Inter-item agreement (alpha) for DMSRQ measures ranged from .71 to .93 (median=.86). Test-retest reliability measured by intraclass correlation ranged from .82 to .93 (median=.86). 3 of 9 measures showed statistically significant ($p<.05$) shifts in means over time. None of the changes met the threshold for minimum detectable difference (MDD=0.5 baseline standard deviations); all changes were less than 0.2 standard deviations.

All correlations between DMSRQ measures and criterion measures were statistically significant ($p<.01$) in the expected direction. DMSRQ has 4 measures that correspond directly to the criterion measure of treatment satisfaction (Convenience, Efficacy, Negative Events, Treatment Satisfaction). Correlations between corresponding DMSRQ and criterion measures (range=.347 to .629, absolute values; mean=.529) were stronger than between other measures that did not correspond directly, indicating convergent validity.

Correlations of adherence with the 4 DMSRQ measures corresponding to the criterion measure of treatment satisfaction ranged from .384 to .450 (absolute values; mean=.411); correlations of adherence with the corresponding criterion measures of treatment satisfaction ranged from .282 to .486 (absolute values; mean=.399).

This study suggests that the DMSRQ has good reliability and validity, and provides a more comprehensive set of measures than existing treatment satisfaction questionnaires.

866-P

Weight History as a Screening Tool for Identifying Undiagnosed Diabetes and Pre-Diabetes in Japanese Men: The Toranomon Hospital Health Management Center Study (TOPICS)

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The majority of individuals with diabetes or pre-diabetes remain undiagnosed and identifying such individuals has become a major priority. Evidence has shown that obesity or a history of overweight can be a strong indictor of diabetes in assessments that do not include testing. In this study, we cross-sectionally investigated whether weight history, which does not require blood drawing or laboratory testing, could be used to identify individuals with undiagnosed diabetes or pre-diabetes.

Participants were 18076 Japanese men without known diabetes aged >20 y who undertook a health examination. Information on weight at age 20 y and lifetime maximum weight was retrospectively obtained using a standard questionnaire. Undiagnosed diabetes was defined as a fasting plasma glucose level (FPG) ≥126 mg/dl and/or HbA1c ≥6.5% with no history of diagnosed diabetes. Pre-diabetes was defined as FPG 100-125 mg/dl and/or HbA1c 5.7-6.4%.

Prevalence of undiagnosed diabetes or pre-diabetes was 767 and 7560, respectively, among the 18076 participants. Results of logistic regression analysis showed that each 5-kg increment in Δ weight (maximum - 20 y) increased the risk of having undiagnosed diabetes by 39% (95% CI; 33-46%) and that of pre-diabetes by 25% (22-28%). An additional adjustment for present adiposity attenuated the association although it remained significant. Results of the investigation of the combined effect of present adiposity (BMI ≥25 or <25) and weight history (Δ weight (maximum - 20 y) <=10 kg or >10 kg) on prevalence of undiagnosed diabetes and pre-diabetes showed that a history of Δ weight (maximum - 20 y) >10 kg increased the risk of having undiagnosed diabetes by 72% (41-110%) in lean men and by 97% (100-83%) in obese men. We observed similar results in predicting the risk of pre-diabetes.

This large cohort study has clarified the usefulness of weight history as a screening tool for detecting high risk populations. A past history of weight, which does not require laboratory measurements, could be used to identify both undiagnosed diabetes and pre-diabetes.

867-P

White Matter Tract Integrity in Type 1 Diabetes in Relation to Disease Parameters and Cognition

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Type 1 diabetes (T1DM) is associated with white matter focal lesions and volume loss and cognitive changes. We aimed to identify changes in tract integrity and determine the relationship with disease variables and cognitive functions.

One hundred T1DM patients and 49 controls underwent MRI, including diffusion tensor imaging (DTI) with 60 directions of encoding. Using the diffusion toolbox and tract-based-spatial-statistics (TBSS), part of FSL4.1 software, we calculated fractional anisotropy (FA), as a marker of tract integrity. Cognitive functions were assessed using an elaborate cognitive test-battery. Analyses were corrected for age, gender, depressive symptoms and multiple comparisons. As the left inferior fronto-occipital fasciculus (IFO) showed the most consistent decrease in integrity in T1DM patients compared to controls we selected the mean FA-value of this tract for each participant, to determine correlations between FA of that particular tract, disease variables and cognitive functions.

T1DM patients were significantly older, had higher HbA1c levels and depression scores compared to controls (all $P<0.05$). Decreased FA was widespread, most notably in the bilateral IFO, corticospinal tracts, parts of the corpus callosum, cingulate gyrus, and in parts of the left temporal cingulate tract. In T1DM patients, the mean FA-value of the left IFO correlated negatively with disease duration ($r=-0.338$) and albumin-to-creatinine ratio (ACR) ($r=-0.287$) and positively with general cognitive ability ($r=0.258$), information processing speed ($r=0.281$), executive functions ($r=0.280$) and attention ($r=0.301$) (all $P<0.01$).

T1DM patients showed widespread decreases in white matter integrity compared to controls, most pronounced in the left IFO. In T1DM patients a reduced integrity of the IFO was associated with worse cognitive performance and longer disease duration higher ACR levels. Longitudinal follow-up should identify possible mechanisms involved in decreasing FA and its relation to cognitive functional changes over time.

Supported by: Dutch Diabetes Research Foundation

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—GLUCOSE MONITORING AND SENSING

[***See also: Presidents Posters 404-PP to 405-PP, page A112.***]

Guided Audio Tour: Glucose Monitoring—From Self-Monitoring of Blood Glucose to a Closed Loop System *(Posters 868-P to 875-P), see page 11.*

868-P

Effect of Aging on the Performance of HbA_{1c} in Screening for Diabetes in Hospital Based Population in China

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The purpose of the study is to examine the impact of aging on the performance of HbA1c in screening for diabetes in hospital based population in China. A total of 10098 subjects with high risk factors, but no previously known diabetes, were recruited from 37 hospitals in 17 provinces and municipalities around China. All subjects underwent standard 75g oral glucose tolerance test (OGTT) and were tested for HbA1c at the same time. We divided the whole population into five groups by age, and plotted the receiver operating characteristic (ROC) curve to evaluate the performance of HbA1c in each group. Kappa index and spearman correlation coefficient were used for agreement and correlation analysis. The result showed that using the OGTT criteria as the gold standard for diagnosis, the area under the ROC curve (AUC) of HbA1c was 0.894 in the whole population. And the optimal HbA1c cut-off point was 6.2%, with a sensitivity of 78.7% and a specificity of 85.6%. While age increases, the AUC, the sensitivity, the specificity, the positive predictive value (PPV), the positive likelihood ratio (PLR) and the kappa index at the optimal HbA1c cut-off point 6.2% all decreases gradually, except negative likelihood ratio (NLR).

Age group (years)	AUC (95% confidence interval)	Sensitivity (%)	Specificity (%)	PPV (%)	PLR	NLR	Kappa index
≤39	0.953 (0.941, 0.965)	86.6	93.8	85.5	14.0	0.14	0.801
40-49	0.914 (0.902, 0.926)	83.3	86.4	81.9	6.1	0.19	0.681
50-59	0.885 (0.873, 0.897)	80.9	83.0	79.5	4.8	0.23	0.610
60-69	0.858 (0.842, 0.875)	76.7	80.3	77.6	3.9	0.29	0.557
≥70	0.805 (0.781, 0.830)	65.7	80.2	77.5	3.3	0.43	0.463
Total	0.894 (0.887, 0.900)	78.7	85.6	80.0	5.5	0.25	0.634

Besides, the correlation between HbA1c and plasma glucose levels in OGTT became weak as age increases. To sum up, HbA1c can be used for screening for undiagnosed diabetes in high risk population, and the optimal HbA1c cut-off point is 6.2% in this study population. However, HbA1c alone for detecting undiagnosed diabetes may be inadequate in the eldly and it is better to combine other parameters. Further studies are needed to determine whether age-specific screening and diagnostic HbA1c criteria are appropriate.

869-P

Accuracy of the GlucoScout® Blood Glucose Monitor in Inpatient Monitoring of Patients with Type 1 Diabetes

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The GlucoScout® (International Biomedical, Inc., Austin, TX) was developed to allow for frequent, intermittent venous blood glucose monitoring in hospitalized patients. This FDA approved device can automatically withdraw and measure plasma glucose levels every 5 minutes for 72 hours using blood samples from a central vein or peripheral vein/artery. The system is closed, so there is no blood loss, and the risk of infection is decreased since the vascular line is not accessed for each blood sample. Since sampling is programmed at automatic frequencies, the system is less disruptive to a patient's sleep and can reduce the nursing/lab requirements when there is a need for frequent sampling. We evaluated the accuracy of the GlucoScout compared with the YSI (Yellow Springs Instrument 2300) glucose analyzer in 9 subjects 8-16 years old who were participating in a TrialNet/DirecNet study to assess the effect of hybrid closed-loop control initiated within 1 week following the diagnosis of diabetes. All data were from one participating center (Stanford).

		Difference (GlucoScout-YSI)	*Relative Absolute Difference (RAD)*[a]	*ISO Criteria*[b] *met*
	N	*Median mg/dl (25th, 75th percentiles)*	*Median (25th, 75th percentiles)*	*(%)*
Overall	437	-2 (-9, +6)	6% (3%, 10%)	97%
Reference glucose level				
<=70 mg/dL	12	-1 (-3, +2)	4% (3%, 7%)	100%
71-120 mg/dL	175	-1 (-6, +5)	6% (2%, 10%)	97%
121-180 mg/dL	157	-1 (-8, +7)	5.5% (3%, 9%)	97%
>180 mg/dL	93	-9 (-22, +5)	7.2% (4%, 11%)	96%

[a] RAD= absolute value of difference divided by YSI value

[b] International Organisation for Standardisation (ISO) criteria: for YSI value ≤75mg/dL, GlucoScout ±15mg/dL; or YSI value >75mg/dL, GlucoScout ±20%.

Accuracy did not vary based on age of the sensor (median RAD=5% and ISO criteria met 97% of time for measurements 24-48 hours post- sensor insertion, and 7% and 100%, respectively, for 48-77 hours).

Conclusion: The GlucoScout fulfilled ISO criteria 97% of the time and is a useful device for frequent blood glucose measurements in an inpatient setting. Accuracy did not vary substantially with reference glucose levels and sensor life; however there were a limited number of hypoglycemic reference glucose values.

870-P

Meta-Analysis of Individual Participant Data in Randomized Trials of Self-Monitoring of Blood Glucose in Non-Insulin Treated Type 2 Diabetes Patients

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Recent randomized controlled trials of self-monitoring of blood glucose (SMBG) for patients with non-insulin treated type 2 diabetes provide differing estimates of benefit. Individual trials were too small to examine differences based on clinical and demographic characteristics. We report an individual data meta-analysis testing the effectiveness of SMBG compared to control, and exploring effects in sub-groups.

Individual participant data was requested from the chief investigators of trials comparing a self-management intervention using SMBG with an intervention not using SMBG. Trials published since 2000, with >80 participants were included. Data included were the primary outcome of HbA1c, and age, sex, weight, duration of diabetes, and, where available, blood glucose, serum cholesterol, and blood pressure. An intention to treat analysis with complete cases used a random effects model, a sensitivity analyses used imputed data and pre-specified sub-group analyses carried out for age, sex, HbA1c at baseline, and duration of diabetes. Data are presented as means adjusted for age, sex and duration of diabetes, with 95% confidence intervals (CI) Six trials provided data on 2552 participants. A mean (CI) reduction in HbA1c of 0.25 (0.14 to 0.35)% (2.7 mmol/mol) was observed at six months for those using SMBG compared to those not using SMBG. A reduction in HbA1c between groups was also evident at 3 months (0.19 (0.08 to 0.29)%) and at 12 months (0.23 (0.09 to 0.38)%). The reduction in HbA1c was consistent across age, sex, HbA1c at baseline and duration of diabetes, although the numbers of older and younger patients, and those with a HbA1c >10% were insufficient for interpretation.

These findings confirm a small overall benefit from SMBG consistent across subgroups defined by a range of demographic and clinical characteristics. Evidence of potential for greater impact on important patient outcomes from innovative use of SMBG, and better targeting of those likely to find SMBG helpful, is required before initiating further trials.

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871-P

The Impact of NICE-SUGAR on ICU Glycemic Control: Evidence from the *Glucometrics* Website

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Epidemiological data and early clinical trials suggested a mortality benefit from attaining euglycemia in the intensive care unit (ICU). In 2009, however, the NICE SUGAR Study (NSS) showed no advantage from intensive vs. standard blood glucose (BG) control during critical care and raised the possibility of a mortality risk. Professional societies subsequently moderated their ICU BG target to 140-180mg/dL, a change that raised concerns about worsening BG control, such that unrestrained hyperglycemia would again become the norm in our ICUs.

Glucometrics (*GM*) is an open-access, university-based website. Participating hospitals upload aggregated, de-identified inpatient BG data into the *GM* database, which returns a report on the quality of BG control using uniform methodology. As its units of analysis, GM uses the patient (pt) BG sample, the 'pt-day', and the 'pt-stay.' *GM* provided us a unique opportunity to compare BG data submitted before vs. 3 months after publication of NSS.

Since initiation, 16.5 million BG data samples have been submitted from 132 hospitals. We focused on 2,104,213 samples from ICUs (668,176 pre-NSS from 21,675 pt-stays over 144,104 pt-days & 1,436,037 post-NSS from 46,032 pt-stays over 287,763 pt-days). Pre-NSS, the mean (±2SEM) and median of the pt-day-mean BGs were 158.2±0.31 & 144 mg/dL (IQR, 119-182), respectively; post-NSS, the corresponding values were 152.7±0.19 & 141 mg/dL (119-172) (P<0.001.) The Table shows pt-day BG ranges and the frequency of pt-days with hypoglycemic (hypo) and severely hyperglycemic (hyper) BGs.

mg/dL	**% Pt-Days with BG Ranges**		
	Pre-NSS	**Post-NSS**	**P-value**
70-109	15.4%	14.8%	<0.001
110-139	30.3%	34.0%	<0.001
140-179	28.0%	29.6%	<0.001
≥180	25.8%	21.3%	<0.001
	% Pt-Days with ≥1 Hypo or Severely Hyper BG		
<40	0.9%	0.7%	<0.001
<70	7.2%	5.9%	<0.001
≥300	10.4%	7.9%	<0.001

% Pt-Days with BG Ranges

Based on *GM* data, we find no evidence for deterioration in BG control in ICUs post-NSS. Indeed, a modest improvement is observed, with a greater % of values between 110-179, less <110 and >180, and less hypo and severely hyper excursions. *GM* may continue to serve as a benchmarking tool to assess trends in the quality of inpatient BG management.

872-P

Clinical Evaluation of a New System for Self-Monitoring of Blood Glucose

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The accuracy requirements for blood glucose monitoring systems (e.g., ISO 15197:2003) are expected to tighten. The new OneTouch® Verio™ Pro System features a novel electrochemical test strip and measurement algorithm designed to minimize the effect of common interfering substances and provide highly accurate plasma glucose values for patients with diabetes. A clinical study was performed to evaluate the product's accuracy in the hands of patients with diabetes. Subjects with diabetes (n=131, age 13 to 79 y) participated at 2 clinical sites. During the first site visit, subjects were

For author disclosure information, see page 785.

briefed by a healthcare professional on study procedures but received no training on the use of the new monitoring system. Over a 5-7 day period, subjects then completed orientation on the system at home. During the second and final site visit, subjects performed 2 self-tests using test strips from multiple lots, and technicians performed comparison testing using the YSI 2300 STAT Glucose Analyzer. The number and percentage of accurate results based on standard criteria (ISO 15197:2003) and a tighter product accuracy specification were calculated. As shown in the table, the tighter specification uses 80 mg/dL as the high/low glucose threshold because at this concentration, the accuracy limits of ±12 mg/dL and ±15% coincide with each other. Over 99 percent (99.6%, 270/271) of the lay user self-test results were within the ISO accuracy limits and 96.7% (262/271) were within the tighter limits. Error grid analysis gave 99.6% (270/271) results in zone A and 1 result in zone B. In this study, the new system demonstrated a high level of clinical accuracy and surpassed the standard ISO criteria as well as the tighter product accuracy specification.

