI: 66.8, 218.1) (P-trend=0.0002).

Conclusion: Maternal and offspring genetic risk for T2D exhibited a differential association with birth weight. Further characterization of individual alleles in a larger dataset will enhance our understanding of the causal roles of fetal and maternal genetic determinants of T2D on fetal growth.

IMMUNOLOGY

219-LB

Diabetic Ketoacidosis Triggered by Pembrolizumab in a Patient with Bladder Cancer

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This is a 71-year-old male with history of Hypertension, well controlled type 2 DM on metformin (HbA1c 6.6%), and high grade urothelial bladder cancer treated with transurethral resection of the bladder. Due to cancer progression, he required neoadjuvant chemotherapy followed by Pembrolizumab in July 2017. He presented with fatigue, polyuria and polydipsia in August 2017. He was diagnosed with DKA and managed in the ICU. Workup revealed HbA1c 9%, high GAD-65 antibody (>250 IU/ML), and low C-peptide (0.26 ng/ml). He was stabilized and discharged on insulin. T cell activity is regulated by programmed death ligand-1(PD-L1)/programmed death-1 (PD-1). Tumor cells select specific immune-checkpoint pathways as a mechanism of immune resistance against T cells and evade the antitumor immune response by overexpressing PD-L1. Pembrolizumab is a humanized monoclonal antibody against PD-1 acting as an immune checkpoint inhibitor (ICI). Pembrolizumab is approved for treating metastatic urothelial carcinoma, cisplatin-ineligible cancer or disease progression after cisplatin therapy. ICIs are associated with multi-system immune related adverse events (irAEs) due to the disinhibition of the host immune homeostasis. Most of the irAEs are reversible with supportive treatment, however life-threatening irAEs can occur including severe skin reaction, type 1 DM, hypophysitis, and rhabdomyolysis. In our patient, we suspected pembrolizumab was related to new onset type 1 DM. type 1 DM and DKA were reported in 6 (0.2%) of 2,799 patients on Pembrolizumab in 3 randomized, open-label, and active-controlled clinical trials. There are 12 reported cases of PD-1/PD-L1-associated type 1 DM. The onset of disease from use varied from 1 week to 12 months, with most patients presenting with type 1 DM with DKA. ICIs are breakthroughs in cancer treatment. Clinicians should be aware of their possible irAEs. The development of autoimmune diabetes is rare, but its complications are life threatening if not attended to immediately.

220-LB

Development of DQ-MHC Class II Monoclonal Antibodies—A New, Targeted Therapeutic Approach in Type 1 Diabetes

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Purpose: Type 1 diabetes (T1D) is a disease affecting almost three million Americans; every year 30,000 new cases are diagnosed, 50% of whom are children. There is currently no curative therapy for T1D and the only available treatment is insulin replacement. Substantial recent data demonstrate a strong association between the MHC Class II molecule DQ8 and the development of T1D. Indeed, DQ8 has been shown to present antigenic peptides (such as InsB:9-23 and GAD65) driving activation of CD4+ T cells in T1D patients. The goal of this study was to identify and optimize a monoclonal antibody that binds to DQ8 molecule and blocks the continued activation of DQ8 restricted T cells.

Methods: Hybridoma clones were generated from spleens of BALB/c mice immunized with DQ8 molecule bound with the InsB:9-23 peptide and screened by high throughput flow cytometry using human B-cells expressing DQ8. 28 clones found positive by flow cytometry were functionally tested in a mixed lymphocyte reaction containing a murine T cell line expressing a human TCR specific for the InsB: 9-23 - DQ8 complex. DQ8-103, a murine version of our best candidate antibody (DQ8-27), was tested in transgenic DQ8 mice immunized with GAD65 peptide; Cytokine production from the recall response ex vivo and in vivo was evaluated using a Luminex assay. Immunophenotyping of blood, spleens and draining lymph nodes isolated from immunized DQ8 mice was done by mass cytometry (CyTOF).

Results: We generated a monoclonal antibody against DQ8 (DQ8-27), that was able to bind human DQ8 molecule expressed on human B-cells and on murine splenocytes isolated from transgenic DQ8 mice. The murine version of DQ8-27 (DQ8-103) was able to significantly inhibit T cell activation in DQ8 mice immunized with GAD65 both ex vivo and in vivo, by decreasing the production of pro inflammatory cytokines IL-2 and IFN-γ. Of note, DQ8-103 caused a significant depletion of DQ8+ B-cells in treated mice compared to mice injected with a control antibody.

Supported By: JDRF

221-LB

HBsAg-1018, a Two-Dose Hepatitis B Vaccine, Is Well Tolerated and Effective in Diabetic Patients Aged 60 Years or Older

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Background: Adult patients with diabetes mellitus (DM) have a greater risk of contracting hepatitis B virus (HBV) than the general population, including those ≥ 60 years of age. When infected, patients with DM have more severe HBV-related morbidity and accelerated progression. The CDC recommends HBV vaccination of all adults with DM who are ≥ 60 years of age at the discretion of the treating physician. Due to persistent challenges, including hyporesponsiveness with current 3-dose vaccines, 87% of individuals with DM who are ≥ 60 years of age remain unvaccinated. HBsAg-1018 (Heplisav-B™) is a 2-dose HBV vaccine with demonstrated higher protection rates than a 3-dose vaccine, particularly in populations known to be hyporesponsive. In this post-hoc analysis of a phase 3 trial, we assessed the safety and efficacy of HBsAg-1018 in patients with type 2 DM (T2DM) who were ≥ 60 years of age.

Methods: Patients with T2DM and who were 60-70 years old received either 2-dose HBsAg-1018 at 0 and 4 weeks and placebo at 24 weeks or 3-dose HBsAg-Eng (Engerix-B®) at 0, 4, and 24 weeks. Peak (week 24, HBsAg-1018 vs. week 28, HBsAg-Eng) seroprotection rates (SPRs) and safety were assessed by subgroups (sex, body mass index [BMI], and smoking status).

Results: A total of 480 patients (HBsAg-1018, n=327; HBsAg-Eng, n=153) were included in this analysis. Among patients who received all study injections, the peak SPR was significantly higher with HBsAg-1018 at week 24 (88.2% [231/262]) than with HBsAg-Eng at week 28, giving an overall difference of 29.7% (95% CI: 20.5, 39.1; P<.0001). SPRs with HBsAg-1018 were significantly higher compared with HBsAg-Eng regardless of sex, BMI, or smoking status (P ≤.01). Adverse events, serious adverse events, and deaths were comparable between HBsAg-1018 and HBsAg-Eng.

Conclusion: Two-dose HBsAg-1018 provides better protection against HBV than a 3-dose vaccine (HBsAg-Eng) with a similar safety profile in patients ≥ 60 years of age with T2DM regardless of subgroup.

222-LB

Regulation of Immune Cell Proliferation by microRNAs

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Transplantation of cadaveric islets is currently the only clinically recognized cell therapy for treatment of type 1 diabetes. Long-term success of this therapy is severely limited by multiple factors, including the immune-mediated destruction of transplanted islets. Development of molecular immunosuppressive strategies could offer much efficient graft survival thereby improving graft function and quality of life. Here we demonstrate that one of the novel mechanisms of immune regulation involves inter-cellular transfer of microRNAs via exosomes.

We have established and extensively characterized human islet-derived progenitor cells (hIPCs), which are generated following epithelial-to-mesenchymal transition (EMT) and proliferation (expansion) of human cadaveric islet cells. Initial characterization of hIPCs indicates that they exhibit most of the characteristics of mesenchymal stem cells, including expression of CD73, CD90 and CD105. We observed that hIPCs can significantly inhibit (>90%) in vitro proliferation of different immune cell subsets (CD4+ T, CD8+ T, CD19+ B) of (PHA)-stimulated PBMCs in a co-culture system. RNA-sequencing and validation studies pointed to a potential role of microRNAs in inhibition of T cell proliferation. Recently, microRNAs have been demonstrated to shuttle between cells and are reported to be involved in inter-cellular gene regulation. When microRNAs were analysed in hIPCs alone and in hIPCs co-cultured with PBMCs, we found a small subset of significantly altered microRNAs. These microRNAs showed increase in abundance in PBMCs from co-culture setting and were higher in co-culture supernatant. When exosomal inhibitors were used to prevent the transfer of microRNAs from hIPCs in a co-culture setting, we found that T-cell proliferation was rescued back to normal.

We believe that this study could help in discovering novel immunoregulatory molecules that may have a potential role for improving graft survival in islet transplantation for type 1 diabetes.

Supported By: Diabetes Australia; JDRF

223-LB

WITHDRAWN

224-LB

SH2B3 (lnk) Regulates Type 1 Diabetes Immune Phenotypes

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Background: The type 1 diabetes (T1D)-associated risk gene SH2B Adaptor Protein 3 (SH2B3) encodes a phosphatase with specificity for Janus Kinase 2 (JAK2). We hypothesized that variations in SH2B3 would affect immune signaling pathways relevant to T1D autoimmunity. Here we report: 1.) Occurrence of the SH2B3 risk variant among T1D patients, unaffected first-degree relatives and controls; 2.) Prevalence of SH2B3 risk genotype in African Americans in the Southeastern U.S.; and 3.) Alterations to immune composition associated with the SH2B3 risk variant.

Approach and Results: 1.) The University of Florida Diabetes Institute (UFDI) cohort (n=1946) was analyzed for genetic risk of T1D using a Taqman single nucleotide polymorphism (SNP) genotyping array with coverage of 32 SNPs. Two SNPs (rs3184504 and rs653178) corresponding to SH2B3 were in perfect linkage disequilibrium and will be described here as minor (T1D risk) or common variant. Among Caucasian subjects, the odds ratio (OR) for the minor variant among T1D subjects was 1.30 (1.06-1.59, $p=1.42x10^{-2}$), similar to previous reports. Among African American subjects, the minor variant OR was elevated (2.93, 1.22-7.03, $p=1.30x10^{-2}$), representing the most highly-associated non-HLA gene. Complete blood count (CBC, n=954) and flow cytometric human immunophenotyping (HIP, n=252) were performed on a subset of subjects. Individuals carrying the risk variant of SH2B3 had significantly more blood monocytes and neutrophils but similar numbers of lymphocytes compared to non-carriers. HIP revealed a significantly higher frequency of type 1 ($CXCR3^+$) $CD8^+$ T cells in subjects with the risk variant of SH2B3.

Conclusions: The risk variant of SH2B3 is associated with both increased risk for T1D and seroconversion in Caucasian and African American subjects. Phenotypically, this element of T1D genetic risk presents as increased frequency of some myeloid cell populations and either expansion or polarization of $CD8^+$ T cells bearing the canonical Th1 chemokine receptor CXCR3.

Supported By: American Diabetes Association (1-17-JDF-048 to M.A.W.); P01AI042288

ADA-Supported Research

225-LB

Immunomodulation of Dendritic Cells Using Tannic Acid-Based Capsules

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In type 1 diabetes (T1D), insulin-secreting β-cells are destroyed by autoreactive immune cells, for which tolerance to β-cell antigens is lost. Dendritic cells (DC) are potent antigen-presenting cells in the activation of autoreactive T cells during T1D progression. Activation of naïve CD4 T cells relies on three signals: 1.) binding of the T cell receptor with processed antigenic peptides presented by MHC-II complex, 2.) co-stimulatory molecule interactions, and 3.) synthesis of pro-inflammatory cytokines and reactive oxygen species. We previously demonstrated that dissipation of this third signal impairs autoreactive T cell activation. In this study, we tested the hypothesis that encapsulation of putative T1D autoantigens with an antioxidant-containing biomaterial would induce immune tolerance, following phagocytosis by activated DC. We generated bone marrow-derived DC and co-cultured these cells with LPS and microcapsules comprised of a neutral polymer and multilayers of tannic acid (TA), a known antioxidant. Induction of a tolerogenic DC phenotype was assessed by expression of pro-inflammatory cytokine mRNA by qPCR and secretion of cytokines by ELISA. Our data show that a subgroup of TA-based microcapsules can blunt DC responses, as shown by a significant decrease in mRNA accumulation of the pro-inflammatory cytokines Tnfa ($p \leq 0.01$) and Il12b ($p \leq 0.01$), as well as the chemokine Cxcl10 ($p \leq 0.01$). We also observed a significant decrease in secreted IL-12p70 as measured by ELISA. Future studies will encapsulate autoantigens such as insulin and following phagocytosis, determine if a tolerogenic DC phenotype can abrogate autoreactive T cell responses.

226-LB

Characterization of Islet-Infiltrating Lymphocytes in Type 1 Diabetes

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Type 1 diabetes (T1D) results in the immune-mediated destruction of insulin-producing beta cells in the pancreas. As such, immune intervention to prevent or delay T1D is an appealing therapeutic approach. Development of an antigen-specific intervention that targets the diabetogenic immune response without compromising systemic immunity is complicated by an expanding list of antigenic targets, including post-translationally modified peptides generated at the site of autoimmune attack in the islet. Thus, development of effective antigen-based therapy requires not only antigen identification, but also understanding of the unique antigen processing environment facilitated by the islet itself. Recently, cellular metabolism has emerged as a potent modulator of immune cell function. However, the metabolic state lymphocytic infiltrate in the islet, termed insulitis, is not known. Given the highly vascularized nature of the islet needed to accommodate the metabolic demand associated with insulin secretion, we sought to characterize the islet's distinct metabolic environment and its influence on T-B cell interactions at the site of autoimmune attack. Using a transgenic mouse model that develops accelerated diabetes (VH125SD.NOD), we assessed the metabolic signature of islet-infiltrating lymphocytes compared to those in the spleen and pancreatic lymph nodes. We determined that islet-infiltrating lymphocytes are characterized by decreased glucose uptake in CD4 and CD8 T cell subsets. Mitochondrial mass and polarity were decreased in all subsets compared to secondary lymphoid organs, suggesting reduced metabolic fitness. These studies reveal a metabolic distinction between islet-infiltrating and secondary lymphoid organ lymphocytes and suggest that metabolic features that differentiate immune cells at the site of autoimmune attack are a potential target for selective therapeutic interventions in T1D.

Supported By: National Institutes of Health

227-LB

"Alarming" T-Regulatory Cells (Tregs) to Protect from Type 1 Diabetes (T1D)

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Defects in IL-2 signaling and Tregs correlate with susceptibility to T1D. Helminth burden also negatively correlates with the incidence of T1D. The alarmin IL-33 and its receptor ST2 are elicited in anti-helminth immunity, which also increase Tregs, M2 macrophages and Th2 response. We hypothesized that IL-33 may cooperate with IL-2 in promoting Tregs to protect from T1D. Indeed, a major subset of Tregs express ST2, thus enabling a role for IL-33 in Treg biology. Non-obese diabetic (NOD) mice, which have less Tregs than the nondiabetic NOD.Idd3 congenic mice, also exhibit less $ST2^+$ Tregs (13±3%) than NOD. Idd3 (38±11%). For better cooperativity and preferential targeting of Tregs, we generated a hybrid cytokine (IL233) bearing IL-2 and IL-33 activities in a single molecule. Recent-hyperglycemia onset NOD mice (n≥6/group) were treated with daily injections (3.3pmol/g) of IL-2 and/or IL-33 or IL233 for 5 days. IL-33 alone offered a similar, if not better reversal of T1D with a 70% cumulative incidence (CI) compared to IL-2 alone (80% CI), whereas IL233 offered the best protection with 50% of mice remaining in remission 10-weeks post-treatment. There was a robust increase in the proportion of Tregs in pancreatic lymph node in IL233 group (25±3.7%) compared to 10±3.9%, 16±4.1%, 14±4.3% and 19±4.3% in Saline, IL-2 only, IL-33 only and IL-2 and IL-33 groups respectively. IL233 treatment also increased the levels of Tregs and group-2 innate lymphoid cells in an alternate species (rats) and blocked high-dose streptozotocin (STZ)-induced beta-cell death. Interestingly, the average islet size was bigger in the rats treated with IL233 in the STZ model, indicating a role of IL233 in islet growth and repair. Thus, IL233 utilizes the synergy of IL-2 and IL-33 to promote Tregs and bears strong therapeutic potential for T1D.

Supported By: National Institutes of Health

TRANSPLANTATION

228-LB

Photoactivation of Autologous Transplantation of Subcutaneous Adipose Tissue Improves Glucose Homeostasis

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Photoactivation of autologous transplantation of subcutaneous adipose tissue improves glucose homeostasis Increasing evidences indicated that normal adipose tissue transplantation improves whole-body energy metabolism and glucose homeostasis in a high-fat diet (HFD)-induced obese mice model. Adipose tissue macrophage is associated with glucose homeostasis and insulin resistance in type 2 diabetes and obese humans, offering a potential target for therapeutics. However, whether transplantation of autologous AT that changed macrophage phenotype directly contribute to systemic glucose intolerance has not been determined. Here we specifically developed our device, with more specific wavelengths of light, to activate macrophage phenotype in isolated sWAT from HFD mice. We found that the macrophage polarization, M1 marker genes expression, such as CD11c, IL-6 and monocyte chemoattractant protein-1, but also the M1-to-M2 ratio were increased by an HFD and decreased by photoactivation treatment. Furthermore, autologous transplantation of photoactivated sWAT into a HFD mice reduced blood glucose level and caused significant improvement in glucose tolerance, which was not shown in a sham-operated or non-photoactivated sWAT HFD mice. Moreover, Positron emission/computed tomography scans indicated higher glucose uptake in heart, but not liver, hindlimb muscles, and abdominal subcutaneous white adipose tissue. These data suggested that the correlation with photoactivation to shift ATMs polarization of HFD mice caused significant improvement in glucose homeostasis, and that autologous transplantation might be a promising therapeutic option for the treatment of diabetes.

229-LB

Increased Prevalence of Diabetes Mellitus after Lung Transplantation

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Introduction: Cardiovascular (CV) disease is a significant cause of mortality after lung transplant. However, the prevalence of diabetes and CV risk factors has not been well-characterized in this setting.

Methods: Using an electronic database and chart review, we collected and analyzed retrospective data before and 12-months after lung transplant at our institution between 2010-2016 (n=172).

Results: Between pre-transplant and 12-months post-transplant, there were increases in diastolic BP (71.2 vs. 76.5 mmHg, p<0.0001); weight (71.5 vs. 78.8 kg, p <0.0001); BMI (24.5 vs. 27.0 kg/m^2, p <0.0001); prevalence of diabetes (21.5% vs. 41.4%, p <0.0001); and prevalence of dyslipidemia (20.9% vs. 30.3%, p <0.0001). Also, more post-transplant patients used long-acting insulin (6.43% vs. 12.90%, p=0.047) and beta-blockers (8.77% vs. 18.71%, 0.0087), but fewer patients took ACE/ARB (23.39% vs. 11.61%, p=0.0055). There were no differences in A1C (6.4% vs. 6.1%, p=0.29), fasting plasma glucose (FPG) (5.96 mmol/L vs. 5.49 mmol/L, p=0.35), or proportion of patients taking metformin (5.85% vs. 2.58%, p=0.15), sulfonylurea (3.51% vs. 0.65%, p=0.075), short-acting insulin (5.85% vs. 9.03%, p=0.27), statin (18.71% vs. 13.55%, p=0.21), any anti-hyperglycemic (13.45% vs. 16.77%, p=0.40), or any anti-hypertensive (36.84% vs. 30.97%, p=0.26).

Conclusion: The prevalence of diabetes and CV risk factors observed 12-months after lung transplant was increased compared to pre-transplant. The reasons for this are unclear, but may be related to immunosuppressive medication. Although the prevalence of diabetes is higher after transplant,

the lack of differences in A1C and FPG may reflect the greater use of long-acting insulin in post-transplant patients with diabetes. Further study is needed to determine whether these risk factors contribute to an increased risk of adverse clinical outcomes and whether more systematic surveillance and management of these risk factors might mitigate this risk.

INSULIN ACTION—ADIPOCYTE BIOLOGY

230-LB

Altered Gonadal Fat Stromal Cell Populations in Adipocyte-Specific Oncostatin M Receptor Knockout Mice—A Possible Role for Local SDF1

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The IL-6 family cytokine, oncostatin M (OSM), has several physiological roles, but its exact role in adipose tissue homeostasis is still unclear. We recently reported that high-fat diet-fed male mice with an adipocyte-specific deletion of the OSM-specific receptor (OSMR FKO mice) were insulin-resistant and had increased markers of inflammation in epididymal adipose tissue (eWAT). In the current study, we more closely examined eWAT stromal cell populations in high-fat fed OSMR FKO mice using flow cytometry. Results from flow cytometry studies revealed that, despite no differences in eWAT weights between genotypes, OSMR FKO mice had significantly fewer stromal cells per gram eWAT. Although there were fewer stromal cells overall, a significantly higher percentage of these cells were CD45+ leukocytes. Significant decreases in the numbers of adipose tissue macrophages (CD64+; CD11c+/-) and preadipocytes (CD45-; CD31-; Sca1+) were also observed in OSMR FKO eWAT. A cytokine array was performed on eWAT to assess differences in tissue cytokine profiles that may contribute to the alterations observed in stromal cell populations. Array results indicated a significant decrease in stromal cell-derived factor 1 (SDF1) protein expression in eWAT of OSMR FKO mice. Future studies will focus on the role of adipocyte OSM signaling as a regulator of adipose tissue SDF1 production and stromal cell homeostasis. Overall, our results suggest a homeostatic role for adipocyte OSM signaling in the maintenance of stromal cell populations in gonadal fat.

Supported By: National Institutes of Health (P20GM103528), (P30DK072476), (K01DK106307)

231-LB

AAV-Mediated Overexpression of BMP7 in White Adipose Tissue Induces Adipogenesis and Ameliorates Insulin Resistance

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Obesity and type 2 diabetes are strongly associated and a major health problem because of their alarmingly growing prevalence worldwide. The hypertrophic expansion of white adipose tissue (WAT) promotes ectopic fat accumulation and development of insulin resistance whereas WAT hyperplasia is associated with preservation of insulin sensitivity. Several members of the Bone Morphogenetic Protein (BMP) family have been shown to play a role in white and/or brown adipogenesis and energy homeostasis. Although BMP7 has extensively been reported to induce brown adipogenesis in vitro, its role on WAT expandability and its potential contribution to insulin sensitivity remains to be elucidated. Here, we showed that local administration of adeno-associated viral vectors (AAV) encoding BMP7 in WAT resulted in hyperplasic expansion of WAT together with reduced liver steatosis and amelioration of insulin sensitivity in both HFD-fed and ob/ob obese mice. In contrast, the AAV-mediated overexpression of BMP7 specifically in the liver did not promote WAT hyperplasia although the circulating levels of BMP7 achieved were similar to those obtained after intra-WAT administration of AAV vectors. Nevertheless, when liver-derived BMP7 circulating levels were further increased, body weight and insulin sensitivity were normalised in HFD-fed as well as in ob/ob mice. Altogether, these results unravel a new role of BMP7 on white adipogenesis. In addition, this study suggests the potential of BMP7 gene therapy to ameliorate obesity and insulin resistance.

Supported By: Ministerio de Economía y Competitividad; FEDER; Plan Nacional I+D+I (SAF2014-54866R); Generalitat deCatalunya (2014 SGR 1669), ICREA (to F.B.); European Commission (MYOCURE, PHC-14-2015-667751); European Foundation for the Study of Diabetes; European Foundation for the Study of Diabetes/Lilly (to V.J.); Ministerio de Educación, Cultura y Deporte (to E.C.L., V.S.F., C.M.); Ministerio deEconomía y Competitividad (to J.R.)