ISO 15197:2003 Accuracy Criteria	Subject self-tests within ISO limits, number (%)
Minimum of 95% of results within ±15 mg/dL at glucose <75 mg/dL and within ±20% at glucose ≥75 mg/dL	270/271 (99.6%)
OneTouch® Verio™ Accuracy Specification	**Subject self-tests within specification, number (%)**
Minimum of 95% of results within ±12 mg/dL at glucose <80 mg/dL and within ±15% at glucose ≥80 mg/dL	262/271 (96.7%)

873-P

Effect of a Hybrid Closed-Loop (HCL) on Restoring Metabolic Control at the Onset of Diabetes

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Objective: As part of a NIH-funded TrialNet and DirecNet randomized controlled trial to assess the impact of tight metabolic control at diagnosis of type 1 diabetes (T1D) on islet recovery, we utilized the Medtronic MiniMed ePID system. This system combines an external subcutaneous pump and sensor with a proportional-integral-derivative (PID) algorithm utilizing insulin feedback to provide minute-to-minute insulin delivery based on sensor glucose levels.

Methods: Subjects were admitted within 1 week of diagnosis of T1D (median 6 days) for 3 to 4 days of Hybrid Closed-Loop (HCL) therapy which utilizes the ePID system and about 75% of the estimated insulin was given prior to an unrestricted meal. Reference blood glucose levels were measured every ½ hour. Upon discharge the subjects used a Minimed Sensor Augmented Pump.

Results: The system was utilized an average of 3 days for a total of 1,333 hours in 19 subjects ages 8-16 years. The mean (±SD) reference glucose was 139 (±9) mg/dl, and median insulin dose was 1.2 units/kg/day. The average carbohydrate intake was 7.9 gm/kg-d (range 4.7-13.0). There have been no severe hypoglycemic or hyperglycemic events. The average 24 hour daily sensor values and nighttime (midnight to 7am) sensor results for the days prior to HCL therapy, HCL, and the week following HCL are given in the table.

Conclusion: HCL therapy can rapidly and safely restore metabolic control following diagnosis of diabetes and the improved glycemia is sustained on discontinuation of HCL therapy.

Sensor Glucose Data	Pre-HCL (blinded)		During HCL (unblinded)		One Week post HCL (unblinded)	
	Daytime	Nighttime	Daytime	Nighttime	Daytime	Nighttime
Number of Subjects	10	13	19	19	18	18
Hours of Glucose Readings	35	14	51	21	102	41
Mean glucose (mg/dL)	217 ± 53	186 ± 55	147 ± 11	122 ± 11	124 ± 12	130 ± 21
% in range (71-180 mg/dL)	39%	45%	76%	93%	88%	86%
% ≤70 mg/dL	0.0%	4.3%	1.5%	1.5%	3.2%	2.8%
% ≤50 mg/dL	0.0%	0.2%	0.2%	0.0%	0.2%	0.5%
% > 180 mg/dL	61%	51%	22%	5%	8%	11%
% > 250 mg/dL	29%	20%	3%	0%	1%	1%

874-P

The Accuracy and Precision of the Axis-Shield Afinion HbA1c Measurement Device

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The Afinion HbA1c™ ("AF", Axis-Shield, Oslo, Norway) is a newer point of service device for measurement of HbA1c using a boronate affinity method unlike the DCA Vantage ™ ("DCA", Siemens Medical Solutions Diagnostics, Tarrytown, NY). The AF is faster (results in 3 min) and may be easier to use than the DCA, but its accuracy and precision have not been compared with the DCA in pediatric practice at multiple sites. Capillary blood was collected from 399 subjects with T1DM at 4 sites (age 3-49 yrs; mean HbA1c 8.3 ± 1.7%; 47% female; 70% white). Each sample was measured for HbA1c using both the AF and DCA and at the DCCT/EDIC Central Laboratory at the Univ. of Minnesota by HPLC. Six repeated measurements for each of six National Glycohemoglobin Standardization Program (NGSP) samples were also performed using the AF and DCA at each of 3 sites, and at the Central Laboratory (LAB).

The AF tended to read higher HbA1c results than the LAB, and the DCA tended to read lower, but their median absolute differences were similar (Table). AF had a slightly higher percentage of values within ±0.3% and ±0.5% of the LAB compared with DCA (p=0.02). Accuracy varied according to HbA1c. For AF, the mean difference from LAB was +0.24, +0.18, +0.06, +0.05 and +0.18 for LAB values <7.0%, 7.0-<8.0%, 8.0-<9.0%, 9.0-<10.0% and ≥10.0%, respectively. Corresponding means for DCA were -0.04, -0.13, -0.26, -0.35 and -0.35. Corresponding percents within ±0.3% of LAB in these subgroups were 76%, 76%, 78%, 72% and 58% for AF and 94%, 82%, 56%, 50% and 42% for DCA. The within-sample standard deviation for NGSP measurements was 0.18% for AF, 0.23% for DCA, and 0.06% for LAB.

In conclusion, the Afinion gives acceptable accuracy for measuring HbA1c and compares well with the DCA and LAB in patients with T1DM. Results varied across the HbA1c range, especially for the DCA which tended to read lower as HbA1c increased.

	AF vs Lab	DCA vs LAB
Mean difference (95% CI)	+0.15% (+0.12%, +0.18%)	-0.20% (-0.24%, -0.17%)
Median absolute diff (quartiles)	0.2% (0.1%, 0.4%)	0.2% (0.1%, 0.5%)
Within ±0.3%	73%	68%
Within ±0.5%	91%	81%
Regression Equation	AF = 0.99*LAB + 0.27	DCA = 0.94*LAB + 0.26
95% Limits of Agreement	(-0.4, +0.7)	(-0.9, +0.5)

875-P

Non-Invasive Measurement of Plasma Glucose from Exhaled Breath in Healthy and Type 1 Diabetic Mellitus Subjects

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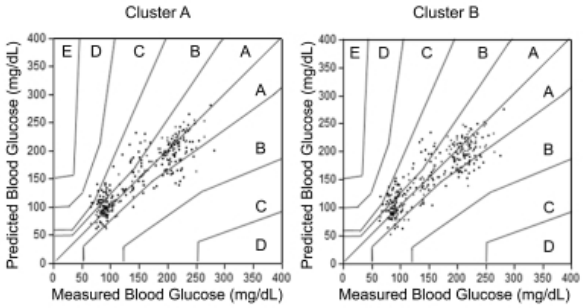
Current management of diabetes hinges on repeated blood glucose testing. Unfortunately, patient compliance is hampered by the discomfort of available methodologies, which often are painful and cause skin callusing. We propose breath analysis as an alternative non-invasive technique for glycemic testing, using integrated measurements of exhaled volatile organic compounds (VOCs). 8 type 1 diabetic (T1DM) (5F, 25.8±1.7 yrs) and 17 healthy (9F, 28.0±1.0 yrs) subjects underwent a total of 30 4hr studies, in which glycemic fluctuations were induced via i.v. dextrose/insulin infusion (1 hr baseline, 2 hr hyperglycemia-hyperinsulinemia, 1 hr euglycemia-hyperinsulinemia). Simultaneous breath, room air, and blood samples were collected at 12 time points. Concentrations of ~100 VOCs were determined by gas chromatography and matched with direct plasma glucose measurements. Multi-linear models to reconstruct plasma glucose concentrations for each subject were generated by least squares regression on several subsets of exhaled VOCs. Two groups of 4 gases (Cluster A: acetone, methyl nitrate, ethanol, ethyl benzene; Cluster B: 2-pentyl nitrate, propane, methanol, acetone) were used as covariates for our models, resulting in very strong correlations with direct measurements (0.883 and 0.869 respectively) across ~300 samples. Our study demonstrates that plasma glucose can indeed be accurately predicted via a non-invasive breath-based methodology over a broad range of clinically relevant experimental conditions in both healthy and T1DM subjects. While currently laborious and expensive, this technique can be developed into portable, affordable, and clinically applicable devices

that are likely to greatly facilitate diabetes screening, prevention, and everyday monitoring.



Parkes consensus error grid plot for T1DM: Plasma glucose predicted from Clusters A and B are plotted against direct measurements for 30 study visits (T1DM and healthy). Impact on clinical action is rated from A (no effect) to E (altered with potentially dangerous results). 286/290 and 293/295 predictions fell into Zone A-B using Clusters A and B, respectively.

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ADA-Funded Research

Guided Audio Tour: Glucose Monitoring and Sensing *(Posters 876-P to 881-P), see page 11.*

876-P

Provider Time Associated with Sensor-Augmented Insulin Pump Therapy in Type 1 Diabetes

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In a recent randomized trial, sensor-augmented pump therapy (SAPT) demonstrated a significant reduction in HbA1c in type 1 diabetes patients compared to multiple daily injections of insulin (MDI). It is important to evaluate provider time required to achieve clinical benefits of SAPT. We analyzed estimates of provider time prospectively reported throughout the 12-month study period.

Time estimates were reported for scheduled and unscheduled visits by type of activity and type of healthcare provider for all patients (7-70 years, n=485). For both scheduled and unscheduled visits, we compared mean time estimates between treatment groups during the pump initiation period (i.e. first 3 months) and after the pump initiation period (i.e. months 4-12) using Student's t-tests.

Across the 12-month period, providers spent approximately 8 more hours on diabetes-related activities for SAPT patients relative to MDI patients (15.6 vs. 7.9 hours, P<0.01). Providers spent more time on diabetes care for SAPT versus MDI during the pump initiation period, but time thereafter was generally similar between treatments (Tables 1 and 2). The majority of time in both groups was spent by certified diabetes educators (CDE).

Our findings suggest that an initial investment of provider time to initiate SAPT was associated with a significant reduction in HbA1c over one year.

Table 1.

By Activity	Pump Initiation: First 3 Months	4-12 Months
	SAPT vs. MDI (hours)	
Therapy Management	2.9 vs. 1.6#	1.9 vs. 1.7*
Device Related Issues	1.1 vs. 0.4#	0.4 vs. 0.3
Adverse Events	0.3 vs. 0.1#	0.3 vs. 0.2*
CareLink Review	2.5 vs. 1.0#	1.7 vs. 1.3#
Training	4.2 vs. 0.9#	0.4 vs. 0.4
Total	10.9 vs. 3.9#	4.8 vs. 4.0#

#P<0.01, *P<0.05

Table 2.

By Provider Type	Pump Initiation: First 3 Months	4-12 Months
	SAPT vs. MDI (hours)	
Physician	0.4 vs. 0.3*	0.5 vs. 0.4
CDE	6.6 vs. 2.1#	2.7 vs. 2.1#
Nurse Practitioner	1.6 vs. 0.6#	0.7 vs. 0.5
Registered Nurse	2.3 vs. 1.0#	0.8 vs. 0.9

#P<0.01, *P<0.05

877-P

Performance Evaluation of the Medtronic MiniMed Enlite Subcutaneous Glucose Sensor

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Increasing the frequency and sustainability of continuous glucose monitoring (CGM) use requires sensors that are accurate, durable, and comfortable. We report an interim analysis of data from 64 subjects who wore the Enlite subcutaneous sensor. The study, a prospective, single-sample, correlational design without controls, was conducted in adults with diabetes, 18-75 yr of age. The Enlite sensor features a small, short introducer needle with automatic retraction and a 90° insertion angle. Sensors were worn on the abdomen and buttock for two 6-day periods. Sensor values were recorded using a Guardian (abdomen) and a CGMS *I*Pro (buttock). All subjects participated in a single 10-hr session during which venous blood glucose was measured by a reference analyzer (YSI 2300 STAT Plus) every 15 min. YSI and sensor values collected during this session were compared for accuracy. Sensor values collected from the abdomen and buttock were compared for precision. After initial calibration, 219 of 254 (86.2%) sensors remained operational for the entire 6 days. Sensor performance exceeded the prespecified accuracy criteria over the entire 6 days of use (mean agreement rate within 20%: 79.2%). More than 96% of paired YSI-sensor values were in Clarke Error Grid zones A and B. The total mean (±SD) absolute relative difference (ARD) was 14.1±13.5%, the median ARD was 10.3%, and the per-day mean ARD ranged from 10.6±8.8% (day 3) to 18.5±18.8% (day 1). Highest accuracy was obtained for glucose values in the >120-240 mg/dl range (Table). Over 79% of values from the buttock site were within 20% of paired values from the abdomen site. No serious safety issues were reported. Performance attributes of the Enlite sensor should facilitate its use in diabetes management. Sensors may be placed on the buttock with no loss of accuracy compared to those placed on the abdomen.

Table: ARD by YSI Reference Values, Combined Abdomen and Buttock Insertion Sites

Glucose (mg/dl)	Any	40-80	>80-120	>120-240	>240-400
Paired Values (N)	3901	410	893	1944	654
Mean (Median) ARD	14.1 (10.3)	14.7 (12.7)*	14.6 (11.1)**	12.0 (8.8)**	14.0 (10.7)**

*absolute values in mg/dl
**absolute relative values in %

878-P

Prototype 4th Generation of Dexcom Continuous Glucose Monitoring System with Improved Home Alert Rates

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This study evaluated the safety and performance of the prototype 4th generation Dexcom real-time CGM system. The study enrolled 60 adult subjects (>18 yrs) at 4 US centers; 56 (93%) of the subjects had T1DM and 4 (7%) had insulin-requiring T2DM. Subjects inserted and wore either 1 or 2 sensors for 7 days. A subgroup (n=30) wore 2 sensors to evaluate system precision. Subjects participated in one 8-hour in-clinic session with blood draws every 15 minutes on study day 1, 4, or 7 to collect YSI and SMBG reference glucose measurements. For the remainder of the week, CGM was used as an adjunct to SMBG. Subjects were instructed to confirm hypoglycemic and hyperglycemic episodes identified by CGM with their SMBG meter.

There were no serious adverse events, sensor fractures, or infection complications experienced by the study population. Subject characteristics (age, duration of diabetes, BMI) did not have significant impacts on the CGM System performance. Subject age range from 18 to 69 yrs old; their duration of diabetes range from 1 to 47 yrs; and the BMI of these subjects range from 18.2 to 43.8 and represented a random sample for the intended use population. The overall mean and median of Absolute Relative Difference (ARD) vs. YSI was 15.0% and 11.2%, respectively. Precision ARD was 11.7% ± 7.6% (mean ± SD). 92% of the sensors lasted the full 7 days. The overall system bias from reference YSI glucose was less than 10 mg/dL based on the regression analysis. The hypoglycemic and hyperglycemic alert rates were improved compared to the previous generation of CGM Systems. Furthermore, true alert/alarm rates during home use showed improvements (Table 1).

For author disclosure information, see page 785.

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This study is the first to evaluate the prototype 4th generation Dexcom CGM System. The performance compares positively to the CGM Systems in the market in terms of accuracy, precision, alert rates, and sensor life. The newly designed CGM System improves safety and performance.

Table 1. Home Use Alert/Alarm Rates

Alert /Alarm	Total	True Alerts / Alarms		False Alerts / Alarms	
	n	n	%	n	%
High Alert (200 mg/dL)	471	433	91.93	38	8.07
Low Alert (80 mg/dL)	285	231	81.05	54	18.95
Low Alarm (55 mg/dL)	69	51	73.91	18	26.09

879-P

Glycemic Variability and Clinical Outcomes in General Surgery Patients Treated with Basal Bolus and Sliding Scale (SSI) Insulin

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Glycemic variability (GV) is an independent predictor of mortality in critically ill patients. In patients admitted to general medicine and surgery services, however, the impact of GV on clinical outcome is not known. Accordingly, this analysis was performed to determine the significance of GV in predicting hospital complications in a prospective randomized trial of insulin treatment (Rabbit Surgery) in general non-cardiac surgery patients at Emory University Hospital. GV was calculated from all hospital BG values including pre-meal and bedtime measurements using mean standard deviation (SD). A total of 211 patients (age: 58±11 yr, admission BG: 190±92 mg/dl, A1C: 7.72±2.2%, ±SD) with a BG between 140-400 mg/dl and T2DM >3 months were randomized to glargine + glulisine (n=104) or SSI (n=107). The mean daily BG level after the 1st day of basal bolus and SSI was 145±32 mg/dl and 172±47 mg/dl, respectively, p<0.01. There were no differences in mortality (1% vs. 1%); but, basal bolus significant reduced the frequency of a composite of post-op complications including wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia (24.3% vs. 8.6%); p=0.003. The mean post-op GV by SD was 34.6±22 mg/dl. GV was positively associated with mean post-op BG (p<0.01), and with the ability to achieve the post-op target BG of 80-140 mg/dl (p<0.01). However, in multivariate analysis adjusted for age, gender, history of DM, severity of surgery and hypoglycemia and mean BG, GV was found not to be associated with mortality or with hospital complications (p= NS).

In summary, in this prospective randomized clinical trial in patients with T2DM undergoing general surgery, glycemic variability was not found to be associated with increased risk of post-operative mortality or hospital complications. Analyses of large prospective and randomized control trials are needed in order to determine the impact of glycemic variability in predicting clinical outcome and optimizing glycemic control in noncritically ill patients in general surgery setting.

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880-P

Improvements in Accuracy in the Hypoglycemic Range across Sequential Generations of Continuous Glucose Monitors (CGM)

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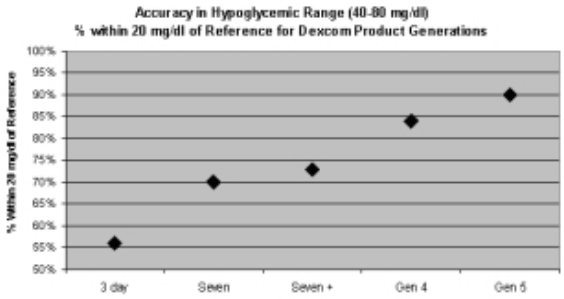
Hypoglycemia requiring emergency medical assistance is common in insulin-treated patients and has significant human and economic sequelae. Real-time CGM is rapidly becoming a standard of care for helping patients control their diabetes and has the potential to decrease hypoglycemia by alerting patients to impending or actual hypoglycemia. Accurate performance in the hypoglycemic range is essential to provide reliable alerts. Further improvements in accuracy and reliability of CGM technology should improve patient confidence, utilization, safety, and outcomes.

The graph below displays the improvements in hypoglycemia performance across sequential generations of Dexcom sensors. The SEVEN PLUS, Dexcom's currently marketed CGM system, includes its third generation system. Clinical studies have demonstrated that 73% (n=277) of results are within 20mg/dl in the hypoglycemic range of 40-80 mg/dl. A prototype 4th generation CGM system (Gen 4), with a newly designed membrane and improved algorithms, has demonstrated improvements in performance with 84% (n=653) within 20mg/dl in the hypoglycemic region. Finally, a prototype 5th generation CGM system (Gen 5) has demonstrated 90% (n=194) within 20mg/dl in the hypoglycemic region. The Gen 5 sensor has additional improvements in sensor technology.

Because of rapid improvements in CGM performance, recent clinical outcome studies have utilized older generation sensors with less hypoglycemic accuracy. As sensor performance improves, outcomes in CGM using patients should be substantially better than what has been demonstrated in past clinical trials and is currently reported. Further, continued improvements in reliability and accuracy may support non-adjunctive use of CGM and better meet the needs of a fully closed loop artificial pancreas.



881-P

Use of Structured SMBG Helps Reduce A1c Levels in Insulin-Treated Diabetic Patients

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In Japan, all insulin-treated diabetic patients are encouraged to perform self-monitoring of blood glucose (SMBG), which is fully reimbursed. Although most patients perform SMBG frequently, A1c levels have not improved. We assessed the impact of structured SMBG on A1c levels in insulin-treated diabetic patients. In this 6-month, prospective study, we randomized 86 insulin-treated patients (4 type 1 diabetes, 82 type 2 diabetes) to routine SMBG (Group A, n=41) and structured SMBG (Group B, n=42), using the Accu-Chek®360° View Blood Glucose Analysis System (tool), a paper tool that collects 7-point glucose profiles (before and after meals, and at bedtime) over three consecutive days. Group A patients continued their usual SMBG method; Group B patients continued their usual SMBG method and completed the tool monthly over the 6-month period. Patients were seen monthly and therapy was adjusted based on available SMBG data. A1c values were measured at baseline and 3 / 6 months (NGSP equivalent). Values were compared by 2 sample T test with equal variances. Patients were 60.0 (12.3) years old, had a BMI of 26.6 (4.6)kg/m^2, and had had diabetes for 14.8 (8.1) years, mean(SD). On average, patients had been practicing SMBG for 6.4 (3.4) years. A total of 83 patients completed the study; 41 in Group A, 42 in Group B. At 6 months, there was significantly ($p < 0.007$) greater improvement in A1c levels in Group B compared to Group A.

Group	Baseline A1c	3 Months A1c	6 Months A1c
Group A (n=41)	7.9 (0.5)	7.7 (0.7)	7.8 (0.7)
Group B (n=42)	7.9 (0.5)	7.5 (0.6)	7.4 (0.7)
P value	<0.808	<0.138	<0.007*

Of the Group B patients who completed the study, a subgroup of 28 patients (67%) completed more than 80% of the tool each month. In this highly compliant group, there was an even greater improvement in A1c than Group A [7.3 (0.6) vs 7.8 (0.7), p< 0.001]. Use of structured testing via the Accu-Chek ®360°View system can facilitate improved glycemic control in insulin-treated diabetic patients.

882-P

Accuracy and Precision of Glucose Monitoring Are Relevant to Treatment Decision Making and Clinical Outcome in Hospitalized Patients with Diabetes

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We evaluated the accuracy and precision of three blood glucose meters (BGMs) frequently used in hospital setting: Accu-Chek Aviva (Roche Diagnostics), Precision-Xceed (Abbott Diagnostics), and Glucocard X-Sensor (Menarini Diagnostics) in 600 hospitalized patients with type 1 (n=200) or type 2 (n=400) diabetes. Plasma glucose was measured using the WHO Glucose-Oxidase method. We focused to whether improvement in the accuracy of BGMs would improve clinical outcomes.

Median plasma glucose values [141.2mg/dL (13-553)] were significantly different from that produced by the BGMs (P<0.001). Bland-Altman analysis indicated that Accu-Chek Aviva and Precision-Xceed underestimated hypoglycemia (plasma glucose ≤55mg/dL) by a 0.8 and a 0.9 bias respectively, while Glucocard X-Sensor by a 1.0 bias. Hyperglycemia (plasma glucose ≥250mg/dL) was overestimated with Accu-Chek Aviva and Precision-Xceed by a -0.9 bias and with the Glucocard X-Sensor by a -1.0 bias. Asymptomatic hypoglycemia was detected in 28% of type 1 and in 18% of type 2 diabetes patients. In all cases, the BGMs were unreliable in sensing hypoglycemia and none met ADA's accuracy goals. Linear regression analysis demonstrated that low blood pressure and hematocrit significantly affected glucose measurements obtained with the BGMs (P<0.05).

In hospitalized diabetes patients, BGMs failed to sense hypoglycemia and over-sensed hyperglycemia to some extend. Patients and caregivers should be aware of these restrictions of the BGMs.

883-P

Accuracy of the CONTOUR® Link Blood Glucose Monitoring System

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The CONTOUR® Link blood glucose monitoring system (BGMS) wirelessly transmits blood glucose test results to MiniMed Paradigm™ insulin pumps and the Guardian™ REAL-TIME continuous glucose monitoring (CGM) system. The CONTOUR® Link BGMS is currently cleared for use outside the US. Accuracy of the CONTOUR® Link BGMS was assessed according to ISO 15197:2003 guidelines and more stringent criteria. Fingertip capillary blood from 100 subjects was tested with the CONTOUR® Link BGMS and an YSI analyzer (lab reference). Each sample was tested with 2 reagent lots, n = 2 per lot, total of 400 readings. More stringent accuracy criteria were evaluated by calculating percentage of meter results within ±15 mg/dL (±0.83 mmol/L) of YSI results for glucose <100 mg/dL (<5.6 mmol/L) and within ±15% for glucose ≥100 mg/dL (≥5.6 mmol/L). The CONTOUR® Link BGMS exceeded ISO 15197:2003 accuracy criteria, with 98.5% of results falling within ±15 mg/dL (±0.83 mmol/L) or ±20% of the reference method (Table 1).

#of samples within criteria	**% readings within 20% or ±15 mg/dL (±0.83 mmol/L)**
394/400	98.5
Glucose concentration (n)	**% readings within specified error limits (n)**
	±20%
[3]75 mg/dL (324)	98.5 (319/324)
	±15 mg/dL
<75 mg/dL (76)	98.7(75/76)

Additionally, 96.8% of results were accurate according to the more stringent criteria (Table 2).

# of samples within criteria	**% readings within 15% or ±15 mg/dL (±0.83 mmol/L)**
387/400	96.8
Glucose concentration (n)	**% readings within specified error limits (n)**
	±15%
[3]100 mg/dL (304)	96.1 (292/304)
	±15 mg/dL
<100 mg/dL (96)	99.0 (95/96)

The Parkes-Consensus Error Grid analysis showed 99.8% (399/400) of results in Zone A, 0.3% (1/400) in Zone B. No results were outside Zones A and B, indicating that deviations of meter readings from reference values had no or minimal effect on clinical action.

In summary, the performance of the CONTOUR® Link BGMS exceeds ISO 15197:2003 accuracy standards as well as those based on more stringent accuracy criteria.

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884-P

Analysis of a Hypoglycemia Prediction Algorithm on an Extensive Library of Ambulatory Data

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The artificial pancreas includes a variety of components: pump, sensor, controller and a safety system. An important element in this safety system is a hypoglycemia predictor. An algorithm was designed to predict hypoglycemia using clinical parameters. Because the continuous glucose monitor (CGM) input is often erroneous, assessment of the signal is performed with clinical constraints to maximize the usefulness of the CGM data. Clinical parameters include limiting the operational range of the algorithm to low CGM values and restricting the rate of change to physiologically possible values. In addition, there is a tunable requirement for successive alarms to trigger a true alarm. The prediction is projected in the future through an adjustable threshold for a variety of prediction horizons (PH).

Ambulatory data were evaluated using the algorithm. These data were extensive, over 750 patient days from 70 subjects, all patients of the Sansum Diabetes Research Institute with a Dexcom 7® sensor. The hypoglycemia period included the hour prior to, and the duration of, CGM values below the threshold. The remainder was considered the non-hypoglycemia period (NHP). The alarms were analyzed for the following metrics: true and false positive alarm ratios (TPR and FPR), and distribution of warning times. The TPR is the number of alarmed events within one hour prior to the event divided by the number of events. The ratio of FPR is the duration of alarms in the NHP divided by the duration of the NHP. The warning times were determined by the time between the initial alarm and the start of an event. Results are shown in Table 1.

Table 1: Results from four algorithm parameter settings (PH, # of Alarms).

	15 min, 1	60 min, 1	15 min, 2	60 min, 2
TPR (%)	86	91	47	69
FPR (%)	1.6	5.3	0.3	1.6
Warning Time>15 min (%)	64	85	29	74
Warning Time>45 min (%)	16	40	5	20

This data set provided a useful platform to evaluate algorithm parameter settings. Increasing the PH or reducing the number of required alarms provides a tradeoff in improving the TPR and worsening the FPR. These results demonstrate that the proposed metrics and algorithm parameters can be effectively used to compare hypoglycemia algorithms.

885-P

Assessing a Predictive Modeling Technique for Proactive Patient Management of Diabetes

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Patients with type 1 diabetes mellitus (T1DM) may achieve better glucose control when they adjust their insulin based on predicted blood glucose rather than reacting to current glucose levels. Our objective is to develop and assess a computerized model for predicting blood or interstitial glucose in T1DM patients on the insulin pump and continuous glucose sensor.

The approach drew on previous work from the organizational field of knowledge management and extended that work to provide inputs for a patient-oriented inference model. The inputs were used to drive an "Adaptive Neural Fuzzy Inference System" (ANFIS) where the artificial neural network evaluates the inputs, creates rules, and outputs a predicted glucose concentration. The inputs into the model are time of day, mealtime glucose concentration, carbohydrate intake, and insulin intake. The output is the predicted glucose at 5 minute intervals for a 120 minute period following a meal. Data sets from 2 patients over 8 weeks were used to prototype, train, and assess the model. The model was built using the grid partitioning method which produced 125 inference rules.

The ANFIS learned as patient data were input and the actual output (blue line) vs. predicted graph (red line) became more correlated over a two hour period (Figure 1). The average error of prediction was 31 mg/dl at 30 minutes, 57 mg/dl at 1 hour, and 103 mg/dl at 2 hours. Predictability at 2 hours is less accurate than at 30 minutes because of variability in activity and insulin kinetics. We propose that a rolling prediction model used every 30 minutes will improve the accuracy of the prediction. The utility of this model would be to develop a chip which could be embedded in the pump or sensor to learn from patient data and inform behavior.

For author disclosure information, see page 785.

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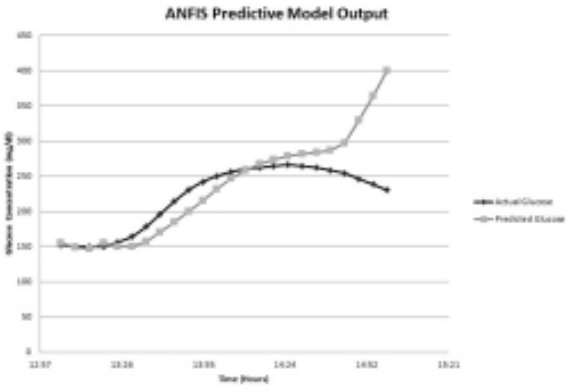
Figure 1: ANFIS Predictive Model Output



Supported by: Walden University

886-P

Association of Frequency of Self-Monitoring of Blood Glucose (SMBG) and HbA1c in the Clinical Practice

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Home glucose monitoring is an important aspect of blood sugar management in individuals with diabetes. The goal of this study was to determine the relationship between the frequency of home glucose monitoring and HbA1c in people with type 1 and type 2 diabetes.

A total of 1076 individuals participated in the study including 668 males and 408 females. There were 325 people with type 1 diabetes, 283 people with type 2 diabetes not treated with insulin and 468 people with type 2 diabetes who were treated with insulin. The average age of participants was 56.7. Individuals were assigned to groups based on the number of home glucose checks performed each day. Average HbA1c values were compared between groups. A one-way ANOVA analysis followed by the Bonferroni method was completed to determine if the number of home glucose checks performed each day had an effect on HbA1c.

Individuals with type 1 diabetes had average HbA1c values of 8.65% for fewer than 2 checks/day, 8.58% for 2 to 3 checks/day and 8.22% for more than 3 checks/day. These values were not significantly different. The average HbA1c values for people with non-insulin using type 2 diabetes were 7.82% for 0 checks/day, 7.37% for 0 to 1 check/day and 7.38% for more than 1 check/day. HbA1c was found to be significantly different between the group who performed 0 checks/day and the group who performed between 0 and 1 check/day (p=0.036). HbA1c was not significantly changed when more than 1 home glucose check was performed. Individuals with insulin treated type 2 diabetes had HbA1c values of 9.26% for less than 1 check/day, 8.65% for 1 to 2 checks/day and 8.43% for more than 2 checks/day.

Performing less than 1 home glucose check/day resulted in a significantly higher HbA1c compared to those who performed 1 to 2 or more than 2 checks/day (p<0.001).

The frequency of home glucose monitoring was shown to have an influence on HbA1c in people with type 2 diabetes. An increased frequency of home glucose checks can improve blood sugar management.