232-LB

WITHDRAWN

INSULIN ACTION—CELLULAR AND MOLECULAR METABOLISM

233-LB

CB4211 Is a Potential Treatment for Metabolic Diseases with a Novel Mechanism of Action—Sensitization of the Insulin Receptor

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Metabolic dysfunction and insulin resistance are common underlying factors in the pathogenesis of nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and many age-related diseases, including obesity and type 2 diabetes. CB4211 is a novel peptide analog of MOTS-c, a mitochondrially encoded peptide with a potential role in metabolic homeostasis. CB4211 reduces free fatty acid release from cultured adipocytes, improves NAFLD activity score (NAS) in STAM® mice, and selectively decreases fat mass in DIO mice. We investigated the mechanism of action (MOA) of CB4211 in regulating fatty acid metabolism, glucose homeostasis, and insulin sensitivity. CB4211 potentiated insulin mediated inhibition of lipolysis in isoproterenol stimulated adipocyte cultures without changing maximal response, while CB4211 alone had no effect. Inhibitors of IR auto-phosphorylation (GSK183705A) or downstream PI3K/Akt signaling pathway components (wortmannin, Akti-1/2) abolished the antilipolytic effects of insulin alone and in combination with CB4211. Further supporting sensitization of insulin signaling, CB4211 enhanced insulin mediated phosphorylation of IR, IRS-1, and Akt, without affecting IGF mediated phosphorylation of IGF-1R. Consistent with activity through IR, CB4211 potentiated insulin induced reduction in glucose production in H4-IIE cells. The acute in vivo effect of CB4211 on insulin tolerance was determined in fasted DIO mice. Administration of CB4211 with insulin enhanced insulin sensitivity, prolonging the reduction in blood glucose levels compared to insulin alone.

In conclusion, CB4211 potentiates insulin effects on fatty acid metabolism and glucose homeostasis by acting at the level of IR. The observed MOA of CB4211 therefore supports its potential utility for treatment of NASH, obesity, type 2 diabetes, and other metabolic disorders.

234-LB

Exploring the Role of Insulin and IGF-I Receptor Signaling in the Pluripotency, Differentiation, and Maintenance of Stem Cells

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Pluripotent stem cells (PSCs) express insulin receptors (IR) and insulin-like growth factor-1 receptors (IGF-1R). In human embryonic stem cells (hESCs), IGF-1R is necessary for cell survival, self-renewal and differentiation into endoderm. Data on the role of IR in hESCs is limited; it's been linked to self-renewal and pluripotency of murine neural stem cells. What's still unclear is the significance of IR and IGF-1R in modulating stem cell function, pluripotency and differentiation. We created murine induced PSCs (iPSCs) with double knockout (DKO) of IGF-1R and IR. Analysis of 4 individual iPSC clones from 4 control and DKO mice showed similar cell proliferation and morphology. QPCR of pluripotency markers showed significant decreases in Lin28a ($p<0.005$) and Tbx3 ($p<0.0005$) expression in DKOs; Lin28a protein levels were also decreased. IPSCs from both groups developed into embryoid bodies in vitro and formed teratomas in vivo, indicating equal abilities to differentiate. With directed differentiation towards a neural lineage, DKOs showed upregulation of neural markers Brn2, Pax6, Sox1, Ngn2 and NeuN. We next examined downstream signaling of IR and IGF-1R. Although both groups showed mTor, Akt and Erk phosphorylation in the basal state, mTor phosphorylation in DKOs was significantly lower (28% of controls; $p<0.05$). Total mTor and Akt protein levels in DKOs were also lower (31% and 59% of controls, respectively; $p<0.05$). Prior to stimulation, basal phosphorylation of Stat3 was evident only in DKOs. It was increased 3-fold ($p<0.05$) upon treatment with IGF-1R or insulin (100 nM) compared to controls. Stimulation with LIF (100 unit/mL) led to Stat3 phosphorylation in both groups; this was 1.5-fold greater in DKOs compared to controls ($p<0.005$). These data suggest activation of a receptor independent of IR and IGF-1R and/or alterations in downstream proteins in the canonical IR/IGF-1R pathway that allow DKO iPSCs to maintain pluripotency and undergo differentiation.

Supported By: National Institutes of Health (2T32DK007260-41)

235-LB

DNA Repair Enzyme Ogg1 Regulates Hepatic Insulin Resistance in High-Fat Diet-Fed Obese Mice

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Mitochondrial DNA (mtDNA) damage has been implicated in the development of insulin resistance. The mtDNA is highly specialized and encodes for proteins essential for energy metabolism. Also, mtDNA damage heightens mitochondrial oxidative stress, which is very critical for insulin resistance. OGG1 (8-oxoguanine DNA glycosylase-1) is a DNA glycosylase mediating the first step in the base excision repair which removes 7,8-dihydro-8-oxoguanine (8-oxoG) and repairs oxidized nuclear and mitochondrial DNA. Previous studies showed that Ogg1 deficiency results in an increased susceptibility to high fat diet (HFD)-induced obesity, metabolic dysfunction and insulin resistance in mice, suggesting a crucial role of Ogg1 in glucose metabolism. In the current study, we performed a 2-hour hyperinsulinemic-euglycemic clamp to measure tissue-specific insulin sensitivity in wild type (WT) and Ogg1-/- (KO) mice after chronic feeding of low fat diet (LFD as controls) or HFD. On LFD, both WT and KO mice showed comparable body weight and insulin sensitivity. After 16 weeks of HFD, the KO mice were more obese than WT mice with significant increases in whole body fat mass. There was a strong trend of increased insulin resistance with lower glucose infusion rates and whole body glucose turnover and glycogen synthesis in HFD-fed KO mice compared to HFD-fed WT mice. Hepatic insulin action was significantly lower in the HFD-fed KO mice which was consistent with recent evidence showing Ogg1 regulation of hepatic gluconeogenesis in the fed state. This is the first evidence demonstrating that Ogg1 contributes to HFD-induced insulin resistance in liver. Our findings suggest that protecting mtDNA from damage might be crucial to prevent insulin resistance and further identify therapeutic strategies for stimulating OGG1 as potential treatment of insulin resistance.

Supported By: American Heart Association (16GRNT29150012 to L.R.); National Institutes of Health (5U2CDK093000 to J.K.K.)

236-LB

Effect of Insulin Deprivation on Brain Mitochondrial ATP Production and Mitochondrial Proteome in Diabetic Mice

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Accumulating evidence indicates a strong association between diabetic status and degenerative brain disease, including cognitive impairment. Here we hypothesized that although insulin is not necessary for glucose metabolism in brain, like in skeletal muscle insulin is critical for mitochondrial function in brain. We measured oxygen consumption rate (OCR), maximal ATP production rate (MAPR), and reactive oxygen species (ROS) production in isolated brain mitochondria of streptozotocin (STZ) diabetic mice. STZ mice deprived of insulin treatment for 96 hours (D-I), in comparison to nondiabetic mice (ND) showed a significant reduction in State 3 MAPR [1.77±0.14 vs. 2.35±0.27 (pmol/s/ug)], phosphorylation efficiency [0.42±0.04 vs. 0.54±0.07 (mol ATP produced/mol of oxygen consumed)] and respiratory control ratio [2.95±0.16 vs. 3.12±0.18] indicating reduced mitochondrial coupling efficiency during insulin deprivation. Citrate synthase and cytochrome c oxidase activities were significantly decreased in the hypothalamus of D-I compared ND. Surprisingly, no significant differences in ROS emission were detected between ND and D-I suggesting additional factors, potentially elevated ketone bodies, may protect against increased oxidative stress in the D-I brain. Proteomics analysis of the cerebrum found post-translational modification involving oxidative damage of several mitochondrial proteins that potentially cause tau phosphorylation and neurofibrillary degeneration in D-I vs. ND. In STZ mice with continued insulin treatment (D+I), state 3 OCR, MAPR, and phosphorylation efficiency were comparable to ND, demonstrating the restorative effects of insulin and euglycemia on brain mitochondrial function. We conclude that insulin deprivation and hyperglycemia significantly alter brain mitochondrial function. Insulin treatment and control of glycemia could have salutary effects on these parameters.

Supported By: National Institutes of Health

237-LB

Identification and Characterization of a Novel Insulin Sensitizer to Treat Diabetes and Nonalcoholic Steatohepatitis

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Thiazolidinediones (TZDs) enhance insulin sensitivity and have efficacy for treating nonalcoholic steatohepatitis (NASH). However, the use of TZDs, like rosiglitazone and pioglitazone, has been curtailed by significant side effects mediated via the peroxisome proliferator-activated receptor γ (PPARγ). We conducted a screen to identify compounds with insulin-sensitizing effects that did not contain a thiazolidinedione ring and act independently of PPARγ. A lead candidate, MSDC-5514, was selected for further study due to its ability to induce uncoupling protein 1 expression in brown adipocyte precursors and an inability to bind and activate PPARγ even at high concentrations. We gavaged diet-induced obese (DIO) mice with 30 mg/kg/day MSDC-5514 for six days. MSDC-5514 treatment did not affect body weight, but completely normalized glucose tolerance in insulin-resistant DIO mice. DIO mice exhibited elevated plasma insulin, free fatty acid, and triglyceride concentrations compared to lean mice, all of which were corrected by MSDC-5514 treatment. Liver diacylglycerol and triglyceride content, which were markedly increased in DIO mice compared to lean controls, were significantly decreased by MSDC-5514. The resolution of hepatic steatosis may be due to increased fatty acid oxidation since the expression of several genes encoding fatty acid oxidation enzymes was significantly elevated in livers from MSDC-5514 treated mice and directly by treatment of hepatocytes with MSDC-5514 in culture. Markers of liver injury and NASH, including plasma ALT and liver expression of markers of inflammation, stellate cell activation, and fibrosis were also attenuated by MSDC-5514 treatment. Although the molecular target of MSDC-5514 remains unclear, chemical-genetic screens are ongoing to identify the mechanism of action.

In conclusion, these data suggest that MSDC-5514 may be a new PPARγ-independent insulin sensitizer with efficacy for treating diabetes and NASH.

238-LB

Lunapark, a Novel Target to miR-126—Its Potential Role in Maintenance of ER and Glucose Homeostasis

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Strong evidence suggests that an adverse in utero and/or early postnatal environment impacts on long-term risk of developing type 2 diabetes. We showed previously that miR-126 is increased in adipose tissue of mouse offspring born to obese mothers which leads to impaired insulin signaling pathway by silencing IRS-1 at the translational level. However, the full spectrum of targets of miR-126 and consequently the consequences of its overexpression for adipose tissue function are unknown. The aim of the current study was therefore to identify novel targets of miR-126 using the proteomic technique, known as Pulsed Stable Isotope Labeling by Amino Acids (pSILAC). 3T3-L1-cells were transfected with miR-126 and their proteome compared to those transfected with a scrambled sequence. We detected 4567 proteins that were translated in adipocytes and of these 401 demonstrated a >1.3 fold decrease following over-expression of miR-126. Bioinformatic analysis revealed that 43 of these contained a miR-126 seed sequence in their 3'un-translated region. This included known miR-126 targets such as IRS-1 and VCAM-1 as well as novel targets. One of the largest changes in expression was observed for Lunapark and through the use of luciferase assays and western blotting we independently confirmed this was a direct target of miR-126. Lunapark is a key component for stabilization of nascent three-way junctions in the endoplasmic reticulum (ER). Consistent with this role we observed altered levels of mTOR and XBP1 in cells treated with miR-126, reflecting the presence of ER stress. Together, the results suggest that overexpression of miR-126 can lead to both ER stress and Insulin Resistance and therefore represent a novel link between two pathways that contribute to development and progression to T2DM.

Supported By: Fundação de Amparo a Pesquisa do Estado de São Paulo (2017/03525-08); UK Medical Research Council (MC_UU_12012/4)

239-LB

Restoration of Insulin-Receptor Expression in Adulthood Reverses Diabetic Phenotype in Type 2 Diabetes Models

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Type 2 diabetes mellitus (T2DM) is characterized by ineffective insulin action due to adult onset insulin resistance. Insulin receptor (IR) tissue content reduction in diabetes is one key contributor to the defective insulin signaling and diabetes progression. Rescuing IR levels by transgenic complementation attained beneficial effects. However, such an approach has not been considered as a treatment option since it did not always match physiological expression level or tissue selectivity and was accompanied with developmental defects as reported. In the current study, we showed that expression of human IR (hIR) via a single adeno-associated virus (AAV) administration in adult ob/ob mice normalized blood glucose and plasma tri-

glyceride (TG) to the levels of healthy control mice and significantly lowered liver TG level with long-lasting improvement in insulin sensitivity. To further examine if this approach is applicable for treating adult onset diabetes, we generated inducible whole body IR knockout (iIRKO) mice and successfully induced hyperglycemia, hyperinsulinemia and abnormal liver TG level at 3 months of age. Injection of AAV-hIR reversed tamoxifen-induced diabetic phenotype in iIRKO mice. Western blot analysis showed that while ob/ob and iIRKO mice had IR reduction detected in all metabolic tissues, their diabetic phenotypes were largely rescued by liver tropic IR expression via AAV delivery. More interestingly, the current method had no significant effect on IR expression or metabolism in healthy animals, suggesting that the approach restores IR level only as "needed" to maintain normal energy metabolism so it does not increase the risk of excessive insulin action, such as hypoglycemia. The approach described here effectively restores IR expression and insulin signaling with long lasting efficacy and low risk, which supports its therapeutic utility in the treatment of T2DM and metabolic disorders.

240-LB

Metabolic Inflexibility Revisited—Muscle Substrate Oxidation Is Mechanistically Dissociated from Muscle Insulin Resistance in Rats

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The Metabolic Inflexibility Hypothesis and Randle Hypothesis posit that alterations in muscle glucose and fat oxidation are key factors in the pathogenesis of obesity (lipid)-associated skeletal muscle insulin resistance. In order to test these hypotheses we used a stable isotope tracer ([U-^{13}C] glucose) to measure the ratio of pyruvate dehydrogenase flux and citrate synthase flux (V_{PDH}/V_{CS}), a highly tissue-specific index for the proportional contribution of glucose oxidation to total mitochondrial oxidation in vivo. We found that insulin resistant rats fed a high fat diet (HFD) for 4 weeks did not have altered substrate (V_{PDH}/V_{CS}) oxidation in soleus muscle in the fasting state (5.8%±2.5% vs. 2.6%±1.0%). Hyperinsulinemic-euglycemic clamps increased relative glucose oxidation in both normal and insulin resistant rats, although this increase was blunted in insulin resistant rats (51.6±4.9% vs. 33.3±4.5%, p<0.05), which could be mostly attributed to an impairment in insulin-stimulated muscle glucose transport flux (124.4±18.7 vs. 69.3±11.3 nmol/(g · minute), p<0.05). Additionally, we found that an acute infusion of lipid during a clamp in normal rats significantly reduced relative glucose oxidation in soleus muscle (49.0±3.6% vs. 26.7±2.7%, p<0.001) without any effects on insulin-stimulated peripheral glucose metabolism (27.2±1.4 vs. 24.3±1.5 mg/(kg · minute), NS) or muscle glucose transport (143.8±22.4 vs. 138.1±18.3 nmol/(g · minute), NS).

Conclusion: These data show that basal substrate preference in muscle is not altered in insulin resistant rats and that acute modulation of substrate oxidation in normal rats does not affect muscle insulin sensitivity, therefore challenging the Metabolic Inflexibility Hypothesis and Randle Hypothesis in the pathogenesis of lipid-induced muscle insulin resistance.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

INSULIN ACTION—GLUCOSE TRANSPORT AND INSULIN RESISTANCE IN VITRO

241-LB

The Exocyst Complex in Insulin-Stimulated Glucose Uptake in Skeletal Muscle Cells

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Objectives: Skeletal muscle cells are responsible for 80-90% of the insulin-induced glucose uptake in the body. Insulin activation of muscle cells triggers a signaling cascade that results in the exocytosis of membrane-bound glucose transporter type 4 (GLUT4) to the plasma membrane. The eight-protein complex called the exocyst is recognized as having an essential role in the insulin-induced exocytosis of GLUT4 vesicles in cultured adipocytes. We hypothesize that Sec10, a central component of the exocyst complex, is essential for the insulin-induced exocytosis of GLUT4 vesicles in skeletal myoblasts and that the exocyst is a master regulator of glucose homeostasis in metabolic tissues.

Methods/Results: To analyze exocyst-mediated intracellular trafficking in skeletal muscle in vitro, we used L6 GLUT4-myc rat skeletal myoblasts, and CRISPR/Cas9 to create Sec10 knockout (Sec10-KO) clones from these cells. Immunofluorescent staining shows co-localization of exocyst Sec10 and GLUT4 upon insulin signal in L6 myoblasts. Cellular fractionation reveals that GLUT4 delivery to the plasma membrane in response to insulin is impaired in Sec10-KO cells. Also, glucose uptake rates are significantly decreased in Sec-10-KO L6 myoblasts compared to wild type cells upon insulin stimulus. We have also generated a tamoxifen-activated skeletal muscle-specific Sec10-knockout mouse strain to assess the exocyst's role in glucose homeostasis in vivo. Sec10 knockout mice demonstrate impaired glucose tolerance compared to littermate controls.

Conclusion: Based on our findings, Sec10 and the exocyst are necessary for insulin stimulated glucose uptake in skeletal muscle. Ongoing work will further investigate the molecular mechanism of exocyst-mediated GLUT4 trafficking in skeletal muscle.

Supported By: National Institute of General Medical Sciences (1P20GM113134)

INSULIN ACTION—SIGNAL TRANSDUCTION, INSULIN, AND OTHER HORMONES

242-LB

Urocortin-2 Gene Transfer Effectively Treats Type 1 Diabetes in Mice

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Type 1 diabetes (T1D) affects 1.3 million U.S. patients. Tight glucose control reduces microvascular complications and adverse cardiovascular events. Insulin therapy is essential but has shortcomings: a) only 1 in 3 patients achieve targeted glucose control; b) aggressive insulin use increases hypoglycemia; c) 25% of T1D patients develop insulin resistance. We previously reported that urocortin-2 (UCn2) gene transfer increases insulin sensitivity and release in mouse models of type 2 diabetes. In the present study, 3m-old male Akita mice with T1D (due to Ins2 mutation) received IV saline, AAV8.Null or AAV8.UCn2 ($2x10^{12}$ gc/kg). Ten weeks after UCn2 gene transfer we saw normalization of fasting glucose, HbA1c and glucose tolerance (Table). Increased body weight and reduced water intake was seen after UCn2 gene transfer. Hyperinsulinemic euglycemic clamps showed increased insulin sensitivity and skeletal muscle glucose uptake. There was reduced nephropathy and retinopathy and increased survival (Table). Echocardiography showed improved ejection fraction (p<.001), end-systolic dimension (p<.001) and diastolic function (p<.0001). Data acquisition and analyses were blinded. The mechanisms for beneficial effects include increased insulin release and sensitivity. Thus, UCn2 gene transfer may be a viable therapy both for new onset T1D with detectable endogenous insulin, and for later stage T1D to reduce exogenous insulin needs.

Table. UCn2 Gene Transfer in Akita Mice (Type 1 Diabetes).

	Saline or AAV8.Null (n)	AAV8.UCn2 (n)	p
Plasma UCn2 (ng/mL)	1±.2 (14)	12±.9 (14)	<.0001
Urine Output (ml/hr)	.43±.06 (8)	.24±.06 (8)	.04
12 hour Fasting Glucose (mg/dL)	272±25 (8)	106±12 (8)	<.0001
HbA1c (%)	8.2±.4 (5)	5.5±.4 (5)	<.002
Glucose Tolerance Test (AUC)	3128±215 (8)	2062±286 (8)	<.0001
Insulin Release 2h post gluc (ng/ml)	.15±.01 (8)	.29±.4 (8)	.004
Glucose Infusion Rate (mg/kg/min)	12±2.89 (6)	33.6±5.3 (5)	.001
Vast Lat Glu Uptake (μM/m/100g)	8.2±.4 (7)	23.2±2.6 (6)	<.0001
Glomerulus Expansion Score	1.7±.04 (8)	1.5±.04 (8)	.01
Urine Albumin/Creatinine (3hr)	28±3 (8)	17±3 (8)	.01
Retinal Vascular Leak (%)	43±1 (5)	19±5 (4)	.001
200-day Survival (%)	0 (17 of 17 died)	82 (3 of 17 died)	<.0001

Mean ± SE; p from Student's t-test (unpaired, 2 tails); AAV8, Adeno-Associated Virus Type 8.

Supported By: National Institutes of Health; U.S. Department of Veterans Affairs

243-LB

Membrane sn-1,2 Diacylglycerol Mediates Lipid-Induced Hepatic Insulin Resistance In Vivo

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Diacylglycerol (DAG) has been proposed to mediate lipid-induced hepatic insulin resistance. Accumulated hepatic DAG activates PKCε which phos-

phorylates insulin receptor kinase (IRK) at T1160 to inhibit IRK activation and cause insulin resistance. However, the importance of DAG in lipid-induced hepatic insulin resistance remains controversial. To test the physiological effect of acute DAG accumulation on hepatic insulin sensitivity, we used antisense oligonucleotide (ASO) to specifically inhibit hepatic diglyceride acyltransferase 2 (DGAT2) which catalyzes the conversion of DAG to triglyceride. Previously, chronic DGAT2 inhibition was shown to paradoxically decrease hepatic DAG content due to decreased SREBP-1c-mediated lipogenesis and improve hepatic insulin sensitivity. However, we hypothesized that acute DGAT2 inhibition might provide a narrow window to transiently increase hepatic DAG content and allow us to identify the association between DAG, PKCε activation/translocation and hepatic insulin resistance. As hypothesized, an acute (2-day) DGAT2 inhibition increased hepatic DAG content and PKCε activation (cytosol to membrane translocation). DGAT2 ASO-treated rats on regular chow diet displayed impaired insulin-mediated suppression of hepatic glucose production. This defect of hepatic insulin action was at the level of IRK as indicated by impaired insulin-stimulated IRK Y1158/1162 phosphorylation. Furthermore, measured by a novel LC-MS/MS method, hepatic sn-1,2 DAG, which is the DAG stereoisomer capable of activating PKCε, was increased in the subcellular membrane compartment with DGAT2 ASO treatment.

Conclusion: These data support the importance of membrane sn-1,2 DAG in mediating lipid-induced hepatic insulin resistance through "increased membrane sn-1,2 DAG content -> PKCε activation/translocation -> increased IRK T1160 phosphorylation -> decreased IRK Y1158/1162 phosphorylation -> decreased IRK activity" in vivo.

Supported By: Yale University

244-LB

Role of ERK in IRF3-Mediated Immune Responses

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Insulin resistance precedes and contributes to the development of type 2 diabetes mellitus, and it is now believed that chronic inflammation is a major contributor to insulin resistance. Both cellular and secreted factors participate in the pathological and physiological changes that occur to promote inflammation. However, the molecular signaling pathways that drive these processes remain elusive. The mitogen activated protein kinase, extracellular signal-regulated kinase 1 and 2 module (ERK1/2), and the transcription factor, interferon regulatory factor-3 (IRF3), are both activated downstream of Toll-like receptor 4 and associated with the development of insulin resistance. We examined whether inhibition of ERK activity blocked IRF3-mediated immune responses. ERK1 and ERK2 isoforms can have different cellular functions; thus, to determine which ERK isoform is involved in the regulation of IRF3 activity, we performed siRNA to knockdown either ERK1, ERK2, or both in RAW 264.7 macrophages and saw 70% knockdown of each ERK1 and ERK2. Knockdown of ERK1 or ERK2 or both blocked IRF3 translocation to the nucleus with LPS treatment (100 ng/ml, 1 hour), as determined by immunofluorescence using an antibody specific for nuclear IRF3. Because phosphorylated and dimerized IRF3 translocates to the nucleus to regulate the transcription of interferon (IFN)-beta expression, we investigated whether ERK1 or ERK2 inhibited IFN-beta release. Macrophages were treated with LPS (100 ng/ml, 6 hour). LPS induced an IFN-beta production of 791±18.0 pg/ml, but knockdown of either ERK1 or ERK2 decreased the release of IFN-beta to 199±12.3 and 282±32.7 pg/ml, respectively. However, double knockdown of ERK1 and ERK 2 had the greatest inhibition of IFN-beta release (121±15.2 pg/ml).