887-P

Blood Glucose Trends & Prediction of Severe Hypoglycemia in Hospitalized Patients

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Studies have shown an association between inpatient hypoglycemia (hypo) and mortality. Several clinical factors predict inpatient hypo (illness severity, changes in nutrition, and type of anti-hyperglycemic therapy [AHT]), but hospital BG management, and specifically the value of point-of-care (POC) BG monitoring in the prediction of severe hypo, has not been investigated. Nonetheless, in their inpatient hyperglycemia consensus statement, AACE/ADA advised a reassessment of AHT once BG falls <100 mg/dl.

We examined POC BG levels in all diabetic (DM) pts hospitalized on general wards at our hospital during 1 year. Of 480 pts with at least 1 BG <50 mg/dl ('severe hypo'), we identified 365 on SQ insulin or sulfonylurea whose event occurred ≥48 hrs from admission and who had ≥2 BG values recorded during this time. All BGs 48-hrs prior to the hypo event (mean 8.2), were catalogued into five low-normal to mild-moderately low ('mild hypo') glycemic windows: <60, 60-69, 70-79, 80-89, 90-99 mg/dl. Similarly, a randomly selected 48-hr period of BGs (mean 6.5) from DM pts admitted during the same year without severe hypo (n=2387) was sorted into the same ranges. Chi-square tests were used to compare the %BGs catalogued and the proportion of pts with BG<100 between the 2 groups.

The frequency of antecedent mild hypo was nearly 2-fold higher in pts with severe hypo compared to randomly selected 48-hr periods in pts without severe hypo (21.7% vs 11.3%; p<0.0001), becoming increasingly disparate with BG values <90mg/dl (table 1). In addition, a greater proportion of pts with severe hypo (61.1%) had BG <100 in the 48-hrs preceding their hypo event compared to those without (37.6%; p<0.0001). We conclude that inpatients with severe hypo frequently have mild hypo in the 48 hours preceding the event. Accordingly, a BG value <100mg/dl may serve as an important clue to consider adjustment of AHT, supporting recent AACE/ADA recommendations.

	BGs* over 48-h (mg/dl)					
	>100	**90-99**	**80-89**	**70-79**	**60-69**	**<60**
Severe Hypo (2970 BGs)	78.3%	5.6%	5.0%	4.7%	3.2%	3.3%
No Severe Hypo (15,576 BGs)	88.7%	5.7%	2.8%	1.5%	1.0%	0.3%

*antecedent in pts with severe hypo; random in pts with no severe hypo

888-P

Calibration of a Continuous Glucose Monitor (CGM): Effect of Glucose Rate-of-Change

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CGMs sample from interstitial fluid, but are calibrated with blood glucose. During glycemic fluctuations, glucose concentrations in the blood and interstitial fluid are not in equilibrium and as a result, some CGM devices suggest or require calibration when glucose levels are stable. In a home use setting, this limitation can impact patient compliance and CGM usage. This analysis shows the effect of rate-of-change at calibration on CGM accuracy, based on clinical trial data of a Dexcom prototype 4th generation system.

CGM data were collected at 7 US centers from 60 adult subjects (75% Type 1) and 72 pediatric subjects (6 – 18 years), all insulin using. The data was generated from 308 sensors. Each sensor was worn for up to 7 days; calibrated twice per day with fingerstick blood glucose (SMBG); and an additional 6-8 SMBG values per day were collected for accuracy comparison. At each calibration, glucose rate-of-change was estimated using the previous 20 minutes of CGM trend data (provided the data did not exceed the CGM's criteria for noise). The paired CGM-SMBG values collected after that calibration and until the next calibration were placed into a corresponding absolute rate-of-change bin: 0 to 1, 1 to 2 and > 2 mg/dL/min. For each bin, accuracy vs. SMBG was evaluated in terms of Absolute Relative Difference (ARD) and percentage of points within 20 mg/dL (when SMBG <= 80 mg/dL) or 20% (when SMBG > 80 mg/dL). Kruskal-Wallis statistical test was performed on ARD between groups.

Accuracy, across the different rates of change at the time of calibration, is as tabulated below.

Kruskal-Wallis test of ARDs between the three groups yielded a p = 0.2. When calibrated at different rates of change, the accuracy of the Dexcom prototype 4th generation system is not significantly impacted.

Absolute Rate-of-change at Calibration (mg/dL/min)	≤ 1	> 1 & ≤ 2	> 2
Mean ARD	15.7	15.4	17.7
Median ARD	11.5	11.3	12.7
%within 20/20	76.5	77.6	70.0
No. Sensor-SMBG Values	7108	1773	716
No. Calibrations	2687 (72.3%)	725 (19.5%)	303 (8.2%)

889-P

Clinical Evaluation of a New Technology for Blood Glucose Monitoring: Accuracy at Hypoglycemic Glucose Levels

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Monitoring for hypoglycemia is an essential component of home glucose testing; however, most of the data found in published accuracy evaluations fall in the normoglycemic or hyperglycemic ranges. We studied the accuracy of a new monitoring technology (OneTouch® Verio™ Test Strips) at hypoglycemic glucose levels (<70 mg/dL) using data collected in four studies conducted at

two clinical sites. In each study, testing was performed by clinic staff using fingertip blood samples from patients with diabetes. The study population included 414 subjects, and testing was conducted using nine different lots of test strips. With each subject, duplicate tests with each test strip lot were performed with the monitoring system using blood from a single fingertip lancing. The blood glucose concentrations of samples were targeted to achieve the distribution specified in standard testing guidelines (ISO 15197:2003 standard). Plasma glucose reference values were obtained before and after testing with the monitoring system using the YSI 2300 STAT PLUS system. The number and percentage of results within ±15 and ±10 mg/dL were calculated at glucose levels <70 mg/dL and <60 mg/dL. In total, 366 blood glucose results were evaluated at concentrations <70 mg/dL (range 32 – 69 mg/dL). In this glucose range, 366/366 (100%) of meter results were within ±15 mg/dL and 364/366 (99.5%) were within ±10 mg/dL of YSI reference values. At glucose concentrations <60 mg/dL, 174/174 (100%) of the meter results were within ±15 mg/dL and 174/174 (100%) were within ±10 mg/dL of reference values. Reliable detection of hypoglycemia requires accurate monitoring. In this preliminary evaluation, the data from 4 clinical studies suggest that the new monitoring technology is capable of providing highly accurate results at hypoglycemic glucose levels. Further studies will be needed to confirm the long-term performance of the system.

890-P

Clinical Validation of Soluble Insulin Receptor as a Novel Marker for Glycemic Control in Patients with Type 2 Diabetes

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The soluble insulin receptor (sIR) can be detected in human plasma and may be generated through ectodomain shedding, by undetermined sheddase(s) for insulin receptor. However, biological function and clinical significance of sIR are not fully identified. To elucidate the clinical significance of sIR, the relationships between concentrations of sIR and various clinical markers, including blood glucose (BG), HbA1c (A1C) and blood pressure (BP), were cross-sectionally investigated in 50 subjects with neither hypertension nor diabetes (non-HT/DM), 50 non-diabetic patients with hypertension (HT) and 130 patients with type 2 diabetes (T2DM)(80 had hypertension while 50 did not). In addition, sIR was investigated before and after glycemic control in T2DM. Concentrations of sIR (means ± SD; ng/mL) were 1.22±0.25, 1.17±0.26, and 2.16±0.74 in non-HT/DM, HT and T2DM, respectively. The sIR level in T2DM was significantly higher ($p<.001$) than those in both non-HT/DM and HT. No difference was observed between sIR levels in non-HT/DM and HT, and between those in T2DM without and with HT (2.18±0.72 and 2.15±0.76, respectively). Plasma sIR correlated strongly with A1C ($r=.724$, $p<.001$), fasting BG ($r=.701$, $p<.001$) and post-prandial BG ($r=.783$, $p<.001$), and moderately with white blood cell count (WBC) ($r=.330$, $p<.001$), plasma triglyceride ($r=.288$, $p<.001$), total cholesterol ($r=.227$, $p<.001$) levels, and weakly with systolic and diastolic BP ($r=.149$, $p<.03$ and $r=.153$, $p<.03$, respectively), but neither with age, sex, body mass index, duration of diabetes nor the presence of complications. Multiple regression analysis showed that sIR was independently predicted by A1C ($\beta=.620$, $p<.000$), systolic BP ($\beta=.153$, $p=.018$) and WBC ($\beta=.156$, $p=.020$), which explained 49.9% of the variability of sIR ($F=42.2$, $p<.001$), suggesting a strong contribution of A1C to sIR. Furthermore, improvement of glycemic control in T2DM caused significant reductions of both sIR and BG levels ($p<.001$ in both) within one week. In conclusion, these results indicate that sIR could be used as a measure of short-term glycemic control. The relationship between BP and sIR should be investigated in larger scale.

891-P

Comparison of the Simultaneous Use of Two Multisensors for Non-Invasive Continuous Glucose Monitoring

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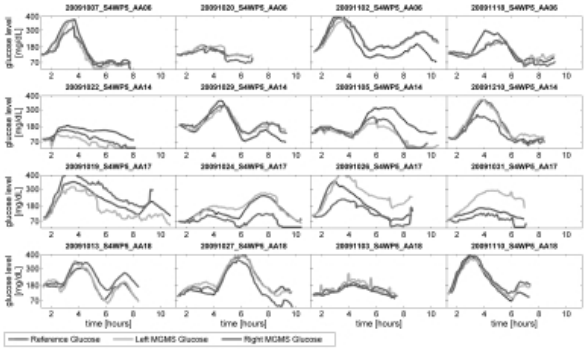
The Multisensor measures skin impedance and optical skin characteristics in several frequency bands of the electromagnetic spectrum. In this study a Multisensor version with fully integrated sensors and battery was experimentally tested, investigating location related measurement characteristics.

Four T1DM patients (age 43±9 y; BMI 24.5±3.7 kg/m^2, duration of diabetes 22±11 y; HbA1c 7.7±0.5%) performed 4 in-clinic study days with a Multisensor attached to the left and right upper arm, leading to 32 datasets from 16 study days. The Multisensors were exchanged between the patients and the left and right arm. Glycaemia was varied using 4 different glucose profiles. Different data evaluation routines were applied to the Multisensor data in order to obtain global (identical coefficients) and personal (personal coefficients) models that were used for cross validation.

Figure 1 shows all 32 glucose profiles obtained during the 16 study days, using the global model with a prospective initial baseline calibration (CEG A 44.9, B 48.0, C 3.6, D 3.0, E 0.5%). The following performance metrics was obtained from the different models. In each model an initial baseline calibration was used at the beginning of each study day (IB) as well as a full day baseline calibration (FB), with Average R2, MAD [mg/dL], MARD [%]. Global IB: 0.76, 47, 32.3; Global FB: 0.75, 29.9, 21.3; Personal IB: 0.85, 43.3, 30.7; Personal FB: 0.84, 24.1, 17.6.

The glucose time courses estimated by the Multisensors from the two arms are repeatably comparable, even with a global model with one initial baseline calibration only. This indicates that the sensor signal characteristics are robust enough to allow changing from one arm to the other using the same device settings and calibration.



892-P

Continuous Glucose Error Grid Analysis (CG-EGA) of the Prototype 4th Generation Dexcom Continuous Glucose Monitoring System and Frequently Sampled Self Monitoring Blood Glucose (SMBG) Data Compare Favorably to a Laboratory Standard

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The clinical performance of the prototype 4th generation Dexcom CGM system and One Touch Ultra2 SMBG meter were compared to the laboratory standard Yellow Spring Instrument (YSI). Subjects participated in an 8-hour in-clinic session with blood draws and fingersticks every 15 minutes on study day 1, 4, or 7 to collect YSI and SMBG glucose measurements.

60 adult subjects (>18 yrs) at 4 US centers were enrolled; 56 (93%) of the subjects had T1DM and 4 (7%) had insulin-requiring T2DM. Subjects inserted and wore either 1 or 2 sensors for 7 days. 30 subjects wore 2 sensors to evaluate system precision. A total of 2354 CGM and YSI matched data were collected from 58 subjects; and a total of 2110 SMBG and YSI matched pair data were collected from 56 subjects during the 8 hours in-clinic session. The correlation of coefficient between CGM-YSI matched pair and SMBG-YSI matched pair is 0.962 (95% CIs: 0.958-0.964), 0.985 (95% CIs: 0.984-0.986). Continuous Glucose Error Grid Analysis, accounted for the system accuracy during glucose rate of change, the combined point and rate error grid zone of CGM-YSI and SMBG-YSI are summarized in Table 1. With reference to YSI, SMBG is more accurate in the hypoglycemia region (96.6% vs. 73.8%), CGM is more accurate in the hyperglycemia region (96.6% vs. 84.8%); and CGM and SMBG performed similarly in the euglycemia region.

This study demonstrates improved CGM system performance with reference to the laboratory standard; it compares favorably to subject-performed frequently-sampled SMBG in the euglycemia and hyperglycemia regions. Compared to prior generations of CGM, the non-adjunctive clinical use of CGM appears more feasible.

Table 1. CG-EGA Comparison between CGM-YSI and SMBG-YSI

Combined point and rate error grid zone	Hypoglycemia BG <= 70 mg/dl		Euglycemia 70 < BG <= 180 mg/dl		Hyperglycemia BG > 180 mg/dl	
	CGM-YSI	SMBG-YSI	CGM-YSI	SMBG-YSI	CGM-YSI	SMBG-YSI
Accurate Readings	73.8%	96.6%	98.7%	98.6%	96.6%	84.8%
Benign Errors	0.0%	0.0%	1.1%	1.1%	2.1%	9.9%
Erroneous Readings	26.2%	3.4%	0.2%	0.4%	1.4%	5.3%

For author disclosure information, see page 785.

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893-P

Cross-Sectional Survey of Patient Perspectives on Continuous Glucose Monitoring

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Continuous glucose monitoring (CGM) systems have been linked to improved glycemic control and quality of life. Yet for uncertain reasons, many patients discontinue using CGM. To investigate why, we surveyed subscribers to a diabetes patient newsletter in March 2010. From the 2,025 respondents (response rate=47%), we studied the population who self-identified as users or ex-users of current or near-current personal CGM systems. 306 were current users (C; 90% type 1, median age 35-44, 57% female), and 83 were ex-users (X; 92% type 1 diabetes, median age 35-44, 60% female; 67% quit in 2009). Ex-users were more likely to be on Medicaid (6% X; 0% C; p=0.002), to have a household income under $15,000 (8% X; 3% C; p=0.03), and to be age 18-24 (10% X; 3% C; p=0.009). No other significant differences in baseline demographics, A1c, household income, or type of diabetes were noted. Ex-users were asked whether certain factors were reasons to quit CGM; their responses are below.

Reasons for Quitting	Percentage Who Checked
System was not accurate	48
Wearing sensor uncomfortable	43
System difficult to use	31
Self-paying, not worth cost	24
No significant improvement in overall diabetes management	24
New insurance does not fund	16
A1c did not improve	14
No longer need CGM to dose insulin	10
Other	24

87% of ex-users reported they would reconsider CGM and wrote in reasons why they might; the most commonly mentioned was improved accuracy (35%).

These self-reported, cross-sectional data come from subjects who show active interest in diabetes by subscribing to a patient newsletter and thus may not reflect the general population; however, the data suggest that current sensors are not accurate enough to satisfy many patients. They indicate that comfort is also a key area of improvement for next-generation products. Surprisingly, financial considerations were a comparatively minor concern. Given CGM's accepted efficacy, analyzing self-reported concerns may be an important method for improving uptake and adherence.

894-P

Detection of Autonomic Nervous System Response in T1DM Patients with Impaired Awareness of Hypoglycemia Using the HypoMon

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Nocturnal hypoglycemia is a feared complication experienced by people with Type 1 diabetes mellitus (T1DM). Its onset is associated with the activation of the autonomic nervous system (ANS), characterised by symptoms such as sweating, tremor and palpitations. A proportion of patients develop 'impaired awareness' and have difficulties recognizing symptoms due to reduced counterregulatory hormone responses. Detection of hypoglycaemia in such patients is paramount because they are at higher risk of severe hypoglycaemia.

The HypoMon® (AIMEDICS P/L) is a real-time physiologically-based alarm for nocturnal hypoglycaemia, utilising multivariate data transforms to detect sub-clinical ANS response. The HypoMon has been validated on over 300 T1DM patients between 10-25 years old, with reference venous blood glucose levels measured using Yellow Springs Instrument (YSI). These studies include a cohort of patients with impaired awareness and normal awareness of hypoglycemia.

The efficacy of the HypoMon in detection of hypoglycemia between the impaired awareness group to that of normal awareness group is compared. The performance is based on two clinical studies where participants were monitored for natural episodes of nocturnal hypoglycaemia. A total of 128 T1DM patients were included, with 37/128 impaired awareness (29%). Hypoglycemia awareness was assessed using Clarkes self-reporting validated survey. Using established classification methods, participants scoring ≥ 4 were deemed as having impaired awareness.

Performance analysis of the aware group (n=98) and impaired awareness group (n=37) showed no difference in the sensitivity and specificity outcomes. The HypoMon's multivariate data transform methods provide an effective alarm for the detection of nocturnal hypoglycemia. Moreover, for T1DM with impaired awareness of hypoglycemia, the data transforms are as robust and effective in detecting nervous system responses to hypoglycaemia as that of the aware group.

	Normal	Impaired	p-value
Sensitivity	86% (12/22 ; 73-100%, 95% CI)	90% (9/10 ; 70-100%, 95% CI)	p=0.829
Specificity	87% (60/69 ; 80-94%, 95% CI)	78% (21/27 ; 80-94%, 95% CI)	p=0.281

895-P

Does Glucose Level at Calibration Influence Accuracy of Continuous Glucose Monitoring Readings *In Vitro*?

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A major limitation shared by the commercially available continuous glucose monitoring systems (CGMSs) is the inaccuracy of their readings when blood glucose levels are changing rapidly, particularly in the hypoglycemic range. Here we examine whether CGMS accuracy per se in the low glucose range improves if calibrations are performed at different and/or low glucose concentrations. To this end, Paradigm®722 Real-Time CGMSs (Medtronic Diabetes, Northridge, CA) and their sensors (n=21) were calibrated in either a 4, 8 or 12mmol/l glucose solution after which the sensors were immersed in a low glucose concentration solution (2.2mmol/l). In other experiments, single or repeated CGMS calibrations at the same or different glucose concentrations (4, 8 or 12mmol/l) were performed prior to testing the sensors in a low glucose solution (2.2mmol/l). Sensors calibrated in the 4mmol/l glucose solution measured low glucose levels more accurately than those calibrated at higher glucose levels, with a mismatch of 0.3±0.0mmol/l compared to 0.6±0.1 mmol/l and 0.8±0.0mmol/l for the sensors calibrated in the 8 and 12mmol/l glucose solutions, respectively (p<0.0001). In contrast, sensors calibrated at different glucose levels were not more accurate at measuring low glucose levels compared to those calibrated once or repeatedly at stable glucose concentrations (8mmol/l), with mismatches of 0.7±0.3, 0.5±0.2, 0.6±0.3 and 0.6 ±0.2 for the sensors calibrated in the 8, 8/8/8/8, 8/4/12/8, and 8/12/4/8 mmol/l glucose solutions, respectively (p=0.16). The lags in CGMS glucose readings were not affected by the type of calibration protocol, with lag times of 10.8±1.0, 11.3±1.3, 9.4±0.9 and 10.1±0.4 min for the sensors calibrated in the 8, 8/8/8/8, 8/4/12/8, and 8/12/4/8 solutions, respectively (p=0.53). In summary, a one-point calibration at lower compared to higher glucose levels improves the precision of CGMS glucose measurements in the lower glucose range. However, multiple calibrations at various glucose levels do not further improve accuracy and lag of the CGMS per se compared to multiple calibrations performed at one glucose level.

896-P

Dynamic Electrochemistry Corrects for Hematocrit Interference on Blood Glucose Determinations with Patient Self-Measurement Devices

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It has been demonstrated that dynamic electrochemistry can be used to correct blood glucose measurement results for potentially interfering conditions, such as humidity, hematocrit (HCT) variations, ascorbic acid and others. The purpose of this laboratory investigation was to assess the potential influence of hematocrit variations on a variety of blood glucose meters applying different measurement technologies. Venous heparinized whole blood was drawn, immediately aliquoted, and manipulated to contain 3 different blood glucose concentrations (80 mg/dL, 155 mg/dL, and 310 mg/dL) and 5 different HCT levels (25 %, 37 %, 45 %, 52 %, and 60 %). After careful oxygenation to normal blood oxygen pressure, each of the resulting 15 different samples was measured 8 times with the following devices: BGStar, Ascencia Contour, AccuChek Aviva and Aviva Nano, Breeze 2, Precision Xceed, OneTouch Ultra II and Verio, FreeStyle Freedom Lite, Glukoman GM, and StatStrip (point of care device, POC). COBAS (Roche Diagnostics) served as laboratory reference method. Stability to HCT influence was assumed, when less than 10 % bias occurred between the highest and lowest HCT levels, when analyzing the mean deviations for all three glucose concentrations. Next to the POC StatStrip device, which is known to measure and correct for HCT (resulting in only 2 % bias), three self-test meters also showed a stable performance in this investigation: dynamic

electrochemistry: BGStar (8 %), static electrochemistry: Ascencia Contour (6 %) and OneTouch Verio (6 %). All other meters failed this test: colorimetry: FreeStyle Freedom lite (16 %), static electrochemistry: AccuChek Aviva (23 %), Aviva nano (18 %), OneTouch Breeze 2 (36 %), Ultra II (34 %), Precision Xceed (34 %), and Glukomen GM (31 %). As HCT variations occur in daily routine (e.g. due to exercise, stay in mountains, hemodialysis etc.), our results may encourage use of meters with stable performance under these conditions. Dynamic electrochemistry as used in the BGStar device (Sanofi-Aventis) appears to be an effective technology to correct for potential hematocrit influence on the meter results.

Supported by: sanofi-aventis

897-P

Efficacy and Safety of Continuous Glucose Monitoring Systems vs. Self-Monitoring Blood Glucose in Patients with Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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There is an ongoing debate concerning the efficacy and safety of continuous glucose monitoring (CGM) systems in diabetes care. We performed a systematic review to evaluate the effect of CGM on glycemic outcomes as compared with self-monitoring blood glucose (SMBG) with conventional glucometer readings in type 1 diabetes mellitus (T1DM).

The assessment was based on randomized controlled trials (RCTs) identified by means of a systematic literature search in medical databases (Medline, EMBASE, Cochrane Library) up to January 2010. Studies met the inclusion criteria if they compared CGM vs. SMBG in T1DM patients on intensive insulin regimen (continuos subcutaneus insulin infusion or multiple daily injections). It was required the same regimen was used in both arms. Weighted mean difference (WMD), standardized mean difference (SMD) or odds ratio (OR) was calculated with 95% confidence interval.

We identified 13 trials including 1125 patients followed for at least 3 months. A meta-analysis of 9 RCTs demonstrated lower glycated hemoglobin (HbA_{1c}) level at the end of follow up in the CGM group compared with SMBG (WMD = -0.31 [-0.50; -0.12]). Pooled data of 13 RCTs showed greater HbA_{1c} change from baseline in favor of CGM (WMD = -0.26 [-0.34; -0.18]). Moreover, in the CGM group a higher percentage of patients achieved predefined target HbA_{1c} (29% vs. 16%; OR = 2.13 [1.39; 3.26]) as well as HbA_{1c} reduction by at least 10% (22% vs. 9%; OR = 2.95 [1.53; 5.71]).

It was also shown that incidence of any hypoglycemic episodes was lower in CGM than in SMBG group (SMD = -0.33 [-0.56; -0.10]). No differences between CGM and SMBG were revealed with respect to the percentage of patients with severe hypoglycemia or duration of hyperglycemic episodes (>180 mg/dL) or hypoglycemic incidents. The safety analysis showed that CGM was well tolerated. Reported adverse events (AEs) included adverse reactions at the sensor implantation site. No severe AEs were observed.

In conclusion, the use of CGM may contribute to improvement of glycemic control and reduction of incidence of hypoglycemic episodes in T1DM.

Supported by: Medtronic Poland

898-P

Evaluating the Long-Term Cost-Effectiveness of Tight Glycaemic Control in Patients with Type 2 Diabetes in China: A Modeling Study of Long-Term Costs and Health Outcomes

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To evaluate the long-term cost-effectiveness of tight glycaemic control compared with moderate glycaemic control in patients with type 2 diabetes Mellitus (T2DM) in China. A published and validated CORE Diabetes Model was used to project long-term (30 years) of health and economic outcomes. Simulated cohorts and treatment effects were derived from 300 diabetic patients in community medical center who were divided randomly into tight glycaemic controlled group (n=145) and moderate glycaemic controlled group (n=155). The tight group was treated with strengthened comprehensive intervention which included self blood glucose monitoring, diabetic education, alimentary control, exercising and medication, HbA_{1c} control (HbA_{1c}<6.5%) and regular visits, while the moderate group was treated as usually in the community medical center. The observation period of both groups continued for 54 months. The market retail prices of medications were calculated to estimate treatment costs. The diabetes management and complications costs were obtained from Chinese published data. An annual discounting rate of 3% was used for both costs and health outcomes. Compared with moderate glycaemic control, the tight glycaemic control were projected to reduce the cumulative incidences of diabetes complications and improve long term health outcomes for patients with T2DM. Background retinopathy, End-Stage Renal Disease, congestive heart failure event, Myocardial Infarction events were reduced 4.3%, 0.8%, 2.6%, 4.0% respectively. Therapy of tight glycaemic control was projected to improve life expectancy 0.476 year and associated with improvements in 0.418 quality-adjusted life years (QALY), but increased direct medical costs by Chinese Yuan (CNY) 5,940 per patient compared to moderate control. However, the incremental cost-effectiveness ratio was calculated as CNY 14,217 per QALY gained. Therapy of tight glycaemic control would be considered cost-effective in T2DM patients compared with moderate glycaemic control, given a willingness-to-pay threshold of CNY 75,375 per QALY (3 times GDP per capita in 2009) gained in China.

899-P

First Experiences with the Multisensor for Non-Invasive Glucose Monitoring under Real Life Conditions

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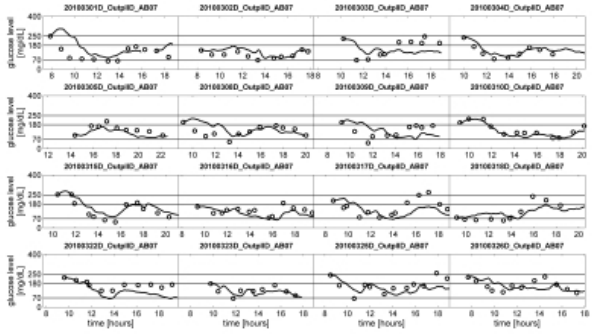
The Multisensor features non invasive sensors for dielectric and optical characterization of skin. In this study, a first version of the Multisensor with fully integrated sensors and battery was applied.

20 T1DM subjects (age 38±13 y; BMI 24.1±3.0 kg/m^2, duration of diabetes 17±13 y; HbA1c 7.5±0.9%) performed 1 in-clinic training day (A), followed by 10 days home-use (B) and another 3 in-clinic days (C). Subjects then were using the Multisensor under nearly unrestricted daily life conditions (D), performing a total of 753 home-use days. A data evaluation routine was applied using only A, B and C to generate one global model. This global model was then prospectively applied to data of D for external validation using a single BG value for baseline adjustment ("calibration") in the beginning of the study day. The model yielded a MARD of 35.4%. A MARD tertiles calculation shows < 25.6% for the 1st tertiles, <38.4% for the 2nd and above 38.4% for the 3rd tertiles respectively. One subject yielded MARD values above 38.4%, for all days while 6 subjects showed an MARD below 25.6% for 40% or more of the test days. The best patient yielded an MARD <25.6% in more than 60% of all test days.

CEG analyses showed 86.9% in A+B, 0.6% in C, 12.1% in D and 0.4% in the E region. Figure 1 shows a representative example of 16 externally validated home use days of one patient.

The Multisensor demonstrates the ability to follow glucose variations under nearly unrestricted conditions, using a purely statistical model. The Multisensor was well tolerated, in some cases skin sensitization occurred particularly in the beginning of home-use. After retraining and fine tuning of Multisensor attachment, skin sensitization could be reduced or disappeared completely again in most cases. The learnings taken from this study will help to further develop the MGMS concept.



900-P

Glycated CD59 Is Independently Associated with the 2-Hour Glucose Response to an Oral Glucose Tolerance Test

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Human CD59, a membrane protein inhibitor of the membrane attack complex of complement, contains a glycation-motif (K41-H44) within its active site and is inactivated by ε-amino glycation of K41. Inactivation of CD59 by glycation has been shown to contribute to complement-mediated damage in target organs of diabetes complications. We hypothesized that blood levels of soluble glycated CD59 (GCD59) may represent a novel marker

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of blood glucose handling that is also directly implicated with vascular diabetic complications. To evaluate the association between GCD59 and the glucose response to an oral glucose tolerance test (2hOGTT) we performed a cross-sectional analysis of 109 subjects who had high risk factors for diabetes and were naïve to drug therapy. All subjects underwent simultaneous assessment of 2hOGTT, fasting GCD59 (using an ELISA test specific for GCD59), and other biochemical and demographic measures. The relationship between GCD59 and the 2hOGTT was evaluated using linear regression, with adjustments for all clinically relevant and univariate predictors of 2hOGTT: age, gender, race, body-mass index, HbA1c, fasting blood glucose, blood pressure, and high-density lipoprotein. Of the 109 subjects, 15 were found to have frank diabetes (13.8%), 29 had impaired glucose tolerance (26.6%), and the remainder had normal 2hOGTT responses. In univariate modeling, higher GCD59 levels were associated with higher 2hOGTT (β=78.5, p<0.0001). In a multivariable model accounting for more than half of the variance in 2hOGTT (R^2=0.54), only GCD59 (β=33.0, p=0.02), fasting glucose (β=1.2, p<0.01), and female gender (β=-36.5, p<0.0001) remained independently associated with 2gOGTT, whereas HbA1c (β=11.8, p=0.26) and other co-variates did not. This evidence that GCD59 is strongly associated with 2hOGTT, and that this correlation may be stronger than that of other conventional predictors of the 2hOGTT is consistent with prior data linking glycation-inactivation of CD59 with the pathogenesis of diabetic complications, and justifies further studies to evaluate GCD59 as a pathogenically relevant biomarker in diabetes.

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901-P

Glycemic Variability and Clinical Outocomes in General Surgery Patients

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Glycemic variability (GV) is an independent predictor of mortality in critically ill patients. In patients admitted to general surgery services, however, the impact of GV on clinical outcome is not known. Accordingly, we determined the impact of GV in predicting 30 day mortality and hospital complications in general surgery patients at Emory University Hospital between 1/1/2006 and 6/30/2006. GV was assessed by the standard deviation of post-op BG values. Severity of surgery was graded as low, intermediate or high risk procedures based on ACC/AHA guidelines on perioperative evaluation for noncardiac surgery. A total of 3,184 patients (age: 56±16 yrs, BMI: 28±7 kg/m^2, [mean±SD]) had a mean post-op BG of 123±28 (non-DM 118±22 mg/dl, DM 139±39 mg/dl). Post-op complications were seen in 20.9%, and the inhospital and 30-day mortality were 1.8% and 2.3%, respectively. The mean GV was 19.8±15.6 mg/dl and it was positively associated with mean post-op BG (p<0.01). In multivariate analysis, adjusted for age, gender, history of DM, severity of surgery hypoglycemia and mean post-op BG GV was found to be significantly associated with mortality only in non-DM patients (p<0.01), but not in patients with DM (p=0.26). Stratifying by mean post-op BG levels (<120 mg/dl, 120-180 mg/dl, and >180 mg/dl), the association between GV and mortality was strong in non-DM (p<0.01, p<0.01, p=0.04, respectively) but was not present in DM patients (p=0.15, p=0.35, p=0.54). Similarly, GV was associated with hospital complications in non-DM (pneumonia, UTI, skin and wound infections, sepsis, acute renal failure and myocardial infarction, p<0.01) but not in patients with DM (p=0.20). Patients with and without DM with ≥1post-op episode of hypoglycemia (BG<70) were found to have larger GV (p<0.01).