In summary, both ERK1 and ERK2 regulate IRF3 nuclear translocation and signaling in macrophages. We propose that ERK positively regulates IRF3-mediated immune responses and inhibition of ERK signaling will protect against insulin resistance.

245-LB

Mitogenic Insulin Receptor A Increases in the Rodent Pituitary at the Onset of Puberty

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Physiological insulin resistance and hyperinsulinemia occurs at the onset of puberty, and is thought to contribute to peri-pubertal growth and development. However, in contrast to IGF-1, little is known about how insulin affects the hypothalamic-pituitary-ovarian (HPO) axis in peri-pubertal girls. Insulin has mitogenic and metabolic activity through splice-variant isoform receptors IR-A and IR-B, respectively. We hypothesize that insulin signaling in HPO tissues contributes to the initiation of puberty, and sought to determine whether IR isoform expression is differentially regulated during puberty.

We evaluated female, FVB/NJ mice: pre-pubertal, 3-4 week old mice (n=4) and peri-pubertal mice (n=7) identified within 24 hours of vaginal opening, an external marker of puberty. IR-A, IR-B, IGF-1R were quantified using a qRT-PCR assay previously validated for receptor comparison. Receptor expression was analyzed by Student's t-test after log transformation.

IR-A was the predominant IR isoform in the prepubertal hypothalamus, pituitary, and ovary, in a 20:1, 10:1, and 2:1 ratio with IR-B, respectively ($p<0.05$, all). At puberty, IR-A did not change in the hypothalamus, whereas IR-A increased by 3.6-fold ($p=0.059$) in the pituitary. IR-B remained largely unchanged during puberty in both the hypothalamus and pituitary (p=NS, respectively). Interestingly, in the peripubertal ovary which has active folliculogenesis and steroid hormone synthesis, both IR-A and IR-B decreased by 33% and 68%, respectively ($p<0.03$). As expected, IGF-1R levels were higher than IR isoforms in HPO tissues, at both developmental stages. Similar to mitogenic IR-A, IGF-1R increased in the pituitary ($p<0.059$) during puberty.

An increase in pituitary IR-A expression at the onset of puberty suggests a role for insulin signaling in regulating pituitary hormone production related to puberty. Obesity, a known risk factor for early puberty development in girls, may alter normal insulin signaling in the HPO axis.

INTEGRATED PHYSIOLOGY—CENTRAL NERVOUS SYSTEM REGULATION OF METABOLISM

246-LB

Identification of Warm-Sensitive Neurons in the Hypothalamic Preoptic Area as Powerful Regulators of Glucose Homeostasis

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Inhibition of warm sensitive neurons (WSN) in the hypothalamic preoptic area (POA) has been suggested to play a key role in the thermogenic response to cold exposure. As this response is enabled by a marked increase of insulin sensitivity in thermogenic tissues, we hypothesized that WSN inhibition mediates the metabolic as well as the thermogenic response, and therefore that WSN activation would have the opposite effects. To test this hypothesis, we utilized pharmacogenetic technology to activate or inhibit a recently identified subpopulation of POA WSN defined by their expression of the neuropeptide, Pacap, using the drug clozapine-N-oxide (CNO). We report that, as predicted, pharmacogenetic activation of this POA WSN population reduces energy expenditure (EE) (Sal vs. CNO: 0.32±0.10 vs. 0.21±0.02 kcal/hour; $p<0.05$) and core temperature (Tc) (Sal vs. CNO: 35.4±0.1 vs. 30.4±0.1°C; $p=0.0001$), while inhibition had the opposite effect (EE: Sal vs. CNO: 0.25±0.03 vs. 0.26±0.03 kcal/hour; Tc: Sal vs. CNO: 35.8±0.1 vs. 36.4±0.2°C; $p<0.05$). The response to pharmacogenetic activation of POA Pacap+ neurons was quite long-lived (~2-3 days) and was accompanied by severe glucose intolerance both 1 hour and 24 hour following CNO relative to vehicle treatment (glucose AUC: 3610±1216 for saline vs. 23985±2742 for 1 hour CNO vs. 28459±2411 vs. 24 hour CNO au; $p<0.05$ vs. saline). Moreover, this marked impairment of glucose tolerance occurred even after a compensatory increase of glucose-induced insulin secretion at the 24 hour time point (Plasma insulin (t=30): 0.42±0.10 for saline vs. 0.45±0.10 ng/mL for 1 hour CNO vs. 1.05±0.20 ng/mL for 24 hour CNO; p=ns). However, despite significant increases in Tc, acute inhibition of POA Pacap+ neurons did not improve glucose tolerance, possibly due to compensation by other WSN populations activated by the thermogenic response. We conclude that POA Pacap+ neurons constitute a subset of WSN that exert profound, previously unrecognized effects on glucose homeostasis.

Supported By: National Institutes of Health

247-LB

The Effects of Antidiabetic Drugs on Cerebral Metabolism in Mice with Central Insulin Resistance

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Objectives: This study focused on the effects of antidiabetic drugs, alogliptin (Nesina), exenatide (Byetta) and pioglitazone (Actos), on astrocyte-neuron metabolic cooperation in mice with central insulin resistance. That may provide theoretical basis for clinical treatment of diabetes related cognitive dysfunction.

Methods: Male C57BL/6J mice were randomly divided into control group (Ctrl), high-fat group (HF), alogliptin (ALO) group, exenatide (EXE) group and pioglitazone (PIO) group. Ctrl group was served normal diet, and then the others were served high-fat diet for 12 weeks. Then ALO group, EXE group and PIO group were respectively treated with alogliptin (25mg/kg/day), exenatide (30ug/kg/day) and pioglitazone (10mg/kg/day) for 4 weeks. The memory was tested using the Morris Water Maze test after 16 weeks. Then

mice were killed and the brains were removed to detect insulin signaling and metabolic parameters. All data were presented as mean±SD and P<0.05 was considered statistically different.

Results: 1.) Antidiabetic drugs improved insulin signaling, IRS1/PI3K/Akt pathway in hippocampus and cortex. 2.) Comparative analysis indicated that the latency in finding the platform significantly decreased, while frequency of crossing platform were increased in ALO group (3.75±1.14), EXE group (3.33±1.07) and PIO group (4.00±1.71) compared to HF group (1.66±1.23) (P<0.05). 3.) The results showed that the expression of glucose transporter (GLUT) 1, GLUT3, monocarboxylate transporter (MCT)1, MCT2 and MCT4 in HF group were significantly lower than those in Ctrl group, no matter in hippocampus and cortex. ALO group, EXE group and PIO group obviously reversed metabolic parameters compared to HF group.

Conclusions: We demonstrated that reprogramming metabolic pathways is an elaborate way by which neural cells respond to central insulin resistance. And antidiabetic drugs can reverse metabolic pathways to protect memory.

Supported By: National Natural Science Foundation of China

INTEGRATED PHYSIOLOGY—INSULIN SECRETION IN VIVO

248-LB

Predicting Future Glycemic Trajectories with a Mathematical Model

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Diverse pathogenesis pathways to type 2 diabetes make optimal care and prevention challenging. Identifying heterogeneous metabolic parameters of patients would be beneficial for developing personalized therapies and prediction of future glycemia. As such, we developed a mathematical model based on Ha et al. Endo 2016,) to extract metabolic parameters of patients and predict their future glycemic trajectories. We fitted longitudinal Oral Glucose Tolerance Test data from a cohort of Pima Indians to predict future glycemic trajectories. First, we estimated three major metabolic parameters from a single OGTT: peripheral insulin sensitivity, hepatic insulin sensitivity, and beta-cell function. Insulin sensitivity estimated by the fitting algorithm correlated well with insulin sensitivity measured by insulin clamp and MINMOD, R^2 =0.5 in both cases. Second, we used the fits to two OGTTs separated in time by several years to estimate capacity of beta-cell function to compensate for insulin resistance. Third, we found a strong correlation between an individual's BMI and insulin sensitivity, R^2 =0.75. Using a range of projected BMIs, the model predicts future glycemia. When measured BMIs from later time points were used, the future glycemic trajectory was accurately predicted. The mathematical model has great potential for clinical application in guiding therapy.

249-LB

Real-Time In Vivo Imaging of Whole Islet Ca^{2+} Dynamics Reveals Glucose-Induced Changes in Beta-Cell Connectivity in Mouse and Human Islets

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Imaging of Ca^{2+} dynamics in the intact islet in vitro has recently been subjected to connectivity analysis informed by similar approaches in neuronal systems. This has revealed the existence of intercellular networks between individual β cells which are increased by high glucose. Here, we sought to investigate if network connectivity also exists in islets in vivo under conditions of near-normal vascularisation and innervation. Donor mouse (C57BL/6J) islets were infected with adenovirus expressing the Ca^{2+} sensor GCaMP6m and transplanted into the anterior chamber of the eye in syngeneic recipients. Under isofluorane anaesthesia, fully implanted islets were imaged using a spinning disk confocal microscope (Nikon Ti-E, 25 x water dipping 1.0 NA objective, 300ms exposure time, 1 frame per second, 488nm excitation). Mean baseline blood glucose was 19mM and rose to >30mM following an IP bolus of 1.5g/L glucose. Human islets were infected with AV-GCaMP6m, transplanted into a nu/nu mouse recipient and imaged under conditions of normoglycaemia (blood glucose 3.9-4.9 mM followed by hyperglycaemia (blood glucose >30 mM). As circulating blood glucose increased, the proportion of connected cells in mouse islets rose from 65.5% to 88.3% (n=3 islets in 3 different animals, p=0.02) whilst the coefficient of correlation (a measure of the strength of the connectivity) showed a tendency to increase from 0.34 to 0.44 (p=NS). Data from human islets also revealed a tendency towards a rise in connectivity from 58.3% to 63.9% in response to rising circulating glucose. These data demonstrate that functional connectivity of Ca^{2+} dynamics between β cells is conserved in vivo in both mouse and human islets, with enhanced connectivity patterns observed in response to rising blood glucose levels. This technique, which allows β cell connectivity to be examined prospectively over time, will provide a powerful new approach for assessing its significance in health and disease.

Supported By: Diabetes UK; UK Medical Research Council; UK Wellcome Trust

250-LB

Therapeutic Potential of EP3 Receptor Antagonists for Treatment of Noninsulin Dependent Diabetes Mellitus across Multiple Preclinical Models

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The EP3 receptor (EP3r) is a member of the EP receptor subfamily, which facilitate a broad range of physiological and pathological prostaglandin E2 (PGE2) actions. Multiple reports have demonstrated that infusion of PGE2 blunts glucose-stimulated insulin secretion (GSIS) in healthy subjects and that inhibition of PGE2 production in noninsulin dependent diabetes mellitus (NIDDM) patients can partially restore impaired GSIS. The suppression of GSIS by PGE2 has been attributed to EP3r, resulting in the suggestion that EP3r antagonism may be an attractive strategy for treatment of NIDDM. We sought to investigate the therapeutic potential of EP3r antagonists in preclinical models. EP3r-mediated suppression of GSIS was validated in vivo using a dose-range (3-30 μg/kg/minutes) of the EP3r-specific agonist sulprostone in conscious rat ivGTTs. Using this model, we defined the EP3r antagonist plasma exposure required to oppose maximal EP3r-mediated GSIS suppression. Efficacy of an EP3r-specific antagonist was then evaluated in the GK, ZDF, and DIO/streptozotocin diabetic rat models. Despite achieving plasma concentrations at least 2-fold higher than the efficacious exposure predicted by the ivGTT model, an EP3r antagonist did not impact GSIS nor glucose homeostasis in these models. We further interrogated the ability of EP3r to suppress GSIS in conscious non-human primates (NHPs) using infusions of both sulprostone and an EP3r-specific antagonist during ivGTT. In NHPs sulprostone resulted in a significant reduction in both the fasting insulin and acute insulin response compared to vehicle. Surprisingly, EP3r agonism also significantly suppressed fasting plasma glucagon. Given the combined effect on islet hormone secretion in NHPs, and the lack of EP3r antagonist efficacy across multiple diabetic rodent models, these results call into question the therapeutic potential of EP3r antagonists for NIDDM patients.

251-LB

Impaired Beta-Cell Compensation and Glucose Effectiveness in Insulin Resistant, Nondiabetic South Asians

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South Asians (SA) are insulin-resistant (IR) and are at increased risk for developing type 2 diabetes mellitus (T2DM) when compared with Caucasians (CA). However, the changes in pancreatic β-cell responsivity, glucose effectiveness (Sg), and insulin clearance in SA are not well characterized. Healthy SA (n=30) and CA (n=30) matched for age, sex, and BMI and with no history of T2DM were evaluated in the Clinical Center. A frequently sampled intravenous glucose tolerance test (FSIVGTT) and a mixed meal test (MMT) were used for minimal modeling (MM). Insulin sensitivity, beta-cell function, and glucose effectiveness were calculated. Tissue-specific surrogate indices of insulin sensitivity and post-prandial incretin levels were also measured. SA were less insulin-sensitive (SI: 3.30±2.72 vs. 7.31±4.89, minutes-1/μU/mL, p<0.001; Matsuda index: 4.34±3.69 vs. 13.26±7.17, p<0.05). Tissue specific IR surrogate indices (hepatic IR index and adipocyte IR index) were higher and muscle insulin sensitivity index was lower in SA. Sg derived from an FSIVGTT was lower in SA (0.025 ± 0.033 vs. 0.012 ± 0.006, minutes-1, p<0.001). Beta-cell responsivity indices estimated by the C-peptide MM [phi (dynamic), phi (static), and phi (total)] were not different between the groups, but the disposition indices were significantly lower in SA. Post-prandial GIP but not GLP-1 levels were higher in SA than in CA. Insulin clearance at baseline and following MMT was also significantly lower in SA. Thus, when compared with age-, sex-, and BMI-matched CA, SA exhibit reduced overall insulin sensitivity in the muscle, liver, and adipose tissue. Despite

similar β-cell responsivity to glucose, the disposition indices in SA were lower, suggesting diminished beta-cell compensation. In addition to defects in insulin-mediated glucose disposal and impaired beta-cell compensation, normoglycemic SA have reduced glucose effectiveness. These results suggest different approaches to prevent and treat T2DM in SA.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases

INTEGRATED PHYSIOLOGY—LIVER

252-LB

GCN5l1 Modulates Cross Talk between Mitochondria and Cell Signaling to Regulate Fox01 Stability and Gluconeogenesis

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The mitochondrial enriched GCN5-like 1 (GCN5L1) protein has been shown to modulate mitochondrial protein acetylation, mitochondrial content and mitochondrial retrograde signaling. Here we show that hepatic GCN5L1 ablation reduces fasting glucose levels and blunts hepatic gluconeogenesis without affecting systemic glucose tolerance. PEPCK and G6Pase transcript levels are downregulated in hepatocytes from GCN5L1 liver specific knockout mice and their upstream regulator, FoxO1 protein levels are decreased via proteasome-dependent degradation and via reactive oxygen species mediated ERK-1/2 phosphorylation. ERK inhibition restores FoxO1, gluconeogenic enzyme expression and glucose production. Reconstitution of mitochondrial-targeted GCN5L1 blunts mitochondrial ROS, ERK activation and increases FoxO1, gluconeogenic enzyme expression and hepatocyte glucose production. We suggest that mitochondrial GCN5L1 modulates post-translational control of FoxO1, regulates gluconeogenesis and controls metabolic pathways via mitochondrial ROS mediated ERK activation. Exploring mechanisms underpinning GCN5L1 mediated ROS signaling may expand our understanding of the role of mitochondria in gluconeogenesis control.

Supported By: National Institutes of Health

253-LB

Liver-Specific Deletion of the Mitochondrial Stress UBL-5 Gene Leads to Fatty Liver That Is Rescued by Pioglitazone Administration or ACE2 Overexpression

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Fatty liver disease is associated with metabolic syndrome, increased risk of type 2 diabetes (T2D), and other metabolic complications. There has been little progress in treatments for fat-induced liver failure and further studies are required for clarification of mechanisms. Mitochondrial dysfunction has been implicated in insulin resistance and is associated with hepatic fat accumulation and T2D. Studies in C. Elegans have shown that UBL-5 is involved in the activation of the mitochondrial unfolded protein response (UPRmt). This pathway upregulates mitochondrial proteases and chaperone proteins to alleviate proteostatic stress. To further explore the role of UBL-5 in the mammalian UPRmt, we generated a tamoxifen-inducible, liver-specific UBL-5 knockout mouse. Liver-specific deletion of UBL-5 in adult mice caused increased plasma hepatic enzymes, gross steatosis and death within 12 days following tamoxifen-induction. Histological examination of the liver revealed severe and diffuse multifocal hepatocellular necrosis, vacuolation, inflammation, lipid accumulation, and apoptosis. Most UPRmt genes (CHOP, ClpP, ClpX, Lonp1, HSP10, HSP70, ATF-5) were downregulated while mtHSP70 was upregulated. PGC1a mitochondrial biogenesis gene was downregulated. Interestingly, angiotensin-converting enzyme 2 (ACE2) expression was also reduced in KO livers. Mice were then treated with pioglitazone, or an ACE2-containing virus to determine if such treatments provide benefit. ACE2 expression was increased with both ACE2 virus and pioglitazone treatment. Liver enzymes showed significant improvement after treatment with both pioglitazone and ACE2.

In conclusion, we have generated a model that develops severe fatty liver disease and have shown that both genetic and pharmacological therapies may diminish this disease process. This study provides the first evidence for a critical role for UBL-5 in hepatic function.

254-LB

Collagen VI-Derived Endotrophin Promotes Hepatic Apoptosis, Inflammation, and Fibrosis in Chronic Liver Disease

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Type VI collagen alpha3 chain (Col6a3) is a biomarker for hepatic fibrosis and poor prognosis of hepatocellular carcinoma (HCC), but its function in liver pathology remains unknown. Analysis of human HCC patients revealed that elevated mRNA levels of COL6A3 in tumor-proximal liver regions were associated with poor prognosis in HCC patients. Here, we show that endotrophin (ETP), a cleaved Col6a3 fragment, significantly augmented hepatocyte apoptosis, inflammation, and fibrosis in chemically induced chronic liver disease models by utilizing either CCl_4 or DEN in the background of hepatocyte-specific ETP transgenic mice, nevertheless ETP per se showed a limited phenotypic changes in liver tissues. Notably, both hepatocytes and non-parenchymal cells in liver tissues were responsible for an increase of ETP levels in chronic liver injuries, and inhibition of ETP with neutralizing antibodies (10B6) ameliorated hepatic apoptosis, inflammation, and fibrosis in these cells. Our results mechanistically implicate ETP as a necessary component for sustained JNK activation in early stage of chronic liver diseases; thus, ETP-JNK axis could be a promising therapeutic target, particularly in individuals with high local levels of COL6A3 in chronic liver disease.

Supported By: Korea Health Industry Development Institute (H14C1277); Bio-Synergy Research Project (NRF-2017M3A9C4065956); National Research Foundation of Korea (2018R1A2B6003878)

255-LB

SGLT Inhibitors Enhance Endogenous Glucose Productions (EGP) in a Preclinical Animal Model

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Aim: SGLT inhibitors was found to paradoxically enhance EGP in type 2 diabetes patients, while reduce EGP in diabetic mice during hyperinsulinemic-euglycemic clamp. In this study, we assess acute and 7-day effects of SGLT inhibitors on EGP in rats by ^{13}C-glucose tracer dilution method to identify a translational rodent model.

Method: SD rats aged 7 weeks were assigned to 3 groups (n=6 each), vehicle, LX4211 (10 mg/kg) and canagliflozin (10 mg/kg). On day 1, rats were fasted for 3 hours and dosed with SGLT inhibitors, LX4211 or canagliflozin before a ^{13}C-glucose IV injection (25 mg/kg) 2 hour post drug administration. Blood were collected at 0, 5, 15, 30, 45, 60, 75, 90, 120, and 150 minutes time points. Plasma ^{13}C-glucose and ^{12}C-glucose levels were detected by LC/MS. EGP was calculated by multiplying fractional glucose turnover rate by pool size. After washout and the same 18 rats were dosed for 7 days, EGP were assessed on day 7.

Results: ^{13}C--glucose IV injection after acute LX4211 and canagliflozin dosing did not significantly changed plasma glucose concentration over time, but led to a rapid rise in plasma ^{13}C-glucose enrichment followed by a time-dependent decrease of ^{13}C-glucose enrichment. The fractional glucose turnover rate and EGP were 3.14±0.35 (SD) percent and 6.28±0.70 (SD) mg.kg^{-1}.minutes^{-1} in vehicle group. Single dose of LX4211 and canagliflozin significantly increased EGP by 27.5% and 57.1%, respectively. After 7-days of treatment, the fractional glucose turnover and EGP were 3.30±0.28 (SD) percent and 6.59±0.56 (SD) mg.kg^{-1}.minutes^{-1} in vehicle group, which was highly consistent to the previous EGP measurement. Moreover, 7 days treatment of LX4211 and canagliflozin significantly elevated EGP by 24.8% and 33.4%, respectively.

Conclusion: This study demonstrated that SGLT inhibitors can increase EGP in animal model as in type 2 diabetes patients. Detecting EGP using ^{13}C-glucose tracer dilution method may facilitate the discovery of novel SGLT inhibitors with differential effects on EGP.

256-LB

Regulation of Systemic Energy Metabolism by a Human-Specific Long Noncoding RNA In Vivo

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Long non-coding RNAs (lncRNAs) are widely expressed in mammals and play critical roles in a broad array of physiological processes. We have recently demonstrated that lncRNAs sense and regulate lipid and glucose metabolism in mice. However, it remains to be determined whether human lncRNAs regulate metabolism in vivo and whether they play a role in the pathogenesis of human metabolic disorders. The lack of knowledge of lncRNA's functions in human metabolism is partly caused by the extremely low sequence conservation between human and mouse lncRNAs, which makes it difficult to apply the functional information of mouse lncRNAs to human physiology. To overcome this limitation, we have produced liver-specific humanized mice in which over 80% of mouse hepatocytes in the liver can be replaced by human ones and have confirmed that human metabolic genes in these mice maintain proper responses to metabolic cues. Using the liver-specific humanized mice, we identify a **F**asting induced, **H**uman-specific, and **L**iver-enriched lncRNA (lncFHL). Knocking down of lncFHL in humanized mice results in decreased expression of genes in Peroxisome Proliferator Activated Receptor Alpha (PPARalpha) pathway, which leads to

decreased fasting plasma glucose and ketone levels. We further find that lncFHL interacts with and affects the mRNA interactions of HuR, a RNA binding protein that suppresses hepatic PPARalpha pathway in human. Finally, by analyzing published genome-wide association studies (GWAS) and expression quantitative trait loci (eQTLs) data, we find the hepatic expressions of lncFHL are associated with human metabolic diseases including diabetes and coronary artery disease. These studies not only provide a proof of principle that the humanized mice could sever as a suitable model to study the metabolic function of human lncRNAs but also demonstrate that regulatory mechanism mediated by human-specific lncRNAs contributes significantly to physiological and pathophysiological metabolic homeostasis.

Supported By: National Institutes of Health

257-LB

Vitamin E Supplementation during Nonalcoholic Steatohepatitis (NASH) Pathogenesis in High-Sucrose, High-Fat-Fed Genetically Obese Mice

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Nonalcoholic fatty liver disease is characterized by dysregulated hepatic oxidative metabolism which may progress to a state of elevated inflammation and fibrosis (NASH). The lipophilic antioxidant vitamin E (VitE) has shown promise as an effective strategy for treating NASH in some clinical trials. Here we tested whether dietary VitE supplementation is sufficient to prevent NASH development and mitigate aberrant glucose and oxidative liver metabolism during overnutrition. Hyperphagic, melanocortin-4-receptor deficient mice ($MC4R^{-/-}$) were fed a chow, western diet (WD) or WD+VitE (500IU/kg diet) ad lib starting at 8 or 20 weeks of age. All mice were studied at 28 weeks of age; thus, 5, 28 week-old $MC4R^{-/-}$ groups were investigated: chow, WD or WD+VitE for 20 weeks, and WD or WD+VitE for 8 weeks. This design allowed us to test whether VitE limits NASH pathogenesis after an intermediate or long exposure to WD. Mice (n=8-11, per group) underwent jugular vein and carotid artery catheterization for $^{13}C/^{2}H$ isotope-based metabolic flux analysis to calculate in vivo liver glucose and citric acid cycle fluxes. Body weight and fat mass were unaffected by WD or WD+VitE feeding for 8 weeks. 20 weeks of WD or WD+VitE, however, increased these parameters relative to chow. Glucose production, gluconeogenesis, and pyruvate cycle fluxes were also elevated by 20 weeks of WD or WD+VitE feeding. Unlike mice fed WD for 8 weeks, WD+VitE for 8 weeks also accelerated gluconeogenesis. All mice fed a WD or WD+VitE had increased hepatocellular steatosis, ballooning, lobular inflammation and activity compared to chow; fibrosis was more extensive in mice fed a WD or WD+VitE for 20 weeks. Thus, the provision of VitE during hyperphagia and WD failed to limit NASH pathogenesis. In fact, shorter term VitE supplementation accelerated WD-mediated changes in glucose production, indicating VitE may actually exacerbate the dysregulation of liver metabolism that occurs in response to chronic overnutrition.

Supported By: National Institutes of Health (R01DK106348)

258-LB

Assessment and Expansion of Models for ^{13}C-Metabolic Flux Analysis (MFA) In Vivo

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Isotope-based MFA is a valuable tool to determine rates of biochemical reactions in vivo, which cannot be assessed by other approaches. Its application in biomedicine may help to uncover metabolic disease determinants in diabetes and obesity. However, various simplifying assumptions have been applied to constrain models used for in vivo MFA studies. These constraints are approximate, and their validity may change with varying experimental conditions. Here we used our flexible flux modeling platform (INCA) to test and eliminate several assumptions imposed on prior estimates of liver gluconeogenesis, anaplerosis, and citric acid cycle (CAC) fluxes in overnight fasted, conscious mice. Male C57Bl/6J mice were given a primed, continuous infusion (160µmol/kg and 40µmol/kg/minutes) of [$^{13}C_3$]lactate intravenously for ~2 hour. ^{13}C-enrichment of plasma and liver metabolites obtained at the end of the study were measured by GC-MS and used to regress liver metabolic fluxes using several different models of in vivo metabolism. In particular, we developed models to assess 1.) the extent of reversibility of 4C reactions of the CAC, 2.) the impact of pyruvate-decarboxylation, and 3.) the influence of secondary isotope recycling on liver flux estimates. Confidence intervals were computed a posteriori to assess uncertainties of individual flux estimates. Glucose production originated largely from PEP. Cataplerosis (PEPCK flux) was ~3.9-4.5 fold higher than citrate synthase, with ~56-67% recycling back to the CAC through pyruvate. The modeling of pyruvate decarboxylation increased the relative ratio of gluconeogenesis to citrate synthase flux by ~18-32% but also reduced the precision of flux estimates. Interestingly, Cori cycling reduced pyruvate kinase flux ~16% relative to cataplerosis. Thus, interorgan crosstalk with the liver can be estimated with fewer assumptions in vivo, providing a potential path for understanding metabolic disease with greater consideration of whole-body physiology.

Supported By: National Institutes of Health (R01DK106348)

259-LB

Evaluation of Hepatic Steatosis and Fibrosis Using Transient Elastography in Partial Lipodystrophy Patients

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Introduction: Partial lipodystrophy (PL) is a rare disease associated with insulin resistance and metabolic dysfunctions, including NAFLD. Global prevalence of NAFLD is ±25%. In PL patients NAFDL prevalence and severity remains unclear.

Aims: To evaluate the presence of hepatic steatosis and/or fibrosis in PL patients using transient elastography (TE) in comparison to a control group.

Materials and Methods: Fifteen patients (7 with PL of the limbs, 8 with Familiar Partial Lipodystrophy Dunnigan-type) and 15 (13 women) controls paired to BMI and age were included. We recruited participants aged 18-65 years-old and a BMI≥25 and ≤35kg/m², excluding other causes of steatohepatitis. Anthropometric measures, metabolic parameters and the presence of steatosis/fibrosis using TE(Fibroscan®) were evaluated. According to literature, the adopted cut-off values in TE for Controlled Attenuation Parameter (CAP) and Liver Stiffness Measurement (LSM) are ≥238dB/m and ≥5,8kPa, respectively. Student t-test was used for continuous variables. Main results are presented as Mean ± SD.

Results: Mean age was 52.93 and 50.26 years-old in PL and control groups, respectively. BMI was slightly but not significantly higher in control group (30,13kg/m² [SD±2,85] vs. 27,43kg/m² [SD±5,30]). Waist-to-hip ratio did not differ. PL group had higher fasting plasma glucose (116.78mg/dL [SD±39,54] vs. 89,58mg/dL [SD±23,34], p= 0,0476). No differences in hepatic lesion biomarkers or lipid profile was noted, except for a lower HDL-c in PL group (40,64mg/dL [SD±9,45] vs. 49,62mg/dL [SD±12,67], p=0,0432). CAP tended to be higher in PL patients [301,82dB/m (SD±54,88) vs. 262,93dB/m (SD±57,44); p=0,0685] and LSM was significantly higher (7,32kPa [SD±3,71] vs. 4,94kPa [SD±1,58], p=0,0260).

Conclusions: Patients with PL presented a trend for increased hepatic steatosis and showed higher values of fibrosis in TE. Therefore, we suggest PL patients should undergo TE for screening of NAFLD.

260-LB

Clinical Features and Hepatic Molecular Characteristics in NAFLD and NASH Patients Compared to Normal Weight Healthy Individuals

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The molecular events underlying the development and progression of nonalcoholic fatty liver disease (NAFLD), covering a wide spectrum from simple hepatic steatosis to the more aggressive inflammatory manifestation, nonalcoholic steatohepatitis (NASH), remain elusive. To promote the understanding of the pathophysiology behind this disease spectrum we characterized lean controls vs. individuals with simple NAFLD and NASH, respectively, by standard clinical measures, histopathology and global mRNA profiling of liver biopsies.

The study included 11 patients with simple NAFLD, 11 patients with NASH (based on the FLIP/Bedossa score) and 15 lean healthy individuals. Liver biopsies from all subjects were evaluated using diagnostic histopathological scoring of steatosis, inflammation, fibrosis and ballooning degeneration of hepatocytes. Global mRNA quantification of liver biopsies was performed by RNA-sequencing.

No steatosis was seen in the lean healthy individuals, whereas all patients with simple NAFLD and NASH displayed moderate steatosis, and to some degree inflammation and fibrosis. Only NASH patients had ballooning degeneration of hepatocytes. Several marker genes such as collagens and galectin-3 showed good correlation with disease severity being markedly upregulated in the NAFLD and NASH groups compared to healthy controls. However, the histopathological categorization of patient samples into NAFLD and NASH did not correlate well with gene expression levels.

We here provide a unique characterization of a cohort of individuals covering the spectrum from healthy lean subjects over individuals with simple NAFLD to patients with NASH. Clinical markers as well as hepatic pathology and gene expression clearly discriminate NAFLD/NASH patients from healthy individuals, but NAFLD and NASH patients appear highly similar at all parameters, except for histopathological scoring of ballooning.

INTEGRATED PHYSIOLOGY—MACRONUTRIENT METABOLISM AND FOOD INTAKE

261-LB

Neuronal FGF-21 Signaling—A Sensor of Dietary Protein Restriction

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The central nervous system is acknowledged as a major regulator of both energy and glucose homeostasis. Our data demonstrate that dietary protein restriction increases energy expenditure and improves glucose homeostasis, and that the metabolic hormone FGF-21 coordinates these adaptive responses. However, the tissue site mediating these FGF-21-dependent effects is unclear. In this study, mice with dysfunctional FGF-21 signaling in either the central nervous system (CNS) or adipose tissue were fed a control or low protein (LP) diet to assess changes in body weight and associated metabolic endpoints. We first deleted the required FGF co-receptor beta-Klotho (Klb) from neurons to test whether CNS FGF-21 signaling is required for increased energy expenditure or improved glucose homeostasis in mice consuming a low protein diet. Our data show that LP diet increased energy expenditure ($p \leq 0.01$) and reduced body weight ($p \leq 0.001$) in control littermates, but these effects were lost in mice bearing CNS-specific deletion of Klb ($p=0.65$). Protein restriction in the context of a high fat diet also improved glucose tolerance ($P \leq 0.001$) and insulin sensitivity ($p \leq 0.001$) in control littermates, but these effects were also lost in mice lacking Klb in the CNS. We next tested whether FGF-21 signaling within adipose tissue contributed to the metabolic effects of protein restriction. However, in this case LP diet reduced body weight ($p=0.90$) and increased food intake ($p= 0.98$) similarly in control littermates and mice bearing adipose-specific deletion of Klb. Collectively, these data highlight CNS FGF-21 signaling as the first known neuroendocrine mechanism to explain the coordinated metabolic changes induced by dietary protein restriction.

Supported By: National Institutes of Health (F32DK11513701, R01DK105032)

262-LB

Changes in Carbohydrate Metabolism are Related to Gut Microbiota Modification after H. Pylori Eradication

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Introduction: Antibiotic treatments cause changes in gut microbiota. Dysbiosis of gut microbiota has been linked to metabolic diseases such as type 2 diabetes mellitus (T2DM). Objective: To evaluate whether changes in gut microbiota due to antibiotic treatment in patients colonized by H. pylori, could be related to improvements in carbohydrate metabolism.

Material and Method: A prospective case-control study were performed. Clinical data, carbohydrate metabolism, and microbiota composition in feces (determined by 16S rRNA gene (V3-V4) sequencing using the Illumina Miseq) before and 2 months after eradication treatment were analyzed.

Results: We studied 40 cases and 20 controls (60% women, respectively). Average age was 47.0 ± 2 vs. 43.6 ± 2.7 years old. 70% vs. 60% had family history of digestive disorders and 42.5% vs. 40% clinical history of gastrointestinal disease. After antibiotics, we found significant changes in gut microbiota profile at phylum, family, genus and species levels. The Chao and Shannon indices showed a decreased in bacterial richness and diversity in patients (pre and post H. pylori eradication) compared to controls. We observed an improvement in glucose homeostasis in cases 2 month after H. pylori eradication treatment, with decrease in HbA1c ($p=0.014$), 60' ($p=0.018$) and 120' ($p=0.019$) glucose post OGTT. Changes in Rikenellaceae, Butyricimonas, E. biforme, B. fragilis, and Megamonas were inversely associated with changes in glucose level and Hb1Ac in patients which got H. pylori eradication.

Conclusion: H. pylori eradication treatment causes alteration in human gut microbiota. The glucose homeostasis improvement found after antibiotic treatment was related to changes in microbial community, particularly in Megamonas and Butyricimonas genus, Rikenellaceae family and E. biforme and B. fragilis species. SCFA-producing and glucose remover bacterias could play an important role in these associations.

263-LB

Integrative Analysis of Human Plasma Proteome/Metabolome Reveals Central Role for Phospholipid, Retinol, and Histidine Metabolism after Gastric Bypass

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Bariatric surgery has emerged as a potent approach to improve obesity-related metabolic comorbidities including type 2 diabetes (T2D). However, molecular mechanisms responsible for metabolic improvement after bariatric surgery remain incompletely understood. We profiled and integrated the fasting plasma proteome (aptamer-based Somalogic platform) and metabolome (MS, Metabolon) from patients with T2D at baseline and up to 3 years after randomization to either gastric bypass (GB) or nonsurgical diabetes/weight management (DMW) within the SLIMM-T2D longitudinal clinical trial (random subset, n=19 per group). To identify top-ranking pathways encompassing both proteomic and metabolomic data, we developed a systems approach employing two interdependent programs: ezlimma (for differential analysis) and Pathway Analysis via Network Smoothing (PANTS). PANTS smooths differential statistics over a large network of interacting proteins/metabolites, calculating significance by permutation. Top-ranking pathways were phospholipid (e.g., choline), retinol (e.g., retinol-binding protein 4, RBP4), and histidine metabolism (e.g., carnosine dipeptidase 1, CNDP1). Quantitative Western blot confirmed 26% reduction in RBP4 in GB vs. DWM; ELISA confirmed 66% reduction in CNDP1 in GB vs. DWM (both $p<0.05$, 3 months). CNDP1 change at 3 months was associated with improved metabolism at 1 year (BMI $r=0.67$, $p<10^{-5}$; HbA1c $r=0.61$, $p<10^{-4}$). Causal inference analysis in the entire cohort identified CNDP1 change at 3 months as the most likely protein to cause improved HbA1c at 1 year ($p=0.01$). Decreased CNDP1 occurred before significant weight loss, suggesting weight-independent impact on glycemia. Investigating modulation of CNDP1 activity, its enzymatic products Ala/His, and related metabolites will be important to determine if these pathways may serve as targets for T2D therapy.

Supported By: MedImmune (to M.E.P.); Charles A. King Trust Fellowship; Medical Foundation (to Y.Y.); National Institutes of Health (RC1DK086918, R56DK095451); Joslin Diabetes and Endocrinology Research Center (DK036836)

264-LB

New Prebiotics to Ameliorate High-Fat Diet-Induced Obesity and Diabetes via Modulation of Microbiome-Gut-Brain Axis

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Role of gut microbiome in obesity and diabetes became apparent from several independent studies, indicating that gut microbiome modulators like prebiotics may improve microbiome perturbations (dysbiosis) to ameliorate metabolic derangements. We isolated water soluble, non-digestible polysaccharides from 5 foods (acorn, quinoa, sunflower, pumpkin and sago seeds) and assessed their impact on amelioration of high fat diet (HFD)-induced obesity and diabetes in mice and human microbiome using fecal slurry culture model. During isolation, purification, biochemical and digestion resistance characterization, and fermentation pattern by human fecal microbiome, we selected acorn and sago derived prebiotics, on the basis of purity, protein contamination and yield. All prebiotics increased short chain fatty acid (SCFA) production along with enhanced microbial diversity. Feeding of acorn and sago derived prebiotics supplemented HFD (5%) for 8 weeks, significantly reduced diet induced glucose intolerance and insulin resistance, without affecting adiposity. Beneficial effects of acorn and sago derived prebiotics were superior than inulin-feeding. Feeding of both prebiotics and inulin increased diversity of gut microbiome and enhanced SCFA production into the mice gut. Metabolic function was positively correlated with increased food conversion ratio indicating enhanced whole body metabolic rate by prebiotic feeding. Gastrointestinal motility was enhanced without changing food intake, after probiotic intervention. Hypothalamic energy signaling in terms of increased pro-opiomelanocortin and decreased agouti-related peptide and neuropeptide Y expression, was modulated by prebiotics administration. These results indicate that newly isolated prebiotics ameliorate HFD-induced defects of glucose metabolism via modulating microbiome-gut-brain axis, and can be used to prevent/treat diet induced obesity and diabetes.

265-LB

Effects of a High-Carb vs. High-Fat Meal on Glycemia, Insulin, Interleukin-6, TNF-Alpha, and Apo-B

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Past studies have shown that food ingestion modulates vascular function within the first two hours of consumption and that food composition such as the amount of carbohydrates vs. fat may play a role. The goal of this study was to assess the effect of a high-carbohydrate (HC) meal vs. a high-fat (HF) meal on potential modulators of vascular function, insulin, interleukin-6 (IL-6), TNF-alfa and Apo-B. We studied a group of healthy volunteers; n=6, age 38 ± 13 years, BMI 24.5 ± 3.8 kg/m2 and systolic blood pressure 125.3 ± 9.1 mmHg. The meals were commercially available; HC meal consisted of 120 gm of carbohydrates (~60% sugars) and 8 gm fat, and the HF meal consisted of 54 gm of carbohydrates (~ 15% sugars) and 28 gm of fat and contained slightly (~20%) less total calories. The meals were ingested within 5 minutes.

Results: Glucose and insulin levels increased in response to either meal but more robustly with HC. Glucose and insulin levels peaked at 30 minutes in response to HC and at 60 minutes in response to HF. IL-6 levels nearly doubled in response to either meal, but the time course appeared different; it peaked at 180 minutes and 60 minutes in response to HC and HF, respectively. TNF-alpha levels remained overall unchanged after either HC and HF meal. Apo-B levels also remained overall unchanged after either HC and HF meal.

Conclusions: Our study shows that food composition differentially affects the magnitude and time course of changes in metabolites, hormones and markers of inflammation. Ingestion of a HF meal resulted in a delayed and lower peak of glucose and insulin and a much earlier peak in IL-6. This early elevation of IL-6 in response to HF may potentially impair vascular function as described in the "big Mac" study. It is unclear if higher insulin levels during this period would be vaso-protective. Further research is needed to better understand the link between food composition and changes in metabolites, hormones and pro/anti-inflammatory mediators and its relation to vascular function.

INTEGRATED PHYSIOLOGY—MUSCLE

266-LB

Beta-Cell Function and Survival Are Modulated Differentially by Type I or Type II Muscle through Specific Myokines

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Type 2 diabetes has a complex pathophysiology implicating several organs as the adipose tissue the liver, the skeletal muscle and the pancreas. Tissue crosstalk is emerging as a determinant way to coordinate the different organs implicated in glucose homeostasis. Among the inter-organ communication factors, muscle-secreted myokines can modulate the function and survival of pancreatic beta-cells. We establish human primary in vitro models of cells isolated from soleus (type I), triceps brachii (type II) and vastus lateralis (mixte) muscles to study the myokines profile secretion using and antibody-based array, the transcriptome using RNA-sequencing, and their sensitivity to TNF-alpha-induced insulin resistance, by assessing the glucose uptake rate. We then investigate how the muscle type and insulin resistance status impact on beta-cell function (glucose stimulated insulin secretion), survival (proliferation and apoptose) in order to identify new myokines in fiber type specific muscle pancreas crosstalk. We show that type I and type II primary myotubes present specific mRNA and myokine signatures as well as different sensitivity to TNF-alpha induced insulin resistance (TNF-alpha failed to induce insulin resistance in type II muscle). We also report here that the impact of myokines on beta-cells proliferation, apoptosis and insulin secretion, depends on fiber types and their metabolic status. Finally, that angiogenin and osteoprotegerin are triceps specific myokines with beta-cell protective actions against proinflammatory cytokines. These results suggest that type I and II muscles could impact insulin secretion and beta-cell mass differentially in type 2 diabetes through specific myokines secretion.

Supported By: Swiss National Science Foundation (N°31-135645); Bo & Kerstin Hjelt Diabetes Foundation; JDRF (31-2008-413); Centre Européen d'Etude du Diabète

267-LB

Unraveling the Athlete's Paradox—Higher Insulin Sensitivity and Lower PKCθ Activation Despite Higher Bioactive Lipids in Endurance-Trained Athletes

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High intramyocellular lipid (IMCL) content associates negatively with insulin sensitivity (IS) in insulin resistant, but not in endurance-trained humans. It has been hypothesized that different cellular distribution of bioactive lipids such as diacylglycerols (DAG) and ceramides (CER) could interfere with insulin action and underlie this "athlete's paradox." We examined endurance-trained athletes (ATH; n=9) and sedentary individuals (SED; n=12) with comparable total IMCL, as measured by ^{1}H-magnetic resonance spectroscopy, who underwent spiroergometry and hyperinsulinemic-euglycemic clamps to assess maximal oxidative capacity and IS, respectively. In skeletal muscle biopsies, translocation of protein kinase C (PKC) θ and ε were determined by Western blotting and concentrations of DAG and CER were measured using targeted LC-tandem mass spectrometry upon separating fractions of cellular membranes, lipid droplets and cytosol by ultracentrifugation. Maximal oxidative capacity and IS were 46% and 47% higher in ATH than in SED (both $p<0.01$), respectively. The membrane:cytosol ratio of PKCθ, which reflects PKCθ activity, was 62% lower in ATH consistent with their increased IS ($p<0.01$), while there was no group difference for PKCε. Total and membrane DAG (40% and 48%, both $p<0.01$) as well as membrane CER (15%, $p<0.05$) were higher in ATH while the respective concentrations in lipid droplets and cytosol did not differ. In SED, IS correlated inversely with all stereoselective subspecies of lipid-droplet DAG. On the other hand, cytosolic sn-1,2 (C16:0-C18:2) and sn-1,3 (C18:1-C18:0) DAG correlated positively with IS in ATH.

In conclusion, higher IS in endurance-trained ATH can be explained by lower muscle PKCθ activation, which may be due to differences in the stereoselectivity and/or subcompartmentation of cellular DAG between ATH and insulin resistant SED.

268-LB

The Induction of TRIB3 Causing Glucose Toxicity in Muscle Requires the O-GlcNAcylation of SP1

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Background: Glucose-induced insulin resistance is mediated by induction of the pseudokinase TRIB3, which requires glucose metabolism via the hexosamine biosynthetic pathway (HBP). We have also shown that the SP1 binding site in the TRIB3 promoter region is essential for glucose's ability to induce TRIB3 in skeletal muscle. However, the mechanism by which glucose regulates TRIB3 gene expression remains unknown.

Hypothesis: Since the HBP provides the substrate for O-GlcNAcylation, we hypothesize that glucose results in O-GlcNAcylation of SP1 and this modulates induction of TRIB3 causing insulin resistance.

Results: When treated with 5mM or 25mM glucose, the induction of TRIB3 gene expression ($P<0.01$) in L6 myotubes is accompanied by upregulation of SP1 expression ($P<0.01$). When fully differentiated L6 myotubes are transiently transfected with SP1 siRNA, knockdown of SP1 produced a corresponding suppression of TRIB3 both in the high and low glucose ($P<0.05$). To identify whether O-GlcNAcylation is involved, we cultured L6 myotubes in either 5mM or 25mM glucose medium with or without OSMI-1, an inhibitor of rate-limiting O-GlcNAc transferase (OGT). OSMI-1 did not affect glucose's ability to augment SP1 2-fold ($p<0.01$), but effectively blocked induction of TRIB3. At the same time, OSMI-1 downregulated O-GlcNAcylation of SP1 and other O-GlcNAc modified proteins.

Conclusion: 1.) Increased TRIB3 mRNA expression parallels with upregulated SP1 expression; 2.) Glucose induction of TRIB3 mRNA and protein is eliminated when HBP flux and O-GlcNAcylation is disrupted by the inhibition of OGT; 3.) SP1 sites are critical in the regulatory action of glucose on the TRIB3 promoter and can be modulated by SP1 O-GlcNAcylation. While further studies are underway, these data provide new insights regarding mechanisms causing glucose-induced insulin resistance, and TRIB3 and TRIB3 promoter regulation are attractive targets for prevention of glucose toxicity in diabetes.