In summary, glycemic variability is associated with post-operative mortality and hospital complications in patients without DM, but not in patients with DM undergoing general surgery. Analyses of prospective and randomized control trials are needed in order to determine the role of glycemic variability as a clinical tool in predicting clinical outcome in noncritically ill patients in general medicine and surgery setting.

902-P

HbA_{1c} May Not Accurately Reflect Glycaemia in Diabetes—Examination of the Relationship between HbA_{1c} and Self Blood Glucose Monitoring Independent of Glycation Gap

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Objective: A disparity between HbA_{1C} and other measures of glycaemia is now recognized as the "Glycation Gap" (G-gap=HbA_{1c} minus Fructosamine derived predicted HbA_{1c}). The G-Gap may affect the accuracy of the relationship between blood glucose parameters and HbA_{1c}. We thus examine that relationship in individuals with diabetes and with an evidenced minimal G-gap (<±0.5%). Methods:This cross-sectional study included 127 individuals with diabetes who had simultaneous estimations of HbA_{1c}, Fructosamine and SMBG and had G-gap <±0.5%. All SMBG comprised data spanning 90 days, with a minimum of 30 blood tests, no more than 3 days between any 2 blood tests and with no less than 10% of readings in any one of the following time blocks (hrs): 06:00-11:00, 11:00-14:00, 14:00-21:00, and 21:00-24:00. Blood glucose parameters calculated were: the 25th, 50th and 75th centiles (indicating the central blood glucose tendency); mean absolute difference (MAD), and inter quartile range (IQR) (indicating variability). Regression analysis was used to determine the factors that predicted HbA_{1c}. Results:Demographic details of the cohort: age 51±14years, Male 52%, type1 diabetes 61.4%, duration of diabetes 21.2±11 years, BMI 28.6±6.3, HbA_{1c} 8.6±0.9%, Fructosamine 348 µmol/l, G-gap 0.06±0.3. In factor analysis, SMBG parameters congregated into 2 components: the first component comprised measures of blood glucose variability which explained 39% of variance of HbA_{1c} (r=0.62, p<0.001), whilst the second component contained measures of the central tendency explaining only a further 10% of the variance (r=0.69, p<0.001, r2 change = 0.09, F= 22.0, p<0.001). Similarly, analysing individual factors the dominant factor was the IQR (r=0.68, p<0.001) with the median adding a significant but secondary and very small contribution (r=0.70, p<0.001, r^2 change=0.03, F=7.12, p<0.001). Conclusions:In a diabetes cohort selected to have no significant G-gap, HbA_{1c} is a weak reflection of glycaemia attainment. Within that it is more closely related to variability of blood glucose than the central or median attainment.

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903-P

Is 1,5 Anhydroglucitol (Glycomark®) a Clinically Useful Test in Type 1 Diabetes?

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Glycomark® is an FDA approved test that measures 1,5 anhydroglucitol concentration in plasma. It is promoted as being a good assessment of postprandial hyperglycemia in diabetes. However, its clinical utility in type 1 diabetes has not been established. We utilized established glucose parameters, both in the blood and the interstitial fluid, to assess its ability to predict hyperglycemia in type 1 diabetes.

One hundred and twelve studies were performed in type 1 diabetic volunteers. A fasting blood sample was drawn for both A1C and the 1,5 anhydroglucitol assay. We then performed five days of blinded-Continuous Glucose Monitoring (CGM) with simultaneous capillary blood glucose measurements. The data supplied from the CGM recording device was correlated with the 1,5 anhydroglucitol value. The following parameters were examined: blood A1C, mean capillary blood glucose, mean interstitial glucose above 180mg/dl, mean postprandial integrated interstitial glucose, percent time spent above 180mg/dl, and mean interstitial glucose.

The glycemic parameters in Figures 1 and 2 showed no statistically significant correlation with the 1,5 anhydroglucitol values. Furthermore, no correlations with any glucose parameters were clinically useful.

Figure 1

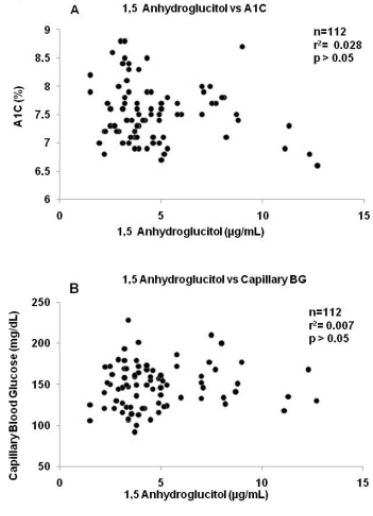

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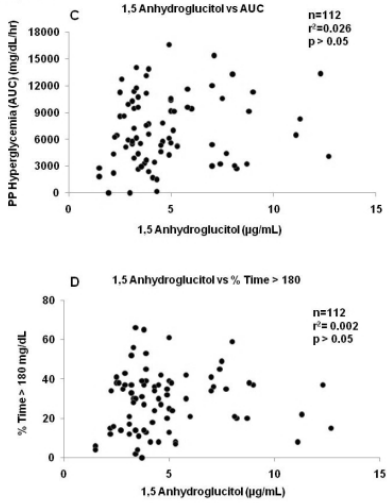
Figure 2



In individuals with type 1 diabetes, 1,5 anhydroglucitol (Glycomark®) should not be used to draw conclusions about other systemic glucose parameters including postprandial hyperglycemia. The clinical usefulness of 1,5 anhydroglucitol (Glycomark®) has yet to be established in type 1 diabetes. **ADA-Funded Research**

904-P

Long Term Performance of a Prototype 4th Generation Continuous Glucose Monitoring (CGM) Device

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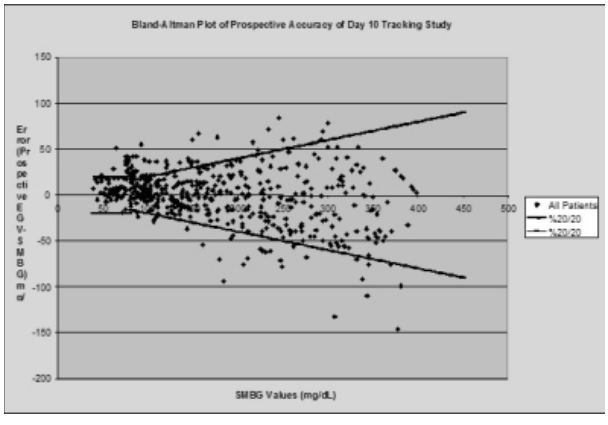
A prototype 4th generation CGM sensor was created with a newly designed membrane system for enhanced low oxygen performance and extended in-vivo sensor life. Twenty subjects were tested in a standard at-home usage trial with two 8-hour in-clinic (one on day 1, one on day 10) glucose tracking sessions in which fingerstick glucose (SMBG) were obtained every 15 minutes. CGM systems were calibrated twice daily. Subjects wore sensors for up to 15 days to observe end-of-life issues.

Overall mean ARD (MARD) for the entire 15-day duration of this study was 15.6% (N=1930, SMBG matched pairs) with a %20/20 of 76.1%.

Day 10 tracking study performance of the sensor was an MARD of 11.5% (N=457, matched pairs), %20/20 of 85% and a %40/40 of 98.2%. MARD in the hypo-range (40 to 80 mg/dl) on day 10 was 18.1%. Prospective accuracy is displayed in Figure 1, a Bland-Altman plot of the Day 10 tracking performance (lines represent %20/20).



Additionally 80% of the sensors displayed >95% of all possible data (72 minutes missed/day) on day 10 which then steadily declined to 50% of the sensors displaying >95% of all possible data by day 15. There were only 2 device failures (10%) for all causes by day 10. Nine failures (45%) were observed by day 15 with the majority of these failures being adhesive related (56%) and the rest were a mix of different performance metrics.

This prototype 4th generation sensor showed very good performance across the glycemic spectrum out to 10 days without a significantly higher sensor failure rate(s) and/or significantly prolonged periods of time off for each sensor.

With further advances in materials and sensors designs, this duration may be extended further in the future.

905-P

Mental Stress-Induced Hyperglycemia in Diabetes Mellitus: Establishment of a Continuous Stress Monitoring System

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Mental stress is one of the crucial factors exacerbating chronic diseases such as diabetes, hypertension and depression. Although it is widely known that the mental stress could be directly related to increase blood glucose in diabetic patients, the pattern of mental stress induced hyperglycemia is not known yet, because we can not quantify or monitor mental stress objectively. Our study was performed to examine a relationship between mental stress measured by real-time HRV (Heart rate variability) and glucose levels in diabetic patients. For the purpose, we developed a new mental stress monitoring system, which we call CAMS (continuous ambulatory monitoring of stress). 30 patients with type 2 diabetes who do not have abnormal HR (Heart rate) at baseline were recruited. The subjects carried HRV monitor for 3 days and recorded their daily lives. During examination, activities with time such as dietary pattern, exercise, sleeping and symptoms like stress, pain and palpitation were recorded in their diaries. CGMS (Continuous glucose monitoring system) were also attached on the subjects and the blood fluctuation was recorded. We analyzed stress index using Low/High frequency, HR and SDNN. We obtained 72 hours blood glucose data from the CGMS and stress parameter from the HRV monitor. Patients' blood glucose showed a tendency to increase as the mental stress increased. When patients experienced emotional stress such as anger or insomnia, blood glucose and stress parameter also increased. We observed that elevated blood glucose level induced by insomnia was maintained until next morning, although stress index was normalized, suggesting that mental stress induced hyperglycemia could last for some period. In this study, we could monitor the real mental stress continuously, figure out how the real stress affects HRV pattern and quantify the mental stress in humans. We also observed the relationship between hyperglycemia and mental stress. We expect that the mental stress monitoring system could be applied to various kinds of chronic diseases and new solutions for more effective management of the diseases.

906-P

Performance of a New Blood Glucose Test Strip

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A new generation of blood glucose sensors that use FAD-GDH enzyme and a proprietary mediator as the key reagent components is being developed.

A clinical trial was conducted to determine the performance of this new blood glucose meter system (BGMS) in the hands of intended users in accordance with ISO 15197:2003 and the British Standard EN13612. 95 subjects, >18 years, median age, 33 yrs, with type 1 (78%) and type 2 (22%) diabetes participated. The subjects performed their own blood glucose tests. The health care provider (HCP) tested both capillary and venous samples from subjects. All meter test results were compared to the YSI laboratory results.

Table 1 shows results according to ISO 15197:2003 guidelines. Results were calculated separately for glucose values < 75 mg/dL and ≥ 75 mg/dL. Similar results were obtained when calculations were performed separately for glucose values <100 mg/dL and ≥ 100 mg/dL (not shown). The average hematocrit was 44% with values ranging from 32 to 52%.

There were no device-related adverse events.

Table 1. Percentages of Accurate Results

Sample Type	Data Comparison	N	Within ±10mg/dL* or ± 10% **	Within ±12.5mg/dL* or ± 12.5%**	Within ±15mg/dL* or ± 15%**	Within ±15mg/dL* or 15%**
Capillary Fingerstick	Subj v YSI	184	98.4%	100%	100%	100%
Capillary Fingerstick	HCP v YSI	183	98.4%	98.9%	99.5%	99.5%
Venous	HCP v YSI	186	98.9%	100%	100%	100%

* < 75mg/dL **≥75mg/dL

Thus, accurate and reliable glucose results were obtained from both fingerstick and venous blood samples with this new blood glucose meter system. Test results with a new generation of blood glucose sensors in development exceeded current accuracy guidelines and met proposed tighter guidelines when performed by the intended users, both subjects with diabetes and HCPs.

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907-P

Physician and Patient Usability of a Web-Based Mobile-Health Diabetes Management System

MARCIA A. TESTA, DONALD C. SIMONSON, *Boston, MA*

Advances in mobile communications and technologies (m-health) offer promise for improving patient self-management of diabetes; however data on the usability of m-health programs are lacking. We evaluated 388 insulin-treated patients with HbA1c ≥ 7.0% (82 T1DM, 306 T2DM, 47% male, age 54±11 yrs, HbA1c 7.8±0.7%) in 52 US clinics during a 6-month, cross-over trial comparing insulin intensification (target HbA1c < 7.0%) with either basal-bolus insulin glargine and premeal glulisine (GG), or bid premix insulin (PRE). Patients used mobile PDAs and transmitted data to a web-based system where clinicians monitored BG, insulin, hypoglycemia, symptoms, adverse events, and recorded titration recommendations and patient communications. Patients completed 241,897 surveys of BG and insulin dosing: before breakfast (n=63,251) 26.1%; before lunch (n=52,290) 21.6%; before dinner (n=59,274) 24.5%; before bedtime (n=54,539) 22.5%; and other times (n=12,538) 5.2%. They recorded 7,494 BG event surveys of symptoms, meals, seriousness, and countermeasures. Event severity levels were: mild (n=3,857) 51.5%, moderate (n=3,028) 40.4%, and severe (n=608) 8.1%. A QOL survey assessed the impact of 43 hypo- and hyperglycemic symptoms. The perceived health scale [(1(worst) – 10(best)] recorded with each survey had an overall mean of 6.74, SD = 1.95, median=7. In addition, 6,777 titration reports were submitted by clinicians involving 10,707 dosing decisions for GG, with 70% agreement with the web-based titration algorithm. Other agreement rates were: glargine (64%); glulisine – breakfast (73%), lunch (71%) and dinner (71%). Reasons for disagreement included insufficient information (12%), unrecorded hypoglycemic events (2%), patient unwillingness (8%), additional information provided (8%), and other reasons (70%). Agreement for the 4,123 PRE doses was: AM dose (52%) and PM dose (56%). The percent of patients reaching HbA1c < 7.0% was greater for GG [54.8% (201/367)] vs. PRE [36.4% (134/368), p < 0.001]. The m-health diabetes management system was utilized effectively by patients and physicians and captured data that allowed insulin intensification to be managed remotely and efficiently in real time.

908-P

Prognosis of Diabetes Related Complications by Continuous Glucose Monitoring Profiles: Data of the JDRF-Study Analyzed by the Glucose-Pentagon-Model

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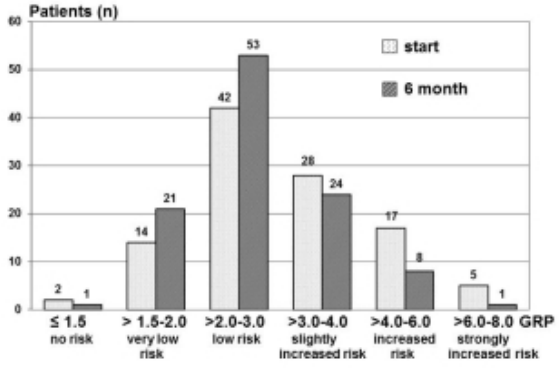
Variability in glycemia in patients with diabetes can be documented by means of continuous glucose monitoring (CGM) but not with capillary self-monitoring of blood glucose or HbA1c measurement. The glucose pentagon model (GPM) takes four parameters obtained by analysis of CGM recordings beside the HbA1c into account. By doing so a risk parameter (GRP) derived from the GPM might allow a better prognosis of the risk to develop diabetes related complications (DRCs) than the HbA1c. Data from 108 patients from the JDRF study (Medtronic CGM-System only) were evaluated: CGM profiles from the start of the study and after 6-month were analyzed by a software that generates the GPM and calculates the GRP. The change in this risk parameter was compared to the risk indicated by the change in HbA1c. The improvement in HbA1c from 7.4% to 7.0% during the study was accompanied by a reduction in mean glucose (from 163 to 156 mg/dl), standard deviation (61 to 57 mg/dl), AUC >160 mg/dl (29.2 to 23.1), and time per day >160 mg/dl (634 to 576 min). The reduction in the risk parameter calculated from the GPM from 3.3 to 2.7 by 18.2% was larger than the risk reduction by 8.6% indicated by the HbA1c.



In summary, the prognosis for the development of DRCs by using the GPM appears to be more valid than that provided by the HbA1c. Long-term studies will more definitively proof that parameters describing variability in glycemia should be part of such risk parameters. (We would like to thank the JDRF for providing us the data for this analysis.)

909-P

Randomized Evaluation of Glycemic Control in the MEdical INtensive Care Unit Using Continuous Glucose Monitoring (REGIMEN Trial): Preliminary Results

CHRISTOPHE DE BLOCK, JENS GIOS, NINA VERHEYEN, BEGONA MANUEL-Y-KEENOY, PETER ROGIERS, PHILIPPE JORENS, LUC VAN GAAL, *Antwerp, Belgium*

Stress hyperglycemia occurs in 50-85% of patients admitted to an intensive care unit (ICU) and is associated with increased morbidity and mortality. However, randomized controlled trials examining the effects of strict glycemic control demonstrated conflicting results. A common finding was the high risk of hypoglycaemia.

This ongoing pilot study evaluates the impact of real-time continuous glucose monitoring (RT-CGM) on glycemic control and risk of hypoglycemia in medical ICU patients with an APACHE-II score ≥20, reflecting severe illness.

So far 35 patients (age 66±10 y; non-diabetic/diabetic patients 27/8; APACHE-II score 28±6) were randomly assigned to RT-CGM (n=16) using the GlucoDay device (A. Menarini Diagnostics, Italy) or to the control group where blinded CGM was applied (n=19). Insulin infusion rates were guided using the same algorithm in both groups (adapted Yale protocol).

During 96-h of monitoring, glycemia reached target (80-110 mg/dl) in 35±11% of time, was between 60-150 mg/dl in 78±6%, and <60 mg/dl in 3±4% of time. In the RT-CGM group percentage of time at target was 37±12% vs 34±10% in the control group (NS) and mean glycemia was 119±17 mg/dl vs 122±11 mg/dl respectively (NS). The percentage of time in hypoglycemia (<60 mg/dl) was very low as compared to other trials, but similar between both groups. The number of arterial blood glucose measurements/day were 5±7 in the RT-CGM group versus 8±8 in the control group. Mean insulin dose infused was 3.2±2.1 vs 3.5±1.8 units per hour respectively (NS). GlucoDay values and arterial glycemia correlated well (r=0.89, p<0.0001, n=635 after 2-point calibration), with 97% of data falling in regions A and B of error grid analysis.

In conclusion, in this pilot trial RT-CGM did not ameliorate glucose control and did not reduce hypoglycemic events, but thanks to a good insulin infusion protocol overall glucose control was already very tight without a significant risk of hypoglycemia.

910-P

Relationship between Gycemic Variations during Late-Night/Early-Morning Hours and Sympathetic Nervous Activation in Japanese Non-Diabetic Patients with Acute Coronary Syndrome (ACS) as Assessed by Continuous Glucose Monitoring (CGM)

YUTAKA MORI, YUKIKO TANIGUCHI, KAZUNORI SEZAKI, KENICHI MATSUURA, JUNICHI YOKOYAMA, KAZUNORI UTSUNOMIYA, *Komae, Japan, Higashi-Murayama, Japan, Tokyo, Japan*

In recent years, there is mounting evidence which suggests that hypoglycemic episodes are implicated in the onset of acute coronary syndrome (ACS) by causing sympathetic nervous activation.

Glucose levels were monitored by using CGM in 14 non-diabetic inpatients with ACS with no history of diabetes and FPG levels < 126 mg/dl or HbA1c levels < 6.1% (JDS value), as well as in 11 non-diabetic control patients with no coronary artery disease. The ACS patients comprised 13 males and 1 female (mean age, 67.8 ± 10.3 years; mean BMI, 23.7 ± 2.4; mean HbA1c, 5.6 ± 0.3%), and the control patients comprised 7 males and 4 females (mean age, 73.6 ± 9.7 years; mean BMI, 23.1 ± 3.4; mean HbA1c, 5.3 ± 0.2%).

The mean glucose level between 23:00 and 07:00 in the ACS and control patients was 87.4 ± 23.4 mg/dl and 94.6 ± 13.9 mg/dl, respectively, while the SD of the glucose level in the ACS and control patients was 11.5 ± 3.8 mg/dl and 5.3 ± 3.1 mg/dl (P < 0.001), with the total area for glycemic variation being 71.6 ± 34.4 mg·hr/dl and 45.3 ± 29.1 mg·hr/dl (P < 0.05) and the MAGE being 29.0 ± 11.9 mg/dl and 12.4 ± 6.6 mg/dl (P < 0.001), respectively, showing that the ACS patients were associated with significantly higher values for these parameters than the control patients. Again, the percentage of time in hypoglycemia was significantly greater at 23.9 ± 35.9% in the ACS patients versus 0 ± 0% in the control patients (P < 0.05). In the ACS patients examined for heart rate, a temporary increase in heart rate was observed during early-morning hours. The use of an α-glucosidase inhibitor, however, led to normalization of the late-night glycemic variations and to alleviation of the increased heart rate in the patients.

Thus, wide nighttime glycemic variations occurred in non-diabetic ACS patients, with hypoglycemic episodes (glucose levels < 70 mg/dl) noted in some patients. Also, a temporary increase in heart rate was observed in the ACS patients, suggesting that late-night glycemic variations contributed to sympathetic nerve activation.

911-P

The Impact of Real Time Continuous Glucose Monitoring in the Classroom/School Environment

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Type 1 diabetes mellitus (T1DM) is the most common metabolic disorder in children. Children with T1DM spend 4 to 7 hours a day in school managing their diabetes often without the help of a school nurse. Teachers are frequently asked to help provide supervision of their diabetes management. As more students are using insulin pumps and real time continuous glucose monitoring systems (RT-CGM) to help manage their diabetes, it is important to assess their impact in the classroom/school environment. We asked the parents, teachers and children who wear RT-CGM in school to complete a validated questionnaire on its impact in the classroom. Twenty of the twenty-one (95%) of families invited agreed to participate in the survey (20 parents and 17 children). Students were enrolled in grades kindergarten to 12 (4 elementary, 7 middle and 9 high school). Of the 20 subjects, 9 had more than one teacher (up to 7 teachers) during the school day. Seventy-two percent of the 65 teachers completed the survey. Twenty-three percent of teachers had received training on the device (up to 1h) from a parent, student or health care professional. Seventy percent of parents, 71% of students, and 77% of teachers found RT-CGM moderately to very useful in the classroom/school environment. However, 18% of the students found the devices to be disruptive in the classroom in comparison to 5% of the parents and 3% of the teachers. Interestingly, only 17% of the teachers reported having heard the vibrations/alarms in class. Although the duration of use of the RT-CGM in the classroom varied (less than a month to over a year), the availability of the device in the classroom increased the comfort level of diabetes management in the classroom (72% parents, 88% students and 45% teachers). As the use of RT-CGM becomes more prevalent in T1DM management, its impact on the classroom and/or school environment should be evaluated in a larger, multi-centered study.

912-P

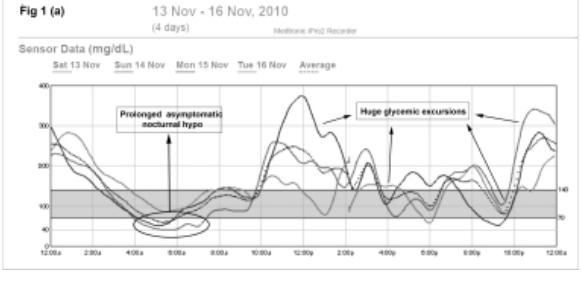
Utility of CGM over Conventional SMBG in Making Treatment Changes in Insulin Requiring T2DM Patients

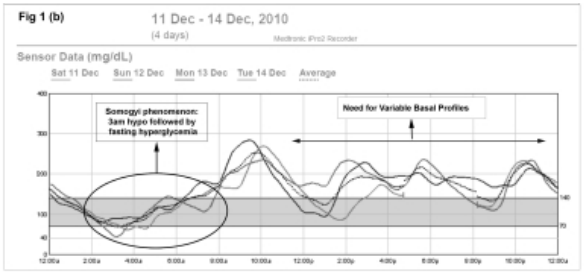
JOTHYDEV KESAVADEV, PRADEEP BABU SADASIVAN PILLAI, ARUN SHANKAR, GOPIKAKRISHNAN GOPALAKRISHNAN, GEETHU SANAL, JAYASREE LALLY, SUNITHA JOTHYDEV, *Trivandrum, India*

Continuous Glucose Monitoring (CGM) is not a routine investigation in T2DM. We assessed utility of CGM among T2DM patients on insulin, already practicing SMBG. 25 patients were enrolled (mean age=54yrs,SD=12.9; mean duration of diabetes=12yrs,SD=5.2), via convenience sampling based on ability and willingness to participate. 10 patients were on basal insulin + OHA and others on basal-bolus regimen + OHA. The study duration was 3-6 days.

A multi-disciplinary team of doctors, dieticians, pharmacist, and nurse educator made detailed analyses of CGM recordings. Observations included those missed in routine SMBG, like nocturnal hypoglycemia, glycemic excursions, Somogyi phenomenon etc.

Figure 1 : CGM profiles of T2DM patients on treatment





These observations were used for patient education, for changing number and type of insulin shots, duration and timing of exercise, timing of snacks and diet composition. In a few, where there was a compelling indication for a variable basal rate, insulin pump therapy was also advised.

		Possible Interventions			
Patterns possible to be identified by CGMS	**No. of cases seen in 25 patients** (total does not match due to overlap)	**Change in type & timing of basal +/- bolus**	**Dietary change**	**Exercise instructions**	**Variable basal insulin**
Wide glycemic excursions	15		x	x	x
Extended post-prandial hyperglycemia	3	x	x	x	
Nocturnal hypoglycemia	3	x	x	x	
Somogyi phenomenon	1	x			x
Overshoot after hypos during day	4	x	x	x	
Other asymptomatic hypo episodes	5	x	x	x	
Others (glycemic variability, quick post-prandial spike, etc.)	10	x	x	x	x

This pilot study suggests CGM unravel glycemic patterns, hitherto undetected in routine SMBG. Unlike T1DM, in T2DM,the pattern though abnormal is consistent over most of the days of CGM which help make concrete treatment decisions. CGM may thus be used as routine investigation to supplement SMBG in making treatment changes in T2DM patients on insulin.

913-P

Validity of GlucoTrack®, a Non-Invasive Glucose Monitor, for a Variety of Diabetics

AVNER GAL, ILANA HARMAN-BOEHM, YULIA MAYZEL, ASSAF AVIHOO, LIOR TRIEMAN, *Ashkelon, Israel, Beer-Sheva, Israel*

Inconvenience, expenses, pain and complexity involved in SMBG lead to its underutilization. Availability of an accurate, painless and easy to use device should encourage more frequent glucose measuring, leading to tighter glucose control. Previous publications suggest that GlucoTrack (GT) shows clinically acceptable results, using a combination of 3 technologies: Ultrasonic, Electromagnetic and Thermal. The measured tissue parameters are integrated into a glucose value by individual calibration, which minimizes the effects of individual quasi-stable factors, such as tissue thickness and structure, and allows adjusting the glucose behavior model for each user. In order to achieve high efficacy, the device should be valid and applicable for the majority of diabetics.

To verify GT suitability for different demographic categories, 106 subjects were evaluated according to gender, age, BMI and diabetes type. The age group was divided into 3 subgroups: 18÷40, 41÷55 and >55 years. BMI was divided into 3 subgroups: <25, 25÷30 and >30 Kg/m^2. In addition, user feedback regarding operation was analyzed.

The Mean Absolute Relative Difference (MARD) of all subjects is 22.2%. MARD values, calculated for the different categories are similar in all subsets. Outliers were not observed in either demographic category:

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			Clarke Error Grid Results	
Category	# of Subjects	MARD (%)	A zone (%)	A+B zones (%)
Male	58	21.8	59	96
Female	48	22.6	59	95
Type 1	17	22.5	57	93
Type 2	89	22.1	60	96
BMI group 1	16	23.4	58	93
BMI group 2	35	22.1	59	95
BMI group 3	55	21.9	61	97
Age group 1	15	19.6	61	96
Age group 2	31	23.4	56	95
Age group 3	60	22.2	61	96

97% of the users found the device to be comfortable to use and 87% of the users declared they'll use the device more frequently than the invasive one.

GlucoTrack performances across demographic categories suggest that the device is equally suitable for type 1 and 2 diabetics of different gender, age and BMI. The users' feedbacks indicate that the device is user friendly and easy to operate, as well as willingness to use it more frequently. Future studies should include race as part of the analysis.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULIN DELIVERY SYSTEMS

[*See also: Presidents Posters 406-PP to 407-PP, page A112.*]

Guided Audio Tour: Insulin Delivery Systems *(Posters 914-P to 921-P), see page 15.*

914-P

Feasibility Analysis of Delivering Correction Bolus Automatically Using Data from CareLink®

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Patients with type 1 diabetes routinely deliver boluses of insulin to correct hyperglycemia. In the pathway to the artificial pancreas, there is interest in understanding the effect of correction boluses and to develop algorithms to deliver automatic boluses. Continuous glucose monitoring (CGM) data from the Medtronic CareLink database was analyzed to explore these questions.

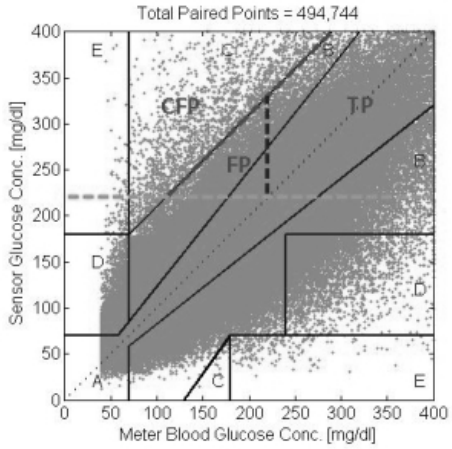
CareLink data from 2170 patients was obtained over 6 months; 494,744 paired sensor glucose (SG) and meter blood glucose (MBG) values were analyzed. Mean MBG at the time of a correction bolus was 235±78 mg/dL and decreased to 158±74 mg/dL between 2–5 hours; 9.6% of post-bolus MBG values were <70 mg/dL.

Abovementioned paired values from CareLink were analyzed to explore the safety of automatic bolusing. An algorithm was developed to give an automatic bolus at a SG >220 mg/dL. True positive (TP, SG and MBG > 220 mg/dL) and false positive (FP, SG >220 mg/dL and MBG <220 mg/dL) events were analyzed, illustrated by points in the A plus lower B and upper B, C and E zones of the Clarke error grid (CEG), respectively (Figure).

An algorithm simulated automatic boluses for each FP event and we determined that only events located in zones C and E resulted in hypoglycemia (<70 mg/dL), which we used to form the clinically-relevant FP zone (CFP). The table represents the percentage of points in each of the CEG zones with the addition of TP and CFP zones.

Analysis of the data revealed that an automated correction bolus, using a glucose sensor, triggering at 220 mg/dl, produced only 3.2 cases of hypoglycemia in 100 incidences, in contrast to 9.6 cases by the subject. Further strategies to promote even greater safety are under development which will be extensively tested with >4,000,000 SG/MBG paired-points from CareLink.