269-LB

HuR Influences Metabolic Flexibility in Skeletal Muscle

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Metabolic Flexibility allows for the oxidation of fuels based on their availability. Respiratory Quotient (RQ) values from subjects with type 2 diabetes mellitus in both basal and insulin stimulated states remain consistent, indicating a decreased ability to switch between available substrates. The molecular mechanisms governing defects in this switching ability are unclear at present. We therefore compared global gene expression in skeletal muscle between obese subjects classified by their sleep and 24 hour RQ as either metabolically flexible or inflexible. From this data we identified a number of transcripts stabilized by the RNA binding protein, HuR, which were enriched in metabolically flexible subjects. This finding prompted us to generate mice with a skeletal muscle specific knockout of Elavl1, the gene encoding HuR ($HuR^{m-/-}$). $HuR^{m-/-}$ mice have a metabolically inflexible phenotype with mild obesity and impaired glucose tolerance compared to control littermates. $HuR^{m-/-}$ mice have an increase in RER; and decreased expression of genes involved in oxidative phosphorylation, fatty acid transport, and mitochondrial fatty acid metabolism, suggesting a decreased ability to use fats as an energy source. $HuR^{m-/-}$ mouse skeletal muscle also shows decreases in protein levels of important modulators of the mTOR signaling pathway, and compensatory increases in transcript levels of HuR target mRNAs. These data highlight the importance of HuR function in skeletal muscle metabolism; and suggest HuR as a mediator of metabolite selection.

Supported By: Nutrition Obesity Research Center (P30DK072476); National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases

270-LB

Perivascular Adipose Tissue Controls Insulin-Stimulated Perfusion and Glucose Uptake in Muscle through Adipomuscular Microvascular Anastomoses

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Insulin-mediated microvascular recruitment (IMVR) regulates delivery of insulin and glucose to insulin-sensitive tissues. We have previously proposed that perivascular adipose tissue (PVAT) controls glucose metabolism and vascular function through outside-to-inside communication and through vessel-to-vessel, or "vasocrine" signaling. Here, we studied this hypothesis in mice by examining effects of removal of local intramuscular PVAT on muscle blood flow and glucose metabolism. Using the hyperinsulinemic, euglycemic clamp (HEC) in combination with positron emission tomography, we found that local PVAT removal transiently reduces muscle glucose uptake by ±50 percent. Contrast-enhanced ultrasonography and intravital microscopy of the gracilis artery (GA) during the HEC showed that PVAT removal abolishes insulin-induced increases in GA diameter and abrogated insulin-stimulated muscle blood volume (microvascular recruitment or IMVR). The effect of PVAT on IMVR was mediated by distinct microvessels or anastomoses, which we showed using lightsheet microscopy of mice expressing mCherry in endothelial cells. Proteomics analysis revealed that PVAT removal significantly alters expression of 109 of 1719 detected proteins in muscle. Observed changes in protein expression included reduction of a mitochondrial protein cluster and of vesicle-associated membrane protein 5 (Vamp5), involved in Glut4 trafficking.

In conclusion, we have found that PVAT within muscle regulates muscle perfusion, glucose uptake and muscle protein expression, communicating with the distal microcirculation via microvascular anastomoses. These data highlight the importance of PVAT in vascular and metabolic physiology, and are relevant for type 2 diabetes and associated muscle dysfunction.

Supported By: Netherlands Organization for Scientific Research

INTEGRATED PHYSIOLOGY—OTHER HORMONES

271-LB

Fasting-Induced Changes in Glucagon Secretion Are Dysregulated in Obesity

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Hyperglucagonemia is a hallmark in obesity and type 2 diabetes (T2DM). Suppression of glucagon signaling improves glycemic control in T2DM. We evaluated glucagon homeostasis in lean and obese mice and people. Discordant with the canonical rise in glucagon with fasting, our studies show that fasting (4, 8, 16 and 24 h) caused a progressive decrease in serum glucagon in diet-induced obese, hyperglucagonemic mice ($P<0.01$), yet a progressive increase in serum glucagon in lean mice ($P<0.01$). Serum insulin decreased with fasting in both lean and obese mice ($P<0.01$). Accordingly, fasting increased the glucagon:insulin ratio in the lean mouse ($P<0.01$), but did not affect the glucagon:insulin ratio in the obese mouse. Two hours of refeeding restored hyperglucagonemia in obese mice ($P<0.01$). Pancreatic perfusion studies in obese, hyperglucagonemic mice confirm that 16 h of fasting decreases pancreatic glucagon secretion ($P<0.01$). Consistent with our findings in the mouse, fasting decreased ($P<0.05$) serum glucagon in obese participants. In contrast, fasting increased serum glucagon concentrations in lean participants ($P<0.05$). As expected, fasting decreased serum insulin in both lean and obese participants ($P<0.05$ for both). As a result, fasting induced a more robust rise in the glucagon:insulin ratio in lean compared to obese participants ($P<0.01$). In addition, mixed meal feeding increased serum glucagon in people with obesity. These findings suggest that the metabolic pathophysiology of obesity may be driven by inappropriate meal-induced regulation of glucagon, resulting in a relatively static glucagon:insulin ratio.

Supported By: National Institutes of Health

272-LB

Adipsin Prevents Beta-Cell Failure in a Mouse Model of Type 2 Diabetes by Blocking Dedifferentiation and Cell Death

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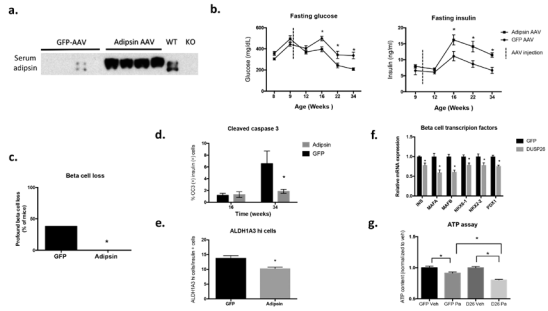
Adipsin and its downstream molecule C3a are complement factors that regulate insulin secretion. In order to assess the effects of adipsin in chronic DM2 and beta cell failure, we used adeno-associated virus (AAV) to replenish adipsin in db/db mice. A robust increase in both serum adipsin and C3a was achieved using AAV-Adipsin compared to control AAV-GFP, even 5 months after the injection (Figure 1a). Adipsin treatment significantly ameliorated hyperglycemia and boosted insulin levels (Figure 1b). More importantly, adipsin treatment increased beta cell mass and prevented beta cell loss in the late stages of DM2 (Figure 1c). Mechanistically, adipsin decreased beta cell death and dedifferentiation (Figures 1d and e). Adipsin also augmented expression of key beta cell transcription factors. Using unbiased transcriptomics, we identified that adipsin treatment downregulated the phosphatase Dusp26 in the pancreatic islets. Interestingly, overexpression of Dusp26 in beta cells and primary islets leads to a loss of beta cell transcription factors and an increase in palmitate-induced cell death (Figures 1f and g). Pharmacological inhibition of Dusp26 increased islet survival in palmitate conditions. Collectively these data suggest that adipsin/C3a and dusp26 directed therapies may represent a novel approach to conserve beta cell mass and achieve long term beta cell health for patients with T2D.

Figure 1. Chronic treatment with adipsin prevents beta cell failure in type 2 diabetes by blocking dedifferentiation and cell death. a) Western blot of serum adipsin in GFP and adipsin-AAV treated *db/db* mice 24 weeks after transduction. *Note: Adipsin has an epitope tag which is why it runs at a higher apparent molecular weight than endogenous adipsin (WT lane)* **b)** Fasting glucose and insulin were assessed at indicated time points before and after AAV injection. (n = 6-10 mice). **c)** Beta cell mass was quantified using insulin IHC and mice with profound beta cell loss 5 months after injection were quantified **d)** Cleaved-caspase 3 (CC3) staining was performed in pancreatic islets from *db/db* mice treated with AAV adipsin or GFP controls. CC3+ insulin+ cells were quantified at indicated time points (n=6-10 mice) **e)** Aldehyde dehydrogenase 3 (ALDH1A3) staining in pancreatic islets from treated versus control mice was performed. ALDH1A3 hi insulin + cells were quantified (n=5 mice) **f)** The gene expression levels of key beta cell transcription factors was assayed in INS-1 cells overexpressing Dusp26 or control GFP (n=3) **g)** INS-1 cells overexpressing Dusp26 (D26) or control GFP were subjected to vehicle (Veh) or palmitate (Pa) treatment for 16 hours. Results from cellular viability assay measuring cellular ATP are shown



Supported By: American Diabetes Association (1-18-PMF-032 to N.G-B.)

273-LB

Effects of Acute Experimental Hyperglycemia on Oxidative Markers and AGE-RAGE Dynamics in Obese Humans

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Chronic hyperglycemia promotes oxidative stress and advanced glycation end product (AGE) formation, leading to recognition by the AGE receptor (RAGE). AGE-RAGE binding and inflammation perpetuates diabetic complications, however the study of these phenomenon present inherent challenges in vivo. Therefore, our purpose was to evaluate the effects of acute experimental hyperglycemia on AGEs, oxidative markers, and RAGE expression in healthy, obese subjects (n=10; 31.2±1.2 kg/m^2; 56±3 y) subjected to hyperglycemic clamps (+5.4 mM above basal). Plasma was assayed at baseline, 2, and 24 h post glucose-infusion for well-known AGE-free adducts (CML, CEL, G-H1, MG-H1, 3DG-H) and oxidative markers (MethSO, AAA) via LC-MS/MS as well as soluble RAGE (sRAGE) isoforms via ELISA. Urine was also assayed (basal and 24 h) for AGEs and oxidative markers (normalized to creatinine) and skeletal muscle biopsies were used to study RAGE expression via Western blot. Most circulating factors (MethSO, AAA, CEL, MG-H1, and G-H1) decreased ($p<0.05$) over time, while CML increased ($p<0.05$) and 3DG-H remained unchanged ($p>0.05$). In urine, only MethSO was seen to increase at 24 h ($p<0.05$). Plasma:Urine ratios were decreased ($p<0.05$) for MethSO, AAA, CML, MG-H1, while ratios were increased ($p<0.05$) for CML. All species of sRAGE isoforms (total, cleaved and esRAGE) were unchanged ($p>0.05$). In skeletal muscle tissue, there was a trend ($p<0.1$) for decreased RAGE protein expression at 2 h which returned to baseline at 24 h. This study demonstrates AGEs and oxidative markers are sensitive to the physiological dynamics of acute hyperglycemia in obese, but otherwise healthy humans. The differential findings presented here were surprising and may be explained by increased AGE-RAGE binding or AGE sequestration, osmotic diuresis and/or oxidative defense mechanisms. These findings are relevant for postprandial glucose excursions and highlights the importance of appropriate glucose management.

274-LB

Individual and Combined Glucose-Lowering Effects of Glucagon Receptor Antagonism and Dipeptidyl Peptidase-4 Inhibition

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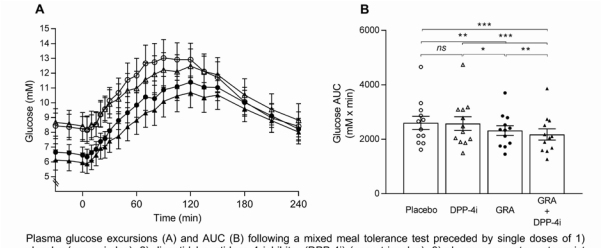
Type 2 diabetes is characterized by absolute or relative hypoinsulinemia and hyperglucagonemia. Dipeptidyl peptidase 4 inhibitors (DPP-4i) augment insulin secretion and decrease glucagon secretion, but if glucagon is removed from the metabolic equation, the effect of DPP-4i is unknown. In a randomized, placebo-controlled, double-dummy, double-blinded, cross-over study, patients with type 2 diabetes (n=12, age [mean (SD)]: 60.9 (7.8) years, BMI 34.6 (7.1) kg/m^2; HbA1c 50.3 (10.5) mmol/mol) underwent four 4-hour liquid mixed meal tests preceded by single-dose administration of 1.) placebo, 2.) DPP-4i (5 mg linagliptin) 2 hours before the meal, 3.) glucagon receptor antagonist (GRA) (300 mg LY2409021) 12 hours before the meal, and 4.) GRA + DPP-4i. Compared to placebo, fasting plasma glucose (FPG) was lowered by GRA but not DPP-4i. Adding DPP-4i to GRA did not lower FPG further. Compared to placebo, DPP-4i increased insulin responses to the meal (C-peptide AUC) ($P<0.01$), but did not result in a difference in plasma glucose excursions (Figure). GRA alone lowered glucose AUC, and the combination of GRA and DPP-4i lowered glucose AUC further.

In conclusion, the combination of DPP-4i and GRA has additive effects on postprandial glucose excursions. This seems to be driven by the efficient reduction in FPG by GRA combined with additional reduction in postprandial glucose excursions by DPP-4i.

Figure.



Plasma glucose excursions (A) and AUC (B) following a mixed meal tolerance test preceded by single doses of 1) placebo (open circles), 2) dipeptidyl peptidase 4 inhibitor (DPP-4i) (open triangles), 3) glucagon receptor antagonist (GRA) (filled circles) and 4) GRA+DPP-4i (filled triangles). Data are mean ± SEM. *** $P < 0.001$ ** $P < 0.01$, * $P < 0.05$, ^{ns} $P > 0.05$.

Supported By: Novo Nordisk Foundation

275-LB

Soluble RAGE Sequesters Advanced Glycation End Products following an Overnight Fast in T1DM Patients

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Context and Objectives: Advanced glycation end products (AGEs) promote the development of diabetic complications through activation of their receptor (RAGE). Isoforms of soluble RAGE (sRAGE) sequester AGEs and thus protect against RAGE-mediated diabetic complications. Low cellular energy, such as during fasting, activates sRAGE production. We investigated the effect of an overnight fast on circulating substrates, hormones, AGEs, and sRAGE isoforms in 26 individuals with type 1 diabetes (T1DM).

Participants and Methods: Blood was collected from young (18-30 years) T1DM patients on insulin pumps before and after an overnight fast. Circulating AGEs were measured via LC-MS/MS and sRAGE isoforms were analyzed via ELISA. $eGFR_{cystatin\text{-}c}$ was calculated based on circulating cystatin-c measured via ELISA.

Results: Glucose, insulin, glucagon, and $eGFR_{cystatin\text{-}c}$ decreased while cortisol increased following the overnight fast ($p<0.05$). NEFAs and cholesterol did not change ($p>0.05$). AGEs (CML, CEL, 3DG-H, MG-H1, and G-H1) decreased (21-58%, $p<0.0001$) while total sRAGE, cleaved RAGE (cRAGE), and endogenous secretory RAGE (esRAGE) increased (22-24%, $p<0.0001$) following the overnight fast. The changes in sRAGE isoforms were inversely related to MG-H1 (rho=-0.493 to -0.589, $p<0.05$) and the change in esRAGE was inversely related to the change in G-H1 (rho=-0.474, $p<0.05$). Multiple regression analysis revealed a 1 pg/mL increase in total sRAGE, cRAGE, and esRAGE independently predicted a 0.42-0.52 nM decrease in MG-H1.

Conclusions: Following an overnight fast, sRAGE isoforms were increased and sequestered MG-H1. Sequestration of AGEs by sRAGE has been shown to attenuate AGE/RAGE-mediated complications. Energy restriction appears to be important for protection against AGE/RAGE-mediated complications.

276-LB

Resistance to Diet-Induced Obesity in Mice Lacking OPA1 in Adipose Tissue Occurs Independently of Fat-Derived FGF-21 and BAT Function

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Optic Atrophy 1 (OPA1) is a mitochondrial protein that regulates mitochondrial dynamics and function. The role of OPA1 in adipose tissue physiology and systemic metabolism is incompletely understood. We generated mice lacking OPA1 in adipose tissue (OPA1 Ad-KO) and demonstrated that OPA1 deletion in adipose tissue completely prevents diet-induced obesity (DIO). This metabolic protection occurs concomitantly with increased levels of FGF-21 in adipose tissue and the circulation and higher energy expenditure. In the present study, we sought to determine the contribution of fat-derived FGF-21 and brown adipocyte function to the phenotype observed in OPA1 Ad-KO mice. To test whether changes in BAT function are responsible for the resistance to DIO, soon after weaning, OPA1 Ad-KO mice were fed either 60% high-fat diet (HFD) or 10% fat diet (control diet) for 8 weeks at thermoneutral conditions (30^{o}C), when BAT function is dampened. To test whether fat-derived FGF-21 is required for the resistance to DIO in OPA1 Ad-KO mice, we generated mice lacking both OPA1 and FGF-21 in adipose tissue, by using the cre recombinase under the control of the adiponectin promoter (DKO). We, then, fed 4-week old DKO mice either 60% HFD or 10% control diet for 4 weeks. OPA1 Ad-KO mice fed a HFD under thermoneutral conditions failed to gain weight. Diet-induced increases in total fat mass was completely prevented. Although BAT mass was equally increased in WT and Ad-KO mice, gonadal and inguinal fat pads were significantly reduced in OPA1 Ad-KO mice fed HFD. Likewise, after 4 weeks of high-fat feeding, DKO mice had significantly reduced body weight and total fat mass compared to WT mice.

In conclusion, our data suggest that reducing BAT function is not sufficient to induce fat expansion in OPA1 Ad-KO mice in response to HFD. Additionally, here we show that adipose tissue-derived FGF-21 is dispensable for the resistance to DIO observed in OPA1 Ad-KO mice.

Supported By: American Heart Association

277-LB

Thiazolidinediones' Insulin-Sensitizing Properties Depend on Adiponectin-Mediated Reductions in Certain Ceramide Species

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Adiponectin release from adipocytes is stimulated by the thiazolidinedione (TZD) class of PPARγ agonists in a time-dependent fashion, with an increase within 10 days followed by a more robust effect within 3 weeks. Our previous work suggested that adiponectin exerts its metabolic effects in part by enhancing the deacylation of the sphingolipid ceramide, a lipotoxic metabolite stimulated by exposure to saturated fats or inflammatory mediators. Adiponectin receptors in fact display potent ceramidase activity. Ceramides and diacylglycerols correlate with impaired insulin action. The effects of 10 and 21 days' pioglitazone (Pio; 45 mg/day) treatment on insulin sensitivity was assessed by hyperinsulinemic-euglycemic clamp studies in n=26 type 2 diabetic subjects (Diabetes. 62:1843, 2013). Total and high molecular weight (HMW) adiponectin levels in plasma were determined using a commercial sandwich ELISA kit. Sphingolipids in adipose tissue and plasma were quantified by liquid chromatography-tandem mass spectrometry. Improved hepatic and peripheral insulin sensitivity was seen after 21 days, but not 10 days, of Pio, and were highly correlated with an increased ratio of HMW adiponectin/total levels (r^2=0.90). Variable responses in both total and HMW adiponectin defined subjects as Responders (R;≥1.5-fold increase with Pio) vs. Non-responders (NR; no change). Sphingosine-1P, a beneficial conversion product from ceramides, increased 2-fold and Sphinganine-1P increased 2.5-fold in R relative to NR and placebo (p=0.0286). Pio induced decreases in dihydroceramides and increases in lactosylceramides as a function of time and adiponectin levels, the functional significance of which needs to be further explored. This study suggests the insulin-sensitizing properties of TZDs critically depend on elevating circulating adiponectin levels, with an associated lowering of certain ceramide species involved in insulin resistance and inflammation.

278-LB

Vitamin D Enhances Insulin Sensitivity in Neurons

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Vitamin D deficiency has been linked to diabetes but a causal relationship is not clear. We previously published hypothalamic vitamin D action is critical for glucose tolerance and insulin sensitivity in obese animals. We hypothesized vitamin D also enhanced insulin sensitivity within the brain. Indeed, 48 hours of 1,25D3 (aka calcitriol) increased phosphorylation of Akt in hypothalamic cells (GT1-7). This effect was not observed in the absence of insulin, indicating that vitamin D was enhancing insulin action rather than mediating phosphorylation independently. Phosphorylation of Akt is often mediated by phosphoinositide 3-kinase (PI3K). Wortmannin, a PI3K inhibitor, blocked the effects of vitamin D to enhance pAkt. This supports a PI3K-dependent mechanism of vitamin D action. Vitamin D increased mRNA concentrations of key components of the PI3K/Akt pathway, namely IRS2 and p85. p55 expression, a negative regulator of PI3K, was decreased. Vitamin D did not affect transcription of the insulin receptor, IRS1, Akt, or the vitamin D receptor. Together, these support vitamin D as a regulator of the PI3K pathway in hypothalamic neurons. Additionally, the PI3K pathway has previously been shown to be important in rapid effects of other nuclear hormones. Since we previously published vitamin D depolarizes hypothalamic neurons, we investigated whether the PI3K pathway was also necessary in rapid vitamin D actions. Indeed, vitamin D was unable to depolarize hypothalamic neurons in the presence of the PI3K inhibitor wortmannin. Together, these data support that the action of vitamin D in the brain to influence glucose homeostasis may be through altered insulin signaling in the brain and requires the PI3K pathway for effects. These results are important in light of the known association between vitamin D and insulin resistance. They suggest that although vitamin D enhances insulin sensitivity, its actions are dependent upon a functional PI3K pathway, which is likely altered in an obese, insulin-resistant individual.

Supported By: American Diabetes Association (1-17-JDF-037 to S.S.); United States Department of Agriculture

OBESITY—ANIMAL

279-LB

VEGF-A-Expressing Adipose Tissue Shows Rapid Beiging, Enhanced Survival after Transplantation

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Adipocyte-derived VEGF-A plays a crucial role in angiogenesis and contributes to adipocyte function and systemic metabolism, such as insulin resistance, chronic inflammation and beiging of subcutaneous adipose tissue. Utilizing a doxycycline (Dox)-inducible adipocyte-specific VEGF-A overexpressing mouse model, we investigated the dynamics of local VEGF-A effects on tissue beiging of adipose tissue transplants. VEGF-A overexpression in adipocytes triggers angiogenesis. We also observe a rapid appearance of beige fat cells in subcutaneous white adipose tissue (sWATs) within as early as 2 days post induction of VEGF-A. In contrast to conventional cold-induced beiging, VEGF-A-induced beiging is independent of IL-4. We subjected metabolically healthy VEGF-A overexpressing adipose tissue to autologous transplantation. Transfer of subcutaneous adipose tissues taken from VEGF-A overexpressing mice into diet-induced obese mice resulted in systemic metabolic benefits, associated with improved survival of adipocytes and a concomitant reduced inflammatory response. These effects of VEGF-A are tissue autonomous, inducing WAT beiging and angiogenesis within the transplanted tissue. Our findings indicate that manipulation of adipocyte functions with a bona fide angiogenic factor, such as VEGF-A, significantly improves the survival and volume retention of fat grafts and can convey metabolically favorable properties on the recipient on the basis of beiging.

Supported By: National Research Foundation of Korea (2017R1C1B1008424)

280-LB

p62 Deficiency Leads to Hypogonadism and Infertility via Pituitary Functions Loss in Young Female Mice before Metabolic Disorders Onset

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p62/SQSTM1 is an essential protein adaptor that fine-tunes numerous biological processes by autophagy or related cell signaling pathway. Previous studies have proved that p62 loss lead to mature-onset metabolic disorders including obesity, diabetes and fatty liver in adult mice; and in younger human being those metabolic diseases are close to reproductive dysfunctions, such as PCOS. Here, the metabolism and reproductive function of younger (8 weeks) p62 deficient female mice was observed, and hypothalamus-pituitary-ovary axis was evaluated to explore the possible upstream mechanisms. We found that although p62 deficiency rarely exposes obvious metabolic influences during younger stage of female mice, the deteriorative reproductive function has exhibited, such as attenuated breeding success rate and number of pups per litter. In particular, genetic deletion of p62 causes impaired estrous cycle, thread-like atrophied uteri and low-weight ovary with the lack of corpus luteum, failure of folliculogenesis and ovulation. Next, the low levels of plasma sex steroid hormone estradiol and gonadotropic luteinizing hormone (LH) have also been detected. Furthermore, defected steroidogenesis signaling including decreased StAR and P450scc in p62 KO ovary reveals reduced cholesterol-to-pregnenolone transition, meanwhile, increased Lhcgr mRNA expression in ovarian suggests a compensatory reaction. Consistent with lower serum LH level, significantly decreased mRNA expression of Lhb as well as slightly reduced Fshb also were found in the pituitary of p62 KO female mice. In addition, the elevated expression of Kiss1 mRNA in hypothalamus might discover the compensatory for pituitary function loss. Our findings support the vital role p62 of pituitary on reproductive function in younger individuals, and this effect might be the direct consequence rather than by metabolic disorders induced by p62 deficiency.

Supported By: National Natural Science Foundation of China (81500647 to M.L.), (81471039 to H.Z.); Chongqing Science Foundation (cstc2016jcyjA0502, cstc2013jcsfc10001-5 to M.L.); Miaopu Cultivation Research Foundation of Third Military Medical University (to M.L.)

281-LB

Maternal Dietary Manipulation Programs Offspring's Metabolism

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There is emerging evidence supporting fetal metabolism is determined in utero, and the programmed metabolism persists into adulthood. Understanding how metabolic dysfunction is transmitted through generations will help identify the biological mechanisms underlying obesity and cardiometabolic disease, and provide insight regarding rational strategies for treatment and prevention.

Metabolic parameters were assessed in offspring from dams fed different diets for 4 weeks before pregnancy and during pregnancy and lactation; open standard (OSD), isocaloric low protein (LPD, 8% protein) and high-fat diets (HFD, 60% fat). After weaning, offspring had OSD.

Offspring from dams fed LPD showed 31% reduced birthweights compared to offspring from dams fed OSD, and the difference persisted into 6 months of age. At 3 and 6 months, they exhibited significantly smaller perigonadal fat pad than offspring from dams fed OSD. In addition, they showed significantly higher blood glucose concentration than offspring from dams fed OSD at birth (52.35mg/dl vs. 63.71 mg/dl). In case of offspring from dams fed HFD, they exhibited significantly higher body weights (5.99g vs. 6.56g) and blood glucose level at birth (52.35mg/dl vs. 64.64 mg/dl) compared to offspring from dams fed OSD. The difference of body weights continued to 3 week-old at weaning, and they showed significantly impaired glucose tolerance compared to offspring from dams fed OSD at the same age.

Maternal dietary manipulation strongly influenced metabolic phenotypes such as birthweight, blood glucose concentration at birth and glucose tolerance, and the programed phenotypes persisted into adulthood. Therefore, maternal nutrition programs a glucose intolerant phenotype in offspring indicating that in utero stress augments diabetes risk not only childhood but also adulthood. We expect our findings in this study to help clarify the mechanism how the utero environment affects offspring's metabolism, which would explain in part the intergenerational transmission of obesity.

Supported By: American Heart Association

282-LB

WITHDRAWN

283-LB

Growth Differentiation Factor-15 (GDF-15) Inhibits Gastric Emptying in Rodents as Part of Its Anorectic Mechanism of Action

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GDF-15 is a secreted circulating polypeptide that regulates systemic energy balance. GDF-15 agonists may have therapeutic potential as anorectic agents in obesity and type 2 diabetes. The receptor for GDF-15, Gfral, is expressed on specific neurons in the area postrema (AP) of the hindbrain, and is necessary for the effect of GDF-15 on food intake. Given the role of the AP in vagal control of gastric motility, we sought to investigate the potential effects of GDF-15 on gastric emptying. Food intake reduction by GDF-15 was confirmed in C57Bl/6N mice using BioDAQ continuous food consumption monitoring. Animals were treated sc with recombinant His-tagged human GDF-15 prior to initiation of the dark cycle; GDF-15 treated mice showed significant reduction in food intake relative to vehicle treated controls (12 hour cumulative food intake: 3nmol/kg, -19.9±10.5%; 10nmol/kg, -58.0±10.0%; P<0.0001, n=8). Gastric emptying was assessed using an oral acetaminophen (AAP) absorption test over 90 minute using LC/MS detection. This method was validated using known inhibitor of gastric emptying, Exendin-4 as a positive control; 7.2nmol/kg Exendin-4 significantly reduced integrated AAP absorption by -44.7±5.1% (P<0.01, n=8). In this assay, GDF-15 caused a significant dose-dependent inhibition of gastric emptying, reducing acetaminophen AUC levels by -18.1±10.6% at 1nmol/kg, and by -36.0±9.9% at 10nmol/kg, relative to vehicle treated control mice (P<0.01, n=8). Comparable results were obtained in an independent repetition of the study. We extended the results obtained in mice to SD rats, where we similarly observed a significant reduction in gastric emptying following GDF-15 treatment. Hence, GDF-15 appears to reduce gastric emptying rate in both mouse and rat, potentially contributing to the food intake suppression mechanism of action.

284-LB

Function of Deubiquitinating Enzyme USP1 in Adipogenesis

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Obesity and metabolic disorders are one of the most challenging issues to be solved in modern society. Adipogenesis, which is a cellular differentiation process of pre-adipocyte to become a fully differentiated adipocyte, is a key mechanism in increasing fat mass and lipid accumulation. This process is a very complex multistep and involves numerous cascades of transcriptional factor activation. Accordingly, adipogenesis is regarded as a crucial target in treating or preventing obesity. Post-translational modification is a significant process for a protein to acquire its functional diversity in cell signaling by the addition or cleavage of functional groups. Deubiquitination by deubiquitinating enzyme is one of the important post-translational modifications involved in various signaling pathways. In this study, we screened deubiquitinating enzymes with differentiating 3T3-L1 adipocytes and found out that the mRNA and protein expression of ubiquitin specific peptidase 1 (USP1) was gradually increasing during the adipogenesis process. Also, from the various mouse tissue mRNA sample, ubiquitin specific peptidase 1 displayed higher expression levels on adipose tissues compared to other tissues. From these data, we assumed that this enzyme might be an important factor involved in adipogenesis. In the knockdown study, when ubiquitin specific peptidase 1 is absent, all the adipogenic transcription factors (Peroxisome proliferator-activated receptor gamma, Ccaat-enhancer-binding proteins alpha, beta, fatty acid synthase, and fatty acid binding protein 4) were down regulated. Furthermore, according to the proliferation assay result, ubiquitin specific peptidase 1 3T3-L1 cells had lower proliferation rate which indicates significant effect of USP1 during the mitotic clonal expansion. In consequence, our results indicate that ubiquitin specific peptidase 1 plays an important role in adipogenesis process.

Supported By: Brain Korea 21 Project for Medical Science

285-LB

Sex-Specific Role of Adipose-Derived Lipocalin-2 in Diet-Induced Obesity and Insulin Resistance

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Lipocalin-2 (LCN2) is a 25-kDa secretory adipokine that is up regulated in adipose tissues of genetically obese animals and humans. LCN2 was also proposed to regulate insulin resistance (IR) in animal studies. Besides, we have shown adipose Lcn2 expression to be negatively regulated by estradiol using a mouse reference population of over ~100 strains, the Hybrid Mouse Diversity Panel (HMDP). Recently, LCN2 has also been implicated in recruiting neutrophils to the liver in both alcoholic and nonalcoholic steatohepatitis. To further explore the causal role of LCN2 in diet-induced obesity and its metabolic complications, we carried out systems genetics analyses on multi-omics data collected from both males and females of HMDP fed a high fat/high sucrose (HF/HS) diet: Genotypes, 200,000 high-resolution SNPs; Phenotypes, obesity (fat mass, and weight of three visceral adipose depots), IR (fasting levels of glucose, insulin and HOMA-IR) and steatosis (liver triglyceride levels); and Transcriptomics, mRNA microarrays of adipose and liver tissues. Our analyses revealed female, but not male, adipose-derived LCN2 is mechanistically linked to deregulated adiposity and enhanced insulin resistance. To functionally validate the causal role of female adipose LCN2, we conditionally overexpressed either LCN2 or GFP in adipose tissues of mice of both sexes by adeno-associated viral vectors and subjected them to HF/HS diet. We demonstrated deregulated metabolic homeostasis: increased adiposity (fat mass), glucose intolerance (GTT) and insulin resistance (ITT and HOMA-IR) only in females. Follow-up ex vivo bioenergetics studies in both adipose and liver tissues demonstrated deregulated mitochondrial respiration (lowered in adipose; enhanced in liver) mediated by LCN2 overexpression only in females, thereby revealing mitochondrial dysfunction as one of the key mechanism(s) mediated by LCN2 in diet-induced obesity and its complications.

Supported By: National Institutes of Health

286-LB

Ablation of Galectin-1 Reduces Adipogenesis and Obesity

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Galectin-1 is a member of the animal lectin family that contains a carbohydrate-recognition binding domain (CRD) that binds a B-galactoside. Many studies are reported about the role of galectin-1 in cancer and immune disorders. But, the role of galectin-1 in metabolic dysfunction is not fully understood. We were interested in the role of galectin-1 on metabolic diseases and investigated the mechanism how galectin-1 regulates adipocyte differentiation and high fat diet (HFD) induced obesity. The level of galectin-1 increased during adipocyte differentiation and was predominantly expressed in mouse fat tissues. Galectin-1 knockdown significantly reduced adipocyte differentiation in 3T3-L1 cells and also decreased the expression of peroxisome proliferator-activated receptor (PPAR)-γ, ccaat enhancer binding protein (C/EBP)-α. fatty acid binding protein (FABP) 4 and fatty acid synthase (FASN). When lactose was treated to inhibit function of extracellular galectin-1, there was no effect on adipocyte differentiation. After 10-week high-fat diet (60% fat), Igals1$^{-/-}$ mice had lower body weight and WAT mass than wild type (Igals1$^{+/+}$) mice. The expression levels of lipogenic genes were significantly down-regulated in liver and gonadal WAT of Igals1$^{-/-}$ mice. In addition, Igals1$^{-/-}$ mice had elevated expression of genes involved in thermogenesis in inguinal WAT and BAT. These data suggest that galectin-1 is an important regulator of adipogenesis. We also suppose that galectin-1 might be potential therapeutic target in obesity and fat liver diseases and further study is needed for clinical application.

Supported By: National Research Foundation of Korea (2015M3A9B6073835)

287-LB

Inhibition of Adipose Tissue Angiogenesis Prevents Rebound Weight Regain after Calorie Restriction Independent of Hypothalamic Melanocortin System in Obese Mice Fed a High-Fat Diet

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Prevention of rebound weight gain after dieting is essential to treat obesity. However, its attempts have been unsuccessful and the underlying mechanism remains unclear. In this study, we sought to investigate the role of adipose tissue (AT) vasculature in rebound weight gain after calorie restriction in obese mice fed a high-fat diet (HFD). Obese mice were randomly assigned to 4 groups including mice fed HFD ad libitum (CON), mice under 40% calorie restriction for 5 weeks (CR), 3 days of HFD ad libitum after CR (CRAL), or CRAL treated with TNP-470, an angiogenesis inhibitor (TNP). We compared parameters of energy balance, AT morphometry and remodeling, and hypothalamic neuropeptides gene expression among the groups. Rebound weight gain and food intake were significantly lower and the level of brown AT UCP-1 gene expression was higher in TNP group than CRAL group. Fat mass was significantly lower in TNP group than CRAL group and it was similar to CR group while lean mass was not different between TNP and CRAL groups. Notably, the CD31-positive area was not different in AT between CON, CR, and CRAL groups, indicating that AT vasculature was maintained independently of nutritional status. However, that tended to be lower in AT of TNP group compared to other groups, implicating that inhibition of AT vasculature might be crucial to suppress rebound weight gain after calorie restriction. Consistently, circulating leptin levels were significantly lower in TNP group than CRAL group. However, the pattern of hypothalamic neuropeptides gene expression was different from the changes in food intake among the groups, suggesting an existence of novel regulatory signals independent of melanocortin system. Taken together, these results suggested a critical role of AT vasculature in regulating rebound weight gain and hyperphagia after calorie restriction independent of hypothalamic melanocortin system.

288-LB

IKKß and Wnt/ß-Catenin Signaling Interaction Regulates Adipogenesis and Osteogenesis in Mesenchymal Stem Cells of Nonhuman Primates and Humans

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IκB kinase β (IKKβ), a central coordinator of inflammation through activation of NF-κB, has been implicated in the pathogenesis of obesity-associated metabolic disorders. We recently demonstrated that IKKβ also functions in adipose progenitors to regulate adipogenesis and adipose tissue development in mice. Deficiency of IKKβ in adipose progenitors decreased high-fat (HF)-elicited adipogenesis and protected mice from diet-induced adiposity and insulin resistance. Here we report that IKKβ can regulate both adipogenesis and osteogenesis in mesenchymal stem cells (MSCs) of non-human primates (Macaca fascicularis) and humans. Activation or overexpression of IKKβ increased adipocyte differentiation but inhibited osteoblast differentiation of MSCs isolated from adipose tissue and bone marrow of macaques and humans. By contrast, IKKβ loss of function decreased adipogenesis and increased osteogenesis in macaque and human MSCs. Mechanistically, IKKβ can directly interact with Wnt/β-catenin signaling and phosphorylate β-catenin at serine-33, -37 and -45, leading to its ubiquitination and degradation. Inhibition of canonical Wnt/β-catenin signaling then contributed to the increased adipogenesis and decreased osteogenesis in MSCs. Our findings demonstrate IKKβ as a key molecule that regulates MSC differentiation, and provide a connection between IKKβ and Wnt/β-catenin signaling which may lead to new insights into the pathogenesis of obesity and osteoporosis.

Supported By: National Institutes of Health; American Heart Association

289-LB

Dynamic Changes in the Regulation of Energy Balance after Roux-en-Y Gastric Bypass Are Reflected in Time-Dependent Alterations in Liver Gene Expression

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Roux-en-Y gastric bypass (RYGB) leads to long-term weight loss and diabetes remission. Animal studies have shown that RYGB changes the physiology of energy regulation to favor a lower defended fat mass. To explore these effects, we developed a mouse model of enhanced response to dietary change, where RYGB abrogates the rapid obesogenic effects of re-exposure to a high-fat diet (HFD). HFD-induced obese mice that underwent RYGB- or Sham operation were fed chow for 9 weeks and switched back to HFD for 8 weeks. Glucose regulation was improved in RYGB animals independent of diet or body weight. During the first 2 days on HFD, Sham animals gained significant weight (1.8 g, $p<0.05$) due to a 10.6 kcal increase in energy intake (EI) compared to the chow period ($p<0.05$). In RYGB mice, weight and EI remained unchanged. By week 8 of HFD, Sham controls were 24% heavier than before surgery ($p<0.05$), while RYGB mice continued to maintain a lean weight. There was no difference in EI between groups, but RYGB mice exhibited 26% higher energy expenditure than Sham mice ($p<0.05$). Given the widespread changes in physiology in RYGB animals, we sought to identify differentially expressed (DE) genes in RYGB vs. Sham livers during the dynamic response to HFD. RNA-Seq showed that the number of DE genes after long-term HFD was 5.6 times larger than after 2 days (1,409 vs. 251, respectively), reflecting adaptation to a new metabolic state in Sham mice after chronic HFD. Differential expression of inflammatory, lipogenic, and cell cycle genes was substantially altered over time. These data suggest that the means by which RYGB modulates energy balance to resist the obesogenic effects of HFD is time-dependent. Further assessment of the molecular basis of this dynamic physiological response will provide important insight into the mechanisms most relevant to the therapeutic effects of RYGB and therefore guide development of less invasive therapies for metabolic disease.

Supported By: American Diabetes Association (1-17-PMF-003 to M.A.S.); National Institutes of Health

290-LB

Host Genetic Background and Gut Microbiota Contribute to Differential Metabolic Responses to High Fructose Consumption in Mice

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Both host genotypes and gut microbiota play a role in dietary responses and the control of host phenotypes. High fructose consumption has been strongly implicated in metabolic disorders including obesity, insulin resistance and diabetes, but individual variability in susceptibility has not been examined in diverse genetic backgrounds. We investigated the strain-specific response to fructose in terms of the shifts in gut microbiota as well as host phenotypes related to body mass, glycemic traits, and glucose intolerance using three mouse strains, C57BL/6 (B6), DBA, and FVB. After treatment with 8% fructose water for 12 weeks, the DBA mice demonstrated increased body weight, adiposity, plasma insulin, and glucose intolerance, whereas B6 and FVB mice were resistant to fructose-induced metabolic alterations. We also conducted 16S rRNA-sequencing analysis of gut microbiota and found that DBA had higher Firmicutes/Bacteriodetes ratio and lower basal levels of Turicibacter, Akkermansia, and S24-7_g compared to B6 and FVB. These microbes were correlated with body weight, adiposity, or glucose tolerance. To test the influence of gut microbiota on metabolic phenotypes, we performed fecal transplant by administering the B6 fecal content to DBA mice and vice versa. DBA mice with B6 fecal transplant stayed glucose tolerant and lean with fructose treatment, suggesting that B6 microbes attenuated fructose response in DBA mice. Our findings suggest that fructose induces strain-specific metabolic and microbiota responses, and gut microbiota are partially responsible for fructose sensitivity among mice with different genetic backgrounds.

Supported By: R01DK104363

291-LB

Fructose Consumption Induces Strain-Specific Transcriptomic Response Perturbing Different Pathways in Genetically Diverse Mouse Strains

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Metabolic syndrome (MetS) predisposes individuals to type 2 diabetes mellitus and cardiovascular diseases. Epidemiological and clinical studies support fructose intake as an environmental risk for MetS and the associated metabolic diseases. To explore the role of genomic variability in determining metabolic responses to fructose, we fed three strains of mice, namely C57/B6 (B6), DBA and FVB, with 8% fructose for 12 weeks. Fructose-fed DBA mice gained a significantly higher amount of body weight and glucose intolerance from the 4th to the 12th week, while B6 and FVB showed no differences in these phenotypes over 12 weeks. In addition, elevated insulin levels were found in fructose-fed DBA and FVB mice, and cholesterol levels were uniquely elevated in B6 mice. To explore the molecular underpinnings, we applied RNA sequencing to investigate the effect of fructose on the transcriptional profiles of liver, adipose and hypothalamus tissues. Different strains showed distinct patterns of transcriptional and pathway perturbations in a tissue-specific manner. Among pathways altered in the liver tissue, fatty acid and cholesterol metabolic pathways were prominent in B6 mice, while DBA mice showed unique over-representation of pathways related to PPAR signaling pathway. In adipose tissue, pathways are more related to fatty acid metabolism and oxidation in B6 mice, whereas no metabolic pathways were found to be enriched for differential genes in DBA and FVB mice. In hypothalamus tissue, only B6 showed significant enrichment for pathways involved in protein folding, pancreatic secretion and fatty acid beta-oxidation. Using network modeling, we predicted potential key regulators of fructose response such as FGF-21 and Sqle in the liver, Cav1 and DPP-4 in adipose tissue and Fmod in the hypothalamus. Our findings provide molecular insights into the mechanisms by which fructose contributes to the development of MetS and metabolic diseases.

Supported By: National Institutes of Health (R01DK104363)

OBESITY—HUMAN

292-LB

Iron-Overload Evaluation by Noninvasive Methods in Patients with Nonalcoholic Fatty Liver Disease, Overweight, and Hyperferritinemia

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Introduction: Hyperferritinemia (HF) may reflect the inflammatory status of patients with NAFLD and obesity, but about 33% reflects a real hepatic iron overload. The dysmetabolic iron overload syndrome (DIOS) definition is HF, normal transferrin saturation, and mild hepatic iron overload in a patient with metabolic disorders. The gold standard for diagnosis of iron overload is the liver biopsy. As it is an invasive method, new methods are necessary. Among them, magnetic resonance imaging (MRI) is the most available one.

Methods: This study evaluated patients with HF, overweight and NAFLD. All patients were submitted to liver biopsy. MRI relaxometry (Fat/Iron analysis - 3T machine), measurement of inflammatory markers (TNF α and IL-6), analysis of the expression of ferritin light and heavy chain subunits (FTL and FTH) and serum hepcidin were held. Data were correlated with liver biopsy.

Results: 152 biopsy-proven NAFLD patients were screened but only 67 were included in this study. DIOS frequency was 37%. The cut off of ferritin levels were correlated with iron overload in liver biopsy was 284,3 ng/ml (sensibility of 74% and specificity of 84%). Hepcidin levels were higher in DIOS patients, correlating with hepatic siderosis. IL-6 and TNF α were similar among the groups. The expression of FTH and FTL were similar in role sample, although there was a tendency of FTL in iron overload group. In the other hand, FTL correlates with metabolic syndrome and abdominal circumference, while FTH correlates with in higher fat scores. The MRI was able to identify mild iron overload. The R2 * cut off level was 58,9 s^{-1}.

Conclusions: HF may reflect iron overload when above 284,3 ng/ml; MRI using relaxometry method is accurate to evaluate mild iron overload in DIOS patients; Hepcidin correlates with iron and serum ferritin in NAFLD patients; FTL correlates with metabolic syndrome and abdominal circumference while FTH correlates with in higher fat scores.

Supported By: Fundação de Amparo a Pesquisa do Estado de São Paulo

293-LB

Lifestyle Intervention in Senior Diabetics (LISD) Subanalysis—Autoimmune Profile in the Overweight/Obese Elderly

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Introduction: The LISD trial assesses the effects of intensive lifestyle intervention (ILI) in older adults w/T2D on glycemic control, physical function, and QoL. Within the LISD framework, we examined the autoimmune profile before and after intervention.

Methods: The LISD study is a RCT of 100 individuals w/T2D that are ≥65 year old w/BMI ≥27 who were randomized to healthy control vs. ILI. ILI included 6m of 3x weekly supervised exercise and dietary counseling followed by 6m of community exercise and dietary monitoring. The following were performed at baseline, 6m, and 12m: GAD ab, ZnT8 ab, IA-2FL ab, serum cytokines via MESO QuickPlex, and 2 hour frequently sampled OGTT.

Results: 4/100 participants were + for IA-2FL ab (M: 0.369±0.104) and none for GAD or ZNT8 ab. Compared to IA-2FL - participants, IA-2FL + participants had lower age (68 vs. 71 yo; p=0.001), BMI (32 vs. 35; p=0.001), and insulin secretion (Homa-β 68.7 vs. 227.6; p=0.02 Disposition Index: 729 vs. 6049; p=0.009). There was no difference (p>0.05) in insulin sensitivity (Homa-IR 7.2 vs. 12.1; Matsuda: 2.9 vs. 2.3), hgbA1c (7.3 vs. 7.7), DM duration (15.2 vs. 13.5 year), or need for insulin therapy (1/4 vs. 38/96). 3/4 IA-2FL + participants were randomized to ILI (weight loss of -9.5 and -11.1% at 6m/12m). Changes in IA-2FL titers did not correlate w/changes in body weight or metabolic parameters.

Conclusion: It is thought that the incidence of autoimmune DM in adults has been underestimated, which has led to focus on LADA pathogenesis/prevalence in recent literature. However, the obese elderly population has yet to be examined. Some postulate that obesity/aging leads to inflammation that could be a nidus for autoimmune DM. Interestingly in this understudied population, we found that ab+ status correlates w/a lower BMI, age, and insulin secretion for the same level of glycemic control. Our study serves as a pilot to further investigate autoimmunity in terms of prevalence, phenotype, and pathogenesis of this process in the obese elderly with T2D.

Supported By: American Diabetes Association (1-14-LLY-38 to D.V.)

294-LB

Measurement of Liver Size by Imaging Methods Unveils Fatty Liver and Hepatomegaly in Overweight Mexican-American Children

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The aim of this study was to analyze the relationship between BMI percentile and liver size and to predict the probabilities of fatty liver and hepatomegaly for overweight and obese boys and girls. 1,161 records from children visiting a South Texas pediatric clinic from 2003 to 2018 were assessed. Ultrasonography was requested for patients whenever the patient was gaining excessive weight and the readings for alkaline phosphatase levels were 2 SD above the normal population or when liver enzymes were elevated, SGOT above 50/46, SGPT above 47/41, and GGT above 32/28 for boys and girls respectively. The data analysis was processed under TAMIU IRB approval #2012-01-13. The data was analyzed using logistic regression. The results were as follows. a) Boys and girls logistic regression of BMI percentile vs. Fatty Liver (n=1161, a=-11.83, Wald=49.01, df=1, p<0.05; b=0.12, Wald=43.39, df=1, p <0.05), b) boys and girls logistic regression of BMI Percentile vs. Hepatomegaly (n=1161, a=-9.42, Wald=33.47, df=1, p<0.05; b=.085, Wald=25.73, df=1, p<0.05), c) girls logistic regression of BMI percentile vs. fatty Liver (n=450, a=-8.10, Wald=17.88, df=1, p<0.05; b=.07, Wald=13.53, df=1, p<0.05) d) girls logistic regression of BMI percentile vs. Hepatomegaly (n=450, a=-5.67, Wald=12.04, df=1, p<0.05; b=0.041, Wald=5.65, df=1, p<0.05) e) boys, Logistic regression of BMI percentile vs. Fatty Liver (n=840, a=-22.98, Wald=51.27, df=1, p<0.05; b=.23, Wald=50.58, df=1, p<0.05), f) boys logistic regression of BMI percentile vs. Hepatomegaly (n=840, a=-16.58, Wald=31.79, df=1, p <0.05; b=.16, Wald 29.43, df=1, p<0.05). A cubic curve was also fitted between liver size and BMI percentile for each group. The results of the analysis support that the probability of fatty liver and hepatomegaly increase exponentially as BMI percentile increases, there is also a positive relationship between liver size and BMI percentile.

Supported By: Francisco Cervantes, MDLaredo Pediatrics

295-LB

Weight-Centric Management of Type 2 Diabetes Mellitus

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Background: Obesity and type 2 diabetes mellitus (T2DM) are inextricably linked. Obesity is the pathophysiologic driver of T2DM, and as such, the treatment of obesity can improve glycemic control. Although there is some data from phase 3 trials of anti-obesity pharmacotherapy in patients with T2DM, there is currently a paucity of data related to the weight-centric management of T2DM in clinical practice. Data from clinical trials of these medications suggests that weight loss outcomes in patients with T2DM are inferior, likely due to the weight gain promoting effects of concomitant antidiabetic therapies.

Methods: In a retrospective study, electronic medical records of 359 consecutive new patients seen at the Weill Cornell Comprehensive Weight Control Center from 4/1/14-4/1/15 were reviewed and data related to demographics, medications, weight, and HbA1c was recorded.

Results: 48 of 359 patients had T2DM. Baseline age and BMI were 56.2±10.6 years and 39.5±7.6 kg/m^2 in patients with T2DM and 48±14.7 years and 35.6±6.8 kg/m^2 in patients without T2DM; 54.2% and 70.7% were female, respectively. Management strategies in patients with T2DM included the addition and dose escalation of metformin, GLP-1 agonists, and SGLT2 inhibitors, discontinuation of sulfonylureas and TZDs, and dose reduction of insulin when possible. 56.3% of patients with T2DM were started on anti-obesity pharmacotherapy including lorcaserin, phentermine, topiramate and bupropion. At 12 months, weight loss was 8.9±7.8% in patients with T2DM and 8.6±7.7% in those without T2DM. In patients with T2DM, HbA1c was 7.1±1.1% at initial visit and 6.7±1.3% at 12 months.

Conclusions: In this review, weight loss outcomes were similar in patients with and without T2DM. We show that by using a weight-centric approach to diabetes management, patients can achieve glycemic control with concomitant weight loss.

296-LB

Efficacy of Metreleptin for Weight Loss in Overweight and Obese Adults with Low Leptin Levels

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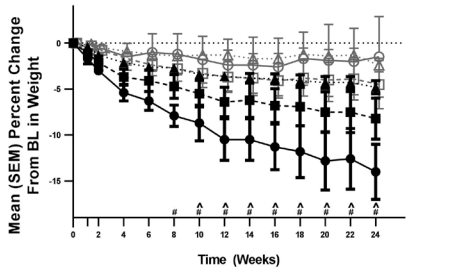
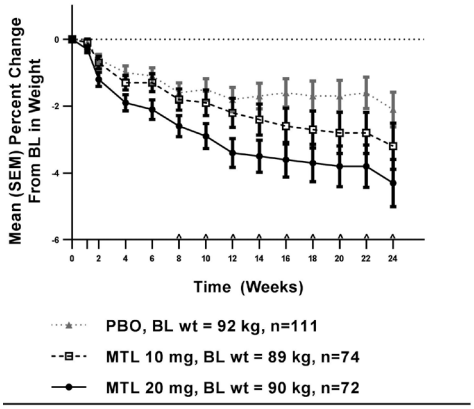
Leptin, an adipokine, regulates appetite, glucose and fat metabolism, and neuroendocrine function. A post-hoc pooled analysis of 4 studies (N=1064) in adults with BMI 27.0-40.0 kg/m^2 showed that metreleptin (MTL), a leptin analogue, reduced weight in subgroups of adults with low baseline (BL) leptin levels (Figure 1). A subsequent study (N=267) in adults with low BL leptin (females, ≤16 ng/mL; males, ≤5 ng/mL) and BMI 27.5-38.0 kg/m^2 was conducted. Subjects (64% female; mean [SD] BL leptin, 14.2 [13.3] ng/mL) received QD subcutaneous MTL 10 mg, MTL 20 mg, or placebo. Both MTL doses decreased weight over time among subjects with low BL leptin (Figure 2). MTL 20 mg showed statistically significant decreases by week 8. MTL was well tolerated. Thus, MTL 20 mg QD holds promise for weight loss among overweight and obese adults with low leptin levels.

Figure 1. Percent Change From BL in Weight by BL Leptin Level and Treatment (Pooled Subgroup Analysis)



* MTL 20-mg dose admistered as MTL 10 mg BID.
# *P*<0.1, MTL 20 mg vs PBO for BL leptin <5 ng/mL females/<2 ng/mL males.
^ *P*<0.1, MTL 20 mg vs PBO for BL leptin <16 ng/mL females/<5 ng/mL males.
BL, baseline; MTL, metreleptin; PBO, placebo; wt, weight.

Figure 2. Percent Change From BL in Weight Among Adults With Low BL Leptin (≤16F/≤5M)



^ *P*<0.1 for MTL 20 mg vs PBO.
≤16F/5M, BL leptin level of ≤16 ng/mL in females/≤5 ng/mL in males.
BL, baseline; MTL, metreleptin; PBO, placebo, wt, weight.

Supported By: Aegerion Pharmaceuticals Inc.

297-LB

Differences in Energy Expenditure between Respiratory Chamber and Metabolic Ward in Inpatient Men and Women

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We previously investigated 16 men with overweight or class I obesity who were admitted to a metabolic ward and engaged in 90 minutes of daily cycle ergometry at a fixed resistance. Subjects resided in a respiratory chamber for 2 days per week. The remaining days were spent in their inpatient rooms. Total expenditure was measured over 2 weeks via doubly labeled water (DLW). We found a surprisingly large (~500 kcal/day) decrease in expenditure when subjects resided in the respiratory chamber as compared to the days spent in their rooms. Here, we attempted to reproduce this finding in non-exercising healthy volunteers.

Purpose: To measure differences in daily energy expenditure between days spent on a metabolic ward vs. days spent in a respiratory chamber.

Methods: 10 adults (2 M, 8 F) aged (mean ± SE) 34 ± 3.5 years with BMI 27.9 ± 2.3 kg/m^2 completed a 7-day inpatient stay on the metabolic ward at the NIH Clinical Center. Two days were spent residing in a respiratory chamber. Study participants received a controlled diet and refrained from exercise. Temperature and clothing were kept constant. Energy expenditure on days spent on the ward was calculated using DLW over 6 days after accounting for the energy expended during the 2 respiratory chamber days.

Results: Average energy expenditure on the ward was 2122 ± 155 kcal/day, with an average of 1996±130 kcal/day expended during the two respiratory chamber days. Therefore, energy expenditure on the metabolic ward was 126 ± 55 kcal/day (p= 0.048) greater than in the respiratory chamber.

Conclusion: Participants expended ~126 kcal/day more on the metabolic ward than in the respiratory chamber. This was a much smaller discrepancy than previously found in exercising men. Failure to reproduce our previous results may have been due to the lack of exercise, the inclusion of women, or the wider range of BMIs in the current study. Further studies are needed to investigate the determinants of energy expenditure differences between ward and respiratory chamber days.

Supported By: National Institutes of Health

298-LB

Effect of Total Meal Replacement Program Compared with a Reduced-Energy Food-Based Diet Plan on Glycemic Status—Results from the OPTIWIN Study

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Background: Weight loss can resolve dysglycemia. We wanted to know whether total meal replacement (TMR) was more effective compared to a reduced-energy food based diet.

Methods: We conducted a 52-week multicenter, open-label RCT in adults with a BMI of 30-55 kg/m^2. Participants (n=330) were randomized to the OPTIFAST Program (OP), a TMR diet (800-980 kcal/day) with behavioral intervention, or to a reduced-energy (-500 to -750 kcal/day) food-based diet with behavioral intervention (FB) based on the Diabetes Prevention Program. In this analysis, we studied the impact of the OP on changes in the prevalence of PREDM and DM from baseline to 26 and 52 weeks compared to FB. Endpoints were analyzed using a modified intent to treat approach, including all randomized participants who initiated treatment with at least one follow-up weight measure (n=273; 82.7%). Missing data were imputed using last observation carried forward. Statistical analysis was performed using SAS Version 9.3.

Results: Results are shown below. OP participants lost more weight and had greater improvement in HbA1c than FB. Diabetes remitted more in OP than in FB in observed cases at 26 weeks. Prediabetes prevalence decreased similarly in both groups.

Conclusions: Total meal replacement (OPTIFAST program) led to greater weight loss and had a significant impact on glycemia in participants with DM and PREDM.

Table.

Measure/Outcome	Optifast Program(N=135)	Food-Based Program(N=138)	
Age in years, mean (SD)	47.0 (11.2)	47.2 (11.3)	
Sex, n (%)			
Female	116 (85.9)	109 (79.0)	
Race, n (%)			
Caucasian	100 (74.1)	95 (68.8)	
African American	22 (16.3)	37 (26.8)	
Asian/Pacific Islander	4 (3.0)	2 (1.4)	
Hispanic	5 (3.7)	4 (2.9)	
Other	4 (3.0)	0	
Baseline characteristics			
Weight in kg, Mean (SD)	106.8 (20.8)	109.9 (23.2)	
BMI in kg/m^2, Mean (SD)	38.4 (5.5)	39.2 (6.2)	
Weight change*, % of initial body weight, Mean (SD)			Difference (p value)
26 week follow-up	12.2 (0.6)	5.9 (0.6)	6.2 (p<0.01)
52 week follow-up	10.3 (0.6)	5.5 (0.6)	4.8 (p<0.01)
HbA1c change* (%), Mean (SD)			
Baseline	5.7 (0.8)	5.7 (0.7)	
26 week follow-up	5.5 (0.5)	5.6 (0.6)	-0.1 (p=0.08)
52 week follow-up	5.5 (0.9)	5.7 (1.0)	-0.1 (p=0.04)
Fasting blood glucose change* (mmol/L), Mean (SD)			
Baseline	5.6 (1.5)	5.6 (1.2)	
26 week follow-up	5.2 (0.9)	5.5 (1.2)	-0.3 (p=0.02)
52 week follow-up	5.4 (1.8)	5.7 (1.9)	-0.2 (p=0.11)
Diabetes status = Yes** in mITT*** population			
26 week follow-up	10/17 (58.8)	18/25 (72.0)	p=0.07
52 week follow-up	11/17 (64.7)	20/25 (80.0)	p=0.19
Prediabetes status = Yes+ in mITT population			
26 week follow-up	29/57 (50.9)	20/49 (40.8)	p=0.33
52 week follow-up	29/57 (50.9)	29/49 (59.2)	p=0.44
Diabetes Status = Yes in observed++ population			
26 week follow-up	7/14 (50.0)	11/16 (68.8)	p=0.008
52 week follow-up	8/14 (57.1)	12/16 (75.0)	p=0.31
Prediabetes Status = Yes in observed population			
26 week follow-up	17/43 (39.5)	11/34 (32.4)	p=0.63
52 week follow-up	16/43 (37.2)	15/34 (44.1)	p=0.64

* Change scores are adjusted for baseline value, age, sex, site, race, and diabetes status using linear mixed models. ** Diabetes status = Yes when HbA1c ≥ 6.5% or subject was on antidiabetes medication. *** mITT population had a least 1 measured weight during follow-up; if diabetes status was missing at a follow-up time point, then the subject was categorized according to baseline status. + Prediabetes status = Yes when HbA1c 5.7%-6.4% without antidiabetes medication. ++ Observed population includes only those who had follow-up at both week 26 and 52.

Supported By: Nestlé Health Science

299-LB

Lipocalin Prostaglandin D2 Synthase (LPGDS) Levels following Sleeve Gastrectomy and a Very-Low-Calorie Diet (VLCD)—A Pilot Study

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Background: Lipocalin prostaglandin D2 synthase (LPGDS) is a bile acid binding protein that has been found to have a significant role in glucose metabolism and appetite. In performing sleeve gastrectomy (SG) and gastric bypass in rodent models, we have also demonstrated LPGDS appears to have an important role in the beneficial metabolic effects seen after sur-

gery. We have sought to correlate if LPGDS has a significant clinical effect in humans for surgical weight loss.

Methods: Serum LPGDS levels were obtained in patients undergoing SG before, and then one month following surgery. Serum LPGDS was also measured in subjects undergoing a very low calorie diet (VLCD) program before, and then one month following the start of the program. LPGDS levels were measured by ELISA and analyzed.

Results: Subjects that underwent surgical loss went from 304.45 +/-74 pounds before surgery to 271.4 +/- 70 pounds one month following surgery. Subjects that underwent VLCD went from 273.1 +/- 65 pounds before the program to 255 +/-61 pounds one month after starting the program. LPGDS levels for surgical weight loss increased from 579.9 +/-161 ng/mL before the program to 694.6 +/- 448 ng/mL one month after surgery. LPGDS for VLCD was 583.1 +/- 187 ng/mL before the program and 598.4 +/- 165 ng/mL one month after starting the program.

Conclusion: LPGDS levels appear to increase after sleeve gastrectomy but not VLCD, although this trend is not statistically significant. Further study is needed to confirm this trend.

300-LB

Sustained Improvement of Obesity in Hypogonadal Men with Type 2 Diabetes (T2DM) Receiving Long-Term Treatment with Injectable Testosterone Undecanoate (TU)—Real-Life Evidence from a Urological Registry Study

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Background: Hypogonadism is highly prevalent in men with obesity as well as T2DM.

Methods: Of 805 hypogonadal men in a urological registry, 311 men (39%) had T2DM diagnosed and treated elsewhere. 141 received TU 1000 mg/12 weeks (T-group), 170 opted against treatment (CTRL). Mean changes over time between groups were compared by mixed effects model for repeated measures with random effect for intercept and fixed effects for time, group and their interaction. Changes were adjusted for age, weight, waist circumference, HbA_{1c}, blood pressure (BP), lipids to account for baseline differences between the two groups.

Results: Mean age: T-group: 61.8±5.3, CTRL: 63.5±4.9 years. Follow-up: mean: 7.5, median: 8 years. T-group: 89.4% were obese, 9.9% overweight, and 0.7% had normal weight. Weight decreased progressively from 113.4±13.9 to 90.7±8.6 kg at 10 years ($p<0.0001$) with statistical significance vs. previous year for the first 9 years. CTRL: 70% were obese, 26.5% overweight, and 3.5% had normal weight. Weight remained stable. Estimated adjusted difference between groups: -25.7 kg ($p<0.0001$). T-group: waist circumference decreased from 112.6±10.7 to 99.6±5.2 cm ($p<0.0001$) with statistical significance vs. previous year for the first 9 years. CTRL: Waist circumference remained stable. Estimated adjusted difference between groups: -17.9 cm ($p<0.0001$). T-group: BMI decreased from 36.3±4.4 to 29.3±2.7 kg/m^2 at 10 years ($p<0.0001$) with statistical significance vs. previous year for the first 9 years. CTRL: BMI remained stable. Estimated adjusted difference between groups: -8.3 kg/m^2 ($p<0.0001$). Since injections were administered in the doctor's office and no patient dropped out, there was a 100% adherence to testosterone therapy (TTh).

Conclusions: Long-term TTh with TU in hypogonadal men with T2DM improved anthropometric measures compared to untreated controls.

Supported By: Bayer AG

301-LB

Elevated ANGPTL5 Level in the Circulation of Obese and Type 2 Diabetic People

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Angiopoetin like protein family is composed of eight members that are involved in regulating various metabolic processes. ANGPTL5 is one of the members of this family that is mainly expressed in the heart and was showed to stimulate the expansion of human cord blood hematopoietic stem cell ex-vivo. This study was designed to investigate the expression level of this protein in the plasma of obese and diabetic people.

Methods: A total of 204 people were enrolled in this study including 109 nondiabetic and 95 type 2 diabetics. The nondiabetic people included 70 non-obese (BMI<30 Kg/m^2) and 39 obese people (BMI<30 Kg/m^2), while the diabetic people included 34 non-obese and 61 obese people. ANGPTL5 plasma level was measured by ELISA.

Results: In this study we showed that ANGPTL5 level was increased in the plasma of diabetic people (5.78±2.59 ng/mL) compared to nondiabetics (4.42 ± 2.32 ng/mL) (p-Value<0.0001). Obese nondiabetics had a significantly higher level of ANGPTL5 (5.12±2.23 ng/mL) compared to non-obese people (4.02 ± 2.27 ng/mL) (p-Value=0.029). Obese diabetic had higher level of ANGPTL5 compared non-obese yet did not reach significance (p-Value=0.064). ANGPTL5 was significantly associated with glycated haemoglobin 1C and insulin resistance as measured by HOMA-IR.

Conclusion: Our data shows for the first time that ANGPTL5 was increased in diabetic and obese people. Given its unique tissue expression in the heart, ANGPTL5 might modulate its response to insulin resistance through its interaction with other proteins including other ANGPTL proteins. Further analysis will be required to better understand the interaction between ANGPTL5 and other metabolic related biomarkers to shed more light on its role in diabetes and obesity.

Supported By: Dasman Diabetes Institute

302-LB

Postmenopausal Women with Endometrial Cancer Have Greater Metabolic Dysfunction and Higher BMI than Women with Benign Endometrium

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Obesity is an independent risk factor for endometrial adenocarcinoma (EC), yet it is unknown which attributes of obesity contribute to EC pathogenesis. We hypothesize that heterogeneity in metabolic health distinguishes which obese women are at risk for EC. We previously found that more premenopausal women with pre-malignant hyperplasia had type 2 diabetes and dyslipidemia than women with benign hyperplasia (BH), despite similar BMI. BH is the ideal control condition since presenting symptoms are similar, yet malignant transformation is negligible. Thus, we sought to compare metabolic abnormalities in postmenopausal women with EC and BH. We reviewed medical records of 284 women who received a biopsy/hysterectomy at our center over 3 years. We examined non-Hispanic white women age 50-65 years with BMI 25-50 kg/m^2, to limit variability in factors known to affect metabolism. 122 women had histologically confirmed EC (n=74) or BH (n=48), and 60% had lab data. Variables were analyzed by chi-squared or Student's T test. Women with EC were older (58 ± 0.5 vs. 53 ± 0.4 years, $p<0.0001$) and had higher BMI (37 ± 1 vs. 32 ± 1 kg/m^2, $p<0.0001$) than women with BH. BMI distribution was markedly different between groups, with a higher frequency and greater severity of obesity among women with EC ($p<0.0001$). More women with EC than BH had type 2 diabetes (19% vs. 4%, $p<0.05$) and hypertension (54% vs. 25%, $p<0.01$). Women with EC had higher triglycerides (140 ± 12 vs. 110 ± 13 mg/dL, $p<0.05$) and lower HDL (55 ± 2 vs. 60 ± 4 mg/dL, p=NS). However, these differences can be explained by the skewed BMI distribution. LDL and total cholesterol as well as statin use (20% vs. 25%) were similar between groups (p=NS). The striking differences in BMI among postmenopausal women with EC and BH highlights the role of obesity in EC pathogenesis. Since BMI affects metabolism, a prospective study of BMI-matched women is necessary to determine whether metabolic dysregulation independently influences cancer development.

Supported By: Yale Diabetes Research Center

ISLET BIOLOGY—APOPTOSIS

303-LB

Improved Beta-Cell Differentiation and Function in Isolated Islets Established in Dynamic Culture to Reduce Hypoxia

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Background: Pancreatic islet transplantation effectively prevents severe hypoglycaemia in type 1 diabetes. Restoration of normal β-cell functional mass remains elusive and we have recently demonstrated loss of β-cell end-differentiation in clinical islet recipients. We hypothesised that reducing islet hypoxia in culture would restore β-cell differentiation and function.

Methods: MIN6 pseudo-islets (PI) and primary human islets (HI) were cultured in either static (SC) or horizontal rotation (RC) culture for 7 days. Hypoxia was detected by pimonidazole (Pim) adduct formation and hypoxia-induced gene expression (qPCR). β-cell end-differentiation was assessed by UCN3 expression and IF staining (urocortin-3$^+$ insulin$^+$ cells/total insulin$^+$ cells) with function assayed by glucose-stimulated insulin secretion (GSIS).

Results: Hypoxia was confirmed in established PI (70±1.0% Pim$^+$). This was reduced in rotation culture (Pim$^+$: 15±1.5% RC vs. 80±2.5% SC; $p<0.05$) with reduced hypoxia-induced gene expression compared with adherent MIN6 (LDHA: 6.0±2.1 RC vs. 86.0±7.8 fold SC; MCT4: RC 2.9±0.4 vs. 54.6±0.6 fold SC; $p<0.05$). RC enhanced UCN3 gene expression (4.2±0.5 RC vs. 2.2±0.2

fold SC; p<0.05) and increased UCN3/insulin co-staining (80±1.2% RC vs. 30±2.4% SC; p<0.0001) with enhanced GSIS stimulation index (4.1±0.1 RC vs. 2.8±0.1 SC; p<0.0001). Hypoxia-induced expression was reduced in HI RC compared with freshly isolated islets (LDHA: 0.3±0.1 RC vs. 1.8±0.04 fold SC; MCT4: 0.08±0.01 RC vs. 1.1±0.2 fold SC; p<0.05) with increased UCN3 expression (5.9±1.6 RC vs. 3.3±0.9 fold SC; p<0.05) and enhanced GSIS stimulation index (4.1±0.9 RC vs. 3.0±1.2 SC; p<0.05).

Conclusion: Hypoxia in established PI and isolated HI was reduced over 7 days in dynamic culture. This was associated with enhanced β-cell differentiation and function providing a potential approach to maximise optimal functional mass in islet transplantation.

Supported By: Oman Ministry of Health

304-LB

Lactogens Prevent ER Stress-Induced ß-Cell Death and Diabetes

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ER stress is highly relevant in the context of diabetes, as inducers of β cell death and dysfunction implicated in the disease - including proinflammatory cytokines and glucolipotoxicity - are known to impair ER function. Previous work has shown that prolactin (Prl) and placental lactogen (PL), which bind to the same receptor (Prl-R), are important for β cell function and proliferation, and enhance survival against cytokines and glucolipotoxicity. Here, we examine the effect of Prl/PL directly on ER stress and the associated unfolded protein response (UPR) in the β cell. ER stress was induced in vitro via tunicamycin in INS1, primary mouse, and primary human β cells, concurrent with Prl/veh treatment. Expression of ER stress and UPR associated genes was measured via qRT-PCR and preliminarily via WB, and insulin-TUNEL co-staining was used to assay for β cell death. As an in vivo model, heterozygous Akita mice - a well-established β cell ER stress model which becomes diabetic by 4 weeks of age - were bred to single-transgenic mice overexpressing PL in the β cell. Prl increases survival of INS1, primary mouse and human β cells against ER stress-mediated cell death in vitro (2.34±0.19% TM vs. 0.73±0.19% TM+Prl, human). Differences in mRNA expression point towards modulation of the PERK/IRE1 UPR arms. Non-Tg Akita mice quickly become and remain hyperglycemic/diabetic, while overexpression of PL in the β cells of these mice significantly improves glycemia in males (663±29mg/dL non-Tg vs. 327±37mg/dL Tg, 12 weeks) and results in normoglycemia in females. In vivo GSIS at 12 weeks shows a trend towards restoration of β cell function in Tg compared to non-Tg Akita mice. Males at this age exhibit improved β cell mass (0.28±0.12mg non-Tg vs. 2.29±0.44mg Tg), with similar trends in β cell proliferation. Taken together, these data demonstrate that Prl/PL can prevent and protect against ER stress in the β cell, in vitro and in vivo. As ER stress is highly relevant to diabetes, modulation of the lactogenic pathway could present a novel therapy for this disease.

ISLET BIOLOGY—BETA CELL—DEVELOPMENT AND POSTNATAL GROWTH

305-LB

The CCR4-NOT Complex Maintains ß-Cell Identity through the Repression of ß-Cell Disallowed Genes

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Loss of β-cell identity, dedifferentiation and reprogramming are recognized as mechanisms of β-cell dysfunction in diabetes. Molecular β-cell identity is not only defined by the expression of signature functional β-cell specific genes but also the repression of several genes recently identified in β-cell research as β-cell disallowed genes. The molecular mechanisms involved in the repression of β-cell disallowed genes are largely unknown. Here, we show that the CCR4-NOT complex, a major deadenylase conserved in eukaryotes, is involved in post-transcriptional regulation of β-cell disallowed genes. β-cell specific depletion of CNOT3 (CNOT3βKO), a CCR4-NOT complex subunit, in mice promotes deceased insulin secretion, early impaired glucose tolerance and the development of overt diabetes at 12 weeks of age. CNOT3βKO islets display decreased insulin content and decreased glucose responsiveness. Furthermore, CNOT3 depleted ß cells exhibit ultrastructural abnormalities including: degranulated β cells, increased immature insulin granules and abnormal mitochondria. RNAseq and qRT-PCR analyses revealed that CNOT3βKO islets have decreased expression of β-cell functional genes: (Ins1, Ins2, MafA, Pcsk2 and Cpe) and increased expression of 9 of the 11 core β-cell disallowed genes: (Slc16A1, Ldha, Pdgfra, Cxcl12, Igfbp4, Oat, Maf, Smad3 and Cd302) and progenitor-like cells genes: (Nanog and Ngn3) supporting the loss of β-cell identity. Using the total RNAseq data, we assessed mRNA stability by calculating the relative amounts of introns and exons for a given mRNA. RNA immunoprecipitation revealed that the CCR4-NOT complex directly binds several upregulated stabilized β-cell disallowed genes: Slc16A1, Tgm2, Cat and Parp3 genes. The present data highlight deadenylation as a novel molecular mechanism regulating β-cell disallowed genes. Thus, we further propose that the CCR4-NOT complex is essential for maintaining β-cell identity by repressing β-cell disallowed genes.

306-LB

Pancreatic ß-Cell Specific Knockout of Grb10 Improves ß-Cell Function by Enhancing ß-Cell Differentiation and Suppressing ß-Cell Dedifferentiation

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Aim: Defects in β cell differentiation are associated with type 2 diabetes in humans. Understanding the basis for β cell differentiation defects may reveal new strategies for diabetes therapy.

Results: We found that Growth factor receptor binding protein 10 (Grb10) is highly expressed in mouse and human pancreas and islets and that β cell-specific knockout of Grb10 in mice increased β-cell mass and insulin content, enhanced insulin secretion from β-cells, and up-regulated mTOR and insulin signaling in islets. Pancreatic β cell-specific disruption of Grb10 expression also improved glucose tolerance in mice fed with a high fat diet and protected adult mice from STZ-induced β cell death. Pancreas-specific knockout Grb10 promoted endocrine progenitors differentiate into β cells during embryonic development. In addition, knockout Grb10 in islets alleviated STZ or high fat diet-induced β cell dedifferentiation.

Conclusion: We have identified Grb10 as a key regulator of β cells differentiation/dedifferentiation and demonstrated that reducing the expression level of Grb10 has a protective effect on β-cell function. Our findings suggest a potential effective therapeutic treatment of both type 1 and type 2 diabetes.

Supported By: National Basic Research Program of China (2014CB910500); National Natural Science Foundation of China (81770775, 91749118, 81370017)

307-LB

Longevity of Beta Cells and Protein Complexes Revealed by Isotope Imaging

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We discovered recently that long-lived cells (LLCs), such as neurons, contain long-lived proteins (LLPs) in the nucleus that can last a lifetime, and their decline during aging impairs nuclear function. Beta cells are LLCs with a slow cell replication process, yet it is unknown whether individual beta cells have different lifespans. We tested this hypothesis by using a hybrid microscopy and mapping platform (MIMS-EM) to identify beta cells and quantify cell and protein turnover in the islets of Langerhans. This is achieved by pulse-labelling mice with an ^{15}N-rich diet followed by a chase period with a control ^{14}N-rich diet for up to 2 years. Here, old cells and protein structures retain ^{15}N while those that turnover incorporate ^{14}N. The levels of ^{15}N and ^{14}N were measured with multi-isotope mass spectroscopy (MIMS) and the ^{15}N-to-^{14}N ratio reports on cell and protein turnover. Importantly, the MIMS data is correlated with scanning electron microscopy (EM) to create high-resolution maps of cells and intra-cellular structures overlaid with age information. Here we report the use of MIMS-EM on mouse islets to discover that beta cells have vastly different ages. In fact, while approximately 75% of beta cells replicate between 2-4 times, almost 25% of all beta cells does not replicate at all after weaning and remain quiescent for an entire lifetime, and therefore, are as old as cortical neurons. Such longevity was also found in other islet cell-types and at the protein super-complex level, where ^{15}N accumulation on the primary cilium of beta cells strongly indicates that this important signaling structure is exceptionally long-lived. Strikingly, and similar to what is found in old rat neurons, beta cells from humans aged >60-years-old lose specific nuclear LLPs and show signs of impaired nuclear function. Together, our data shows that beta cell longevity is heterogeneous and identifies the loss of nuclear LLPs in human beta cells as a potential contributing factor to age-dependent loss of beta cell function.

Supported By: American Diabetes Association (1-18-PMF-007 to R.A.E.D.); National Institutes of Health; W.M. Keck Foundation; NOMIS Foundation

308-LB

Analysis of Transcriptome Data from 261 Individual Laser-Captured Islets from Nondiabetic, Autoantibody-Positive, and Type 1 Diabetic Organ Donors

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The purpose of this study was to obtain comprehensive gene expression datasets from a large number of individual islets, with defined pathological phenotypes, from organ donors with different clinical stages of type 1 diabetes. Here we will present results from an analysis that compared "normal" (Ins+CD3-) islets from the 3 clinical phenotypes: Autoantibody negative nondiabetic (C), Autoantibody positive nondiabetic (AB) and type 1 diabetic (T1D). We obtained pancreatic tissue from 43 male and female nPOD donors with the 3 clinical phenotypes (C=16, AB=11, T1D=16). Staining of islets for both insulin and CD3 resulted in the following histologic subtypes of the 261 islets collected and analyzed for gene expression: Ins+CD3- (n=147), Ins+CD3+ (n=78), Ins-CD3+ (n=12), and Ins-CD3- (n=23). The gene expression profiles of these 261 individual islets were obtained using Affymetrix HTA 2.0 arrays. We compared gene expression profiles of the 147 islets that were Ins+CD3- from each of the 3 organ donor types. The number of transcripts differentially expressed by >1.5 fold and p<0.001 (Student's t-test with FDR<0.05) were as follows: C vs. AB=448; C vs. T1D=240; AB vs. T1D=387. Those gene lists were subjected to a data mining workflow. The 448 transcripts differing between Ins+CD3- islets of C and AB organ donors were dominated by non-coding RNA (33%). Islets from AB donors had reduced transcripts associated with islet regeneration, cell replication, and immune responses. The 387 transcripts differing between Ins+CD3- islets of AB and T1D organ donors expressed increased levels of beta cell specific transcripts and markers of immune responses in T1D islets. A number of oxidative phosphorylation gene transcripts were lower in T1D islets. The 240 transcripts differing between Ins+CD3- islets of C and T1D organ donors demonstrated reduced levels of beta cell specific transcripts but increased HLA class II transcripts in T1D islets

Supported By: National Institutes of Health; JDRF

309-LB

IMG-1 Activates and Mobilizes Insulin-Producing Islet Progenitor Cells (CD133+/Insulin+) In Vitro

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IMG-1 is a novel therapeutic for the treatment of types 1 and 2 diabetes that may have islet regenerative properties. 300 islets isolated from mouse pancreases were cultured in standard media with IMG-1 (0.5µg/mL) and compared with control non-treatment. Within 24 hours, the IMG-1 treated islets became smaller (less clustered) and islet cells appeared to actively migrate away from the clusters. Control islets maintained their clustered morphology and did not show any evidence of cell migration. Three days after IMG-1 treatment, there were both free-floating and attached cells in the culture. The free-floating cells were 30% viable and the attached cells and leftover islets were 85% viable. In contrast, control islet cultures had neither free-floating nor attached cells although islet clusters looked healthy (cell viability >90%). By day 10 of IMG-1 treatment, islet clusters were few in numbers (<10%), no free-floating cells remained, and the attached cells appeared to form colonies. Total cell viability was >90%. Control cells still had no migration or attachment, although within the islet clusters cell viability remained around >90%. At 25 days, islet cells from both cultures were fixed and stained for the progenitor cell marker, CD133, and insulin. IMG-1 treated colonies were 75% insulin-positive by immunohistostaining. Furthermore, these cells were 70% CD133-positive with 60% of the culture being CD133/Insulin double-positive. In contrast, non-treated islets were 90% insulin+ cells, but <5% CD133+ and <5% double positive (CD133/insulin). IMG-1 has a novel effect on islets and induces the activation and migration of islet cells out of the islet. These cells form colonies of CD133/insulin double-positive cells that putatively represent activated beta-cell progenitor cells that can be used to regenerate damaged islets.

ISLET BIOLOGY—BETA CELL—STIMULUS-SECRETION COUPLING AND METABOLISM

310-LB

Dextrose-Sulfonylurea Challenge as a Screening Test for Monogenic Diabetes in Patients Diagnosed with Type 1 Diabetes

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Monogenic diabetes due to ABCC8, KCNJ11, HNF1A and HNF4 can be treated with sulfonylurea (SU). The SEARCH for Diabetes in Youth confirmed most patients with monogenic diabetes are misdiagnosed with T1DM, and that family history and fasting C-peptide do not reliably increase pre-test probability for diagnosis. Confirmatory genetic testing is expensive and methods to improve cost-benefit ratio do not exist. As such, we developed a dextrose-SU challenge to assess C-peptide response to SU as indication of clinically significant underlying β-cell excitation defects. We postulate negative response to hyperglycemia with positive response to SU indicates presence of a genetic defect in glucose-stimulated insulin secretion. This challenge has been completed on 42 subjects with TIDM on insulin therapy. Blood glucose (BG) and C-peptide were obtained at regular intervals prior to and after a 0.5 g/kg IV dextrose bolus, a single dose of glipizide was given 20 minutes after dextrose (0.3 mg/kg max 15mg if <50 kg; 40 mg if >50 kg) and BG and C-peptide were obtained until study completion. Twenty of the 42 subjects had undetectable C-peptide. Twenty-two subjects had detectable C-peptide, 13 of which showed preferential C-peptide response to glipizide (ΔC-peptide 0.41 ± 0.45 ng/mL) compared to hyperglycemia (Δ 0.05 ± 0.03 ng/mL). This suggests islets may show modest but specific response to SU in TIDM. Nine of the 13 who showed preferential response to glipizide completed a dextrose-only challenge 6 months later and retained marginal C-peptide response to hyperglycemia alone (Δ 0.05 ± 0.04 ng/mL). Whole exome sequencing is pending on these subjects. These data suggest the challenge may serve to elicit and stratify C-peptide response to SU, assist in categorizing residual β-cell function, support screening for monogenic diabetes, and increase consideration of SU therapy for appropriate patients.

311-LB

Islet Beta-Cell Specific Deletion of UBL5 Gene Associated with Mitochondrial Stress Leads to Diabetes in Mice and Beta-Cell Impairment/Death

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Hyperglycaemia has been shown to cause oxidative stress in pancreatic β-cells, leading to activation of stress responses such as the mitochondrial unfolded protein response (UPR^{mt}). Failure of these responses to adapt to or repair damage from stress results in dysfunction and death of β-cells. Ubiquitin-like protein 5 (UBL-5) is a protein known to have a crucial role in the UPR^{mt} in C. elegans and upregulated during the UPR^{mt} mammals.

The aim of this study was to determine whether UBL-5 has a role in maintaining β-cell mass and function through modulating the UPR^{mt}, by generating and characterising tamoxifen-inducible islet β-cell specific UBL-5 knockout mice. Homozygous β-cell UBL-5 knockout mice (UBL5-/-) showed glucose intolerance and lower plasma insulin levels during the OGTT while heterozygous mice (UBL5+/-) showed no difference. UBL5-/- had significantly reduced plasma insulin levels during IVGTT compared to control. Interestingly, UBL5+/- had significantly increased plasma insulin levels during IVGTT. Beta-cell mass was also significantly reduced in UBL5-/-, with most showing signs of frank diabetes (blood glucose >20 mM), polyuria and polydipsia, while UBL5+/- had increased β-cell mass. One week post UBL5 deletion, UBL5-/- mice had significantly increased blood glucose levels and islet cleaved caspase-3 levels compared to controls despite no difference in β-cell mass. In addition islets taken from UBL5-/- mice 1 week post UBL5 gene deletion showed significant decrease in insulin secretion, suggesting that β-cell dysfunction precedes the decrease in β-cell mass. Islets taken from UBL5+/- mice had increased insulin secretion compared to control. Real time PCR data showed a decrease in UPR^{mt} genes (Clpx, Clpp, CHOP, Lonp1, HSP10, HSP70, ATF5) with HSP60 showing increased expression in the UBL5-/- mice one week after gene deletion, while the UBL5+/- mice showed an overall increase in most UPR^{mt} related genes.

312-LB

Cyclophilin D-Dependent Mitochondrial Proton Leak in ß Cells Promotes Basal Insulin Secretion

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Prediabetic subjects display hypersecretion of insulin at basal levels of blood glucose, a phenomenon termed basal hypersecretion. The molecular mechanisms underlying basal hypersecretion and how it may lead to beta cell failure are not well understood. Islets isolated from prediabetic animals and humans have an inherently high mitochondrial proton leak. However, the molecular entity responsible for this leak and its role in basal hypersecretion are not known. We hypothesize that basal secretion is regulated by proton leak mediated by the permeability transition pore (PTP) functioning in a low conductance state. Our data indicate that islets from high fat diet animals display basal hypersecretion of insulin, increased mitochondrial proton leak, and increased expression of Cyclophilin D, a PTP regulator. Moreover, acute stimulation of islets with amino acids (leucine/glutamine) and fatty acids (oleate/palmitate) at basal glucose concentrations increases leak. Pharmacological and genetic inhibition of Cyclophilin D reverses nutrient induced islet leak and insulin secretion. Pharmacological stimulation of mitochondrial proton leak is sufficient to induce basal hyper secretion. Inhibition of CypD-mediated proton leak might constitute a novel target to test the role of basal hyperinsulinemia in the development of diabetes and obesity.

Supported By: National Institutes of Health (R01DK099618); Kuwait Foundation for the Advancement of Sciences (CB17-63MM-01)

313-LB

Mechanistic Role of IP3R Calcium Release Channel in Pancreatic Beta-Cell Function

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Background: According to the classic paradigm, insulin secretion is triggered by the influx of extracellular Ca^{2+} via voltage-dependent channels, leading to the fusion of insulin granules. Instead, the mechanisms involved in Ca^{2+} mobilization from internal stores are less defined. The main intracellular Ca^{2+} release channels are inositol 1,4,5-trisphosphate receptor (IP3R) and ryanodine receptor (RyR), whereas Ca^{2+} is returned to the ER primarily by the activity of the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump. We recently demonstrated the importance of RyR in type 2 diabetes mellitus (T2DM), showing that it is essential in glucose-stimulated insulin secretion (GSIS). Conversely, the exact role of IP3R in GSIS remains not fully understood.

Methods and Results: Three isoforms of IP3R have been identified in mammalian cells. Channel opening is stimulated by the binding of second messenger IP3 and by changes in Ca^{2+} concentrations. Studies in rodent and human samples indicate that β cells express all IP3R isoforms. We demonstrated that the expression of all isoforms is significantly increased in human islets from T2DM cadaveric donors T2DM compared with nondiabetic individuals. These results were also confirmed in diabetic db/db mice and in mice fed high-fat diet. Moreover, pancreatic β cells from T2DM patients exhibited dysmorphic and dysfunctional mitochondria, with markedly altered Ca^{2+} uptake. Similar features were found in clonal β cells chronically exposed to high glucose. In vitro, overexpression of IP3Rs was associated with impaired GSIS, whereas IP3R silencing improved β cell function, mitochondrial Ca^{2+} uptake and function, ER stress, and insulin release in response to different secretagogues.

Conclusions: Taken together, our data indicate that IP3Rs are upregulated in human islets from T2DM donors, leading to mitochondrial dysfunction and pancreatic β cell failure, identifying in these intracellular Ca^{2+} release channels a novel therapeutic target to treat T2DM.

Supported By: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases

ISLET BIOLOGY—SIGNAL TRANSDUCTION

314-LB

Altered Expression of Insulin Signaling Proteins in Islets from T2DM Female Mice

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With development and progression of T2DM in KKAʸ mice, pancreatic islets alter their expression of GLUT2, insulin and insulin receptor. The study's goal was to identify glucoregulatory proteins in the insulin receptor signaling pathway that were early markers of islet dysfunction after 4 weeks of uncontrolled hyperglycemia. Isolated islets were pooled from 2 groups of 12 week old mice: insulin-resistant, euglycemic KK mice and insulin-resistant, hyperglycemic KKAʸ T2DM mice. Samples were analyzed for 40 proteins using 221 antibodies in an insulin phospho antibody array. After 4 weeks of hyperglycemia in KKAʸ mice, many proteins were not altered as compared to KK mice (ratio: 0.94-1.02) including insulin receptor (Phospho-Tyr1355), FOXO1A (Phospho-Ser329), PI3-kinase p85-alpha (Phospho-Tyr607), ERK1/2, PP1-alpha, and AMPK1. The phosphorylation states of some proteins were altered including AKT1 (Phosphor-Ser124) (0.77) and IRS-1 (Phosphor-Ser636) (1.25). Three proteins were then selected for ELISA analysis in islets isolated from 4, 8 (onset of T2DM), and 12 week old mice: GLUT2, iNOS (1.41) and CBL (Phospho-Tyr700) (0.78), an E3 ubiquitin ligase. GLUT2 was lower in KKAʸ mice at 4 weeks (KK, 4.0±0.5; KKAʸ, 2.3±0.3, $p<0.001$), but not at 8 or 12 weeks, because GLUT2 decreased with age in both groups (12 weeks: KK, 1.0±0.1; KKAʸ, 1.4±0.1, $p=0.31$) [age*mouse: $F(2,18)=11.104$, $p=0.001$]. CBL-b was higher in KKAʸ mice (KK, 0.50±0.09; KKAʸ, 0.65±0.07) [$F(1,17)=4.527$, $p=0.048$] and decreased with age in both groups (12 week: KK, 0.30±0.02; KKAʸ, 0.45±0.13) [$F(2,17)=12.231$, $p=0.001$]. In contrast, iNOS was lower at 4 week (KK, 3.0±0.3; KKAʸ, 2.0±0.4; $p=0.029$), then higher at 8 and 12 week (KK, 0.8±0.4; KKAʸ, 2.1±0.2; $p=0.007$) with iNOS steady in KKAʸ mice [age*mouse: $F(2,16)=10.902$, $p=0.001$]. With short-term hyperglycemia in KKAʸ mice, many insulin signaling proteins were not altered as compared to diabetes susceptible KK mice. At onset on T2DM in KKAʸ mice, sustained iNOS and elevated CBL-b were early markers of islet dysfunction.

Supported By: Midwestern University

315-LB

Pancreatic Alpha-Cell Function and Identity in Human T2D

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Glucagon is synthesized and released by pancreatic α-cells and, along with insulin, maintains blood glucose levels within the physiological range. We seek to understand the impact of glucose on the biophysical properties of α-cells in T2D. We studied α-cells from human donors (34 nondiabetic, and 14 T2D) and from mice fed a high fat diet (HFD) by whole-cell patch-clamp electrophysiology, with and without combined single-cell RNA sequencing (patch-seq). We found that, opposite to what is observed in β-cells, depolarization-induced exocytosis and Ca^{2+}-channel function is enhanced at low glucose (LG, 1 mM G) and suppressed at high glucose (HG, 5-20 mM G) in nondiabetic (ND) α-cells. This is reversed in α-cells from T2D donors, which display a β-cell-like phenotype where HG amplifies exocytosis and LG inhibits it. Using pharmacological antagonists of Ca^{2+} channels, we found that LG increases P/Q-type Ca^{2+} currents in human α-cells, which are specifically linked to glucagon exocytosis. Similar results were obtained from α-cells of HFD mice for 10-14 weeks, where α-cell exocytosis and glucagon secretion were both enhanced, while exocytosis shifted from a dependency on P/Q-type (α-cell-like) to L-type (β-cell-like) Ca^{2+} channels. Finally, given that the Ca^{2+} responsiveness of α-cells is variable (suggesting cell- to-cell heterogeneity) and the function of α-cells is dysregulated in diabetes, we applied combined computational approaches and single-cell RNA sequencing with patch-clamp analysis (patch-seq) to link single human α-cell function with transcriptomic profiles. We found distinct α-cell sub-populations in human islets that are either resistant to, or sensitive to, dysfunction in the form of a shift towards a more 'β-cell like' functional phenotype in T2D. In all, we provide new information to understand normal function of α-cells and important determinants of glucagon secretion in health and diabetes.

316-LB

Potentiation of TRPM5 with Stevioside in the Beta Cells Stimulates Insulin Secretion

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The calcium-activated monovalent cation channel TRPM5 is expressed in human and murine beta cells. Members of the TRP ion channel family can be activated by a plethora of different stimuli as temperature, voltage, and ligands, including natural compounds. Studies have shown that TrpM5-knockout mice have increased blood glucose levels and an impaired insulin secretion. Mutations in TRPM5 are more prevalent in patients with diabetes or metabolic syndrome. Stevioside is a sweet tasting organic molecule isolated from the leaves of the scrub plant Stevia rebaudiana, it is widely used in consumer foods and beverages. Despite its wide use, the molecular interactions of stevioside in the body remained elusive. Here we show that stevioside potentiates TRPM5 channel activity. This leads to increased calcium dynamics in both human and mouse islets, which relates to increased insulin secretion. We show that the steviol core of stevioside is responsible for the TRPM5-potentiating effect. When mice on a high fat diet are given stevioside, we observe an attenuation of the development of hyperglycemia in a TRPM5-dependent manner. With this work, we elucidate the molecular mechanism of action of stevioside. Furthermore, we provide a deeper insight in the regulation of insulin secretion from the beta-cells and identify TRPM5 as an important part of a healthy secretion pathway. TRPM5 constitutes a novel possible drug target in the battle against type 2 diabetes.

Supported By: European Union (to K.P.)

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WITHDRAWN

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