Clarke Error Grid Zone	% of Points
A	66.54
B	27.02
C	0.50
D	5.86
E	0.08
TP	11.08
CFP	0.45



915-P

Characterization of the Low Glucose Suspend Feature of the Medtronic MiniMed Paradigm Veo Insulin Pump System and Events Preceding Its Activation

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The Veo insulin pump/continuous glucose monitoring system allows for automatic suspension of insulin delivery at a pre-specified low glucose value (low glucose suspend, LGS). It was released in Europe in June 2009. Data from the Veo system in the first half of 2010 were analyzed and events preceding LGS events were characterized using CareLink 3.0 software. There were 935 subjects who used the Veo system for a total of 49867 patient-days; the LGS feature was on for 82% of these patient-days. A total of 27216 LGS episodes occurred. Most (65%) LGS episodes lasted 30 min or less, and only 11% lasted for >115 min. In a subset of 278 subjects with 3 mo continuous sensor wear (during which LGS was on for 92% of the patient-days), the percent of sensor glucose (SG) values <50 mg/dL was 0.92% with LGS on and 1.33% with LGS off (P<0.001), the percent of SG values >240 mg/dL was 11.28% with LGS on and 11.65% with LGS off (P=0.023), and the percent of SG values >300 mg/dL was 3.41% with LGS on and 4.64% with LGS off (P=0.002). For LGS episodes lasting for >115 min, the mean SG was 58.8±12.4 mg/dL at LGS activation, 136.8±64.9 mg/dL at 180 min, and 150.1±68.6 mg/dL at 240 min. Hyperglycemia and food boluses were commonly identified in the 3 hours preceding LGS episodes; other preceding events included bolus wizard overrides, manual boluses and/or pre-programmed basal rate increases, but not multiple boluses (Table). Use of the LGS feature was associated with less hypoglycemia and hyperglycemia, and LGS episodes of 120 min did not lead to hyperglycemia. These findings suggest that LGS frequency, and hypoglycemia, may be reduced by changing how patients respond to hyperglycemia and take insulin for food.

Events in the 180 min Preceding LGS Episodes	LGS Events (%)	LGS Events (n)
Hyperglycemia >180 mg/dL	31.38	8540
Food Bolus	28.45	7742
Manual Bolus	15.10	4110
Basal Increase by >25%	11.77	3204
Bolus Wizard Override	5.29	1440
>60g CHO Recorded	4.42	1204
Temporary Basal Rate	1.13	308
>1 Manual Bolus	0.35	94
>1 Correction Bolus	0.06	17

Supported by: Medtronic, Inc.

916-P

Utilizing a Novel Infusion Site Warming Device To Quicken Insulin Action: The InsuPatch Project

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Accelerating the rate of insulin absorption and action is likely to provide better control of post-prandial glucose excursions in type 1 diabetes (T1D) as compared to current rapid-acting insulins. We performed euglycemic glucose clamps to examine the effect of a novel insulin infusion site warming device, the InsuPatch, on the pharmacodynamics (PD) of a 0.2u/kg of aspart insulin bolus in pump treated subjects. 12 subjects (mean age 13±1years, 4 female, HbA1c 7.3±0.6%) were admitted twice for euglycemic clamp studies performed with and without InsuPatch activation in random order.

The PD effects of InsuPatch are shown in the Table (mean±SD). While maximum glucose infusion rate (GIR_{max}) was unaffected by infusion site warming, time to reach half maximum action ($T_{early50\%}$) and maximum insulin action ($T_{max\ GIR}$) were 19 minutes and 36 minutes earlier with InsuPatch activation, respectively. Area under curve for the first 90 minutes of the clamp study ($AUC_{GIR\ 0\text{-}90min}$) and mean GIR for the first 90 minutes ($GIR_{0\text{-}90min}$) were also greater with InsuPatch than without, confirming the left shift of insulin action profile with site warming.

These PD data indicate that the onset and the overall peak action of a rapid acting insulin bolus is earlier when InsuPatch is activated to warm the infusion site in pump treated patients. This effect could mitigate post-prandial hyperglycemic excursions and improve overall glycemic variability for this patient population.

	No InsuPatch	With InsuPatch	*p*
Pharmacodynamics			
$GIR_{0\text{-}300min}$ (mg/kg/min)	3.7±1	4.3±1	0.04
$GIR_{max\ 0\text{-}300min}$ (mg/kg/min)	7.2±3	8.2±4	0.3
$GIR_{0\text{-}90min}$ (mg/kg/min)	2.9±1	4.2±2	0.002
$AUC_{GIR\ 0\text{-}300min}$	1158±397	1315±424	0.1
$AUC_{GIR\ 0\text{-}90min}$	262±114	366±143	0.004
$T_{early\ 50\%}$ (min)	58±20	39±13	0.02
$T_{max\ GIR}$ (min)	126±28	90±21	0.0001

917-P

Technosphere® Insulin vs Insulin Lispro in Patients with Type 1 Diabetes Using Multiple Daily Injections

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Technosphere Insulin (TI [Afrezza®]) is an ultra rapid acting inhaled insulin with pharmacokinetics suited to control postprandial plasma glucose (PPG) with less hypoglycemia than current therapies. This study compared the efficacy and safety of TI vs insulin lispro (Humalog®) as prandial insulin in pts with type 1 diabetes mellitus (T1DM) who were using an MDI regimen with insulin glargine (G; Lantus®) as basal insulin.

Pts with T1DM (mean age 38.6±11.82, 39.4±11.46 yrs; diabetes duration 16.8±11.54, 17.6±10.37 yrs; BMI 25.07±3.7, 25.63±3.14 kg/m^2) and an A1C >7.0% and ≤9.0% were randomized to 16 wks of TI+G (n=65) or lispro+G (n=65). Prespecified efficacy endpoints included change in A1C, fasting plasma glucose (FPG), and 1- and 2-hr PPG following a standard meal challenge.

At 16 wks, change in A1C was similar in the 2 groups and there was no difference in G doses. The least-squares mean A1C treatment difference from baseline was -0.10% (SE 0.09; 95% CI -0.28, 0.07) for TI+G and -0.03% (SE 0.08; 95% CI -0.19, 0.13) for lispro+G. Treatment group differences for change from baseline in FPG (-32.4 mg/dl [SE 12.4; 95% CI -57.1, -7.7; *P*=0.0107]) and 1- and 2-hr PPG (-66.29 mg/dl, *P*<0.0001; -34.40 mg/dl, *P*=0.0175) were significantly lower with TI+G vs lispro+G. Incidence of hypoglycemia was similar; however, the overall total and mild/moderate hypoglycemic event rates (events/pt-month) were significantly reduced with TI+G vs lispro+G. No differences in pulmonary function tests were observed between treatment groups.

TI use was comparable in A1C reductions to insulin lispro with significantly lower 1- and 2-hour PPG and FPG and fewer hypoglycemia events/pt-month in pts with T1DM on MDI. A long-term study is needed to evaluate the clinical benefit of lower FPG and PPG.

Hypoglycemia							
	Incidence				Event Rate/pt-month		
	TI+G (n=65) n (%)	Lispro+G (n=65) n (%)	Odds ratio (95% CI)	*P* value	TI+G	Lispro+G	*P* value
Mild to moderate	63 (96.92)	63 (96.92)	1.000	(0.137, 7.322) 1.0000	5.97	8.01	0.0269
Severe	15 (23.08)	23 (35.38)	0.548 (0.254, 1.182)	0.1251	0.19	0.18	0.9070
Total	63 (96.92)	63 (96.92)	1.000 (0.137, 7.322)	1.0000	6.17	8.19	0.0345

Supported by: MannKind Corporation

918-P

Measures of Oxidative Stress and Anti-Oxidant Capacity in Plasma Samples from Patients with Type 2 Diabetes before and after Insulin Pump Therapy

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A cohort of 56 poorly controlled (A1C 8.4±1.3%) insulin pump-naive patients consisting of three groups (two or more oral anti-diabetes agents [OADs]; basal insulin with or without OADs; basal-bolus insulin with or without OADs) was subject to a 16 week multi-centre pilot study of insulin pump therapy. All diabetes medications except for metformin were discontinued on initiation of pump therapy. Most patients were managed with 1 or 2 basal rates with resultant mean A1C improvement of 1.2±1.2% (P<0.001). A number of serum biomarker species were determined at initiation and termination of the study including: A1C; insulin; pro-insulin; a measure of antioxidant capacity (oxygen radical antioxidant capacity, ORAC); and measures of oxidative stress (oxidised low density lipoprotein, ox-LDL; protein carbonyls; malondialdehyde, MDA).

Consistent with our hypothesis that improvement in glycemic control using insulin pump therapy in these subjects would result in decrease of these markers, levels of insulin, pro-insulin and oxidative stress markers were depressed by ~10-35% (Table), as compared to baseline. A ~4% depression in ORAC was also observed, a measure that would be expected to increase in the face of reduced oxidative stress. Whilst samples were collected in the fasting state the role of dietary influences cannot be ruled out.

This 16 week pilot study using insulin pump therapy in poorly controlled patients with type 2 diabetes demonstrated markers of oxidative stress and anti-oxidant capacity to decrease, potentially decreasing mediators of inflammation and atherogenesis, in individuals with type 2 diabetes. Future studies should consider measures of endothelial function, coupled with a mechanistic approach to establish the relationship between insulin pump therapy and oxidative stress and to determine if the reduction in glycemia, as indicated by A1C reduction, is the main driver of the observed decrease in oxidative stress markers.

Marker	Change (%)	P
Insulin (pM)	-22.7	0.036
Proinsulin (pM)	-35.4	0.024
MDA (μM)	-19.4	<0.0001
ORAC (μIU/mL)	-3.9	0.013
Protein carbonyls (nmol/L)	-15.1	<0.0001
Ox-LDL (U/l)	-10.5	0.033

919-P

Relationships between Glycemia, Oxidative Stress and Inflammation in Type 1 Diabetic Patients Using Insulin Pumps

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The ALG-OS Study evaluated an algorithm guiding glucose sensor augmented CSII-treated Type 1 diabetes (T1D) patients. More adults with vs. without algorithm achieved HbA1c≤7.0% (72% vs. 35%), with no HbA1c change in adolescents, nor in continuous glucose monitor (CGM) determined glycemic variability (mean amplitude in glucose excursion (MAGE)) and time

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

in good (4-10mmol/l), low (<4mmol/l) or high (>10mmol/l) glucose ranges. Aim of this project was to determine relationships between glycemia and inflammation and oxidative stres in CSII-using T1D patients. T1D subjects (n=57) were evaluated before and after 16 weeks sensor augmented insulin pump use. Glycemia was reflected by HbA1c, serum 1'5 anhydroglucitol, and CGM-related MAGE and low, good and high glucose time. Serum levels of inflammation (CRP, IL-6 and vascular cell adhesion molecule-1 (sVCAM-1)) and oxidative stress (myeloperoxidase (MPO) and urinary F2-isoprostanes (IsoP)/urine creatinine) were measured by nephelometry (CRP), ELISAs (IL-6, sVCAM-1, MPO) and GC/MS (IsoP) and correlated with glycemia. Changes in glycemia were correlated with changes in inflammation and oxidative stress.

Urinary IsoP/creatinine correlated with MAGE at 16 weeks (r=0.34; p=0.02), but not with other glycemia measures. Urine IsoP/creatinine and serum MPO correlated (r=0.36; p=0.01). Apart from an inverse correlation between sVCAM-1 and MAGE at baseline (r=-0.29, p=0.038) there were no statistically significant (p<0.05) correlations between glycemia, inflammation and oxidative stress. Only changes in high glucose time correlated with changes in CRP (r=0.45, p=0.027) and (log)IL-6 (r=0.27, p=0.05).

In CSII-using T1D patients glycemic variability (MAGE) positively correlated with oxidative stress (urinary isoP/creatinine). There were no other statistically significant relationships between glycemia and oxidative stress, nor between changes in glycemia and in oxidative stress. Inflammation levels were not positively related to glycemia, but changes in high glucose time and changes in inflammation positively correlated.

920-P

WITHDRAWN

921-P

Pharmacodynamic and Pharmacokinetic Profiles of Adocia's Fast-Acting BioChaperone Human Insulin Formulation

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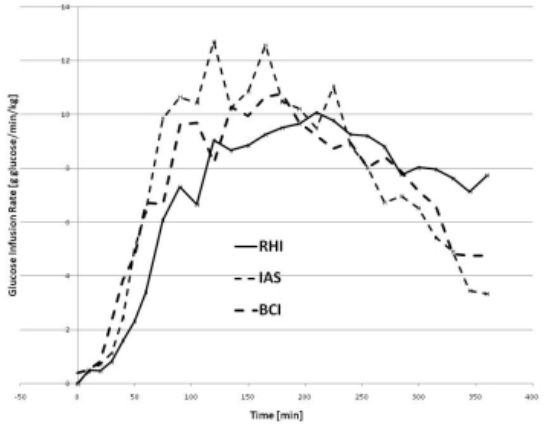
A new human insulin formulation with BioChaperone, a modified dextran, has been demonstrated in animal pharmacology trials to have a very fast onset and short duration of action. The purpose of this double-blind, randomized crossover study was to explore the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of BioChaperone human Insulin (BCI) in comparison with insulin aspart (IAS) and regular human insulin (RHI) in healthy subjects. In three consecutive euglycemic clamp experiments, each subject received 12 IU of the respective insulin and was observed for 6 h. Primary objective was the time to the maximal glucose infusion rate (GIR-Tmax). Secondary objectives included maximal GIR (GIRmax), time to half-maximal GIR (GIR-T50), maximal insulin concentration (INSmax), time to maximal and half-maximal insulin plasma levels (INS-Tmax, INS-T50) and number and type of adverse events. All insulin injections were well tolerated. The PD results are provided in the Figure (error bars were left out for better readibility).



BCI showed a similar onset of action, and similar GIR infusion pattern as IAS. Insulin levels raised as fast as IAS (INS-T50: 15±5 min; vs. IAS: 25±6 min, p<0.05; vs. RHI: 25±7 min, p<0.05) and reached similar maximal concentrations than RHI (INSmax: 52±9 µU/ml vs. RHI: 51±11 µU/ml, n.s.; IAS: 85±28 µU/ml, p<0.05). Our results demonstrate that BioChaperone enhances human insulin absorption to be as fast as a fast-acting insulin analog. The clinical investigation of this product is pursued in patients with diabetes mellitus.

Supported by: Adocia SA

922-P

Analysis of Cardiovascular Adverse Events in Patients with Type 1 or Type 2 Diabetes Enrolled in Selected Therapeutic Trials in the Phase 2/3 Technosphere® Insulin Development Program

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Technosphere Insulin (TI [Afrezza®]) is an ultra rapid acting dry powder formulation of recombinant regular human insulin being developed as an inhaled prandial insulin. A systematic collection of cardiovascular adverse events was undertaken on pooled data from 9 phase 2/3 clinical trials, consisting of 4,467 patients treated for periods from 3 months to 2 years to determine if excess cardiovascular events occurred in patients receiving TI compared with those receiving current antidiabetic therapies, including oral agents and/or insulin. Investigator-reported data were used without adjudication of events. The prevalence of prior cardiovascular disease included in the MedDRA terms myocardial infarction, coronary artery disease, or stroke was <10% in patients with type 1 diabetes but approached 40% in patients with type 2 diabetes. Risk factors were more prevalent in patients with type 2 diabetes (i.e., higher mean age, higher diastolic and systolic blood pressure, use of antihypertensive drugs, abnormal lipoprotein patterns, history of tobacco use, and a higher incidence of a positive medical history for myocardial infarction, heart disease, or stroke).

In controlled trials, the incidence of cardiovascular events did not show increased risk with TI use in type 1, type 2, or the combined type 1 plus type 2 diabetes populations (table).

Comparative Risk of Cardiovascular Events

	TI	Comparator	Relative Risk	95% CI
Type 1 diabetes	31	35	0.85	0.55, 1.30
Type 2 diabetes	167	136	1.02	0.84, 1.24
All diabetes	198	171	1.01	0.84, 1.20

Note: Based on independent broad MedDRA preferred term selection from System Organ Classes: Cardiac, Vascular, Surgical and Medical Procedures, and General Disorders.

The number of patients with ischemic events (angina pectoris, unstable angina, myocardial infarction, ischemic cardiomyopathy, and myocardial ischemia) was low and similar between treatment groups. Cerebrovascular events and other cardiovascular events, such as coronary artery disease and arrhythmic events, were also similarly distributed between treatment groups.

Supported by: MannKind Corporation

923-P

Assessment of Glycemic Variability and CD40 Ligand in the STAR 3 Study

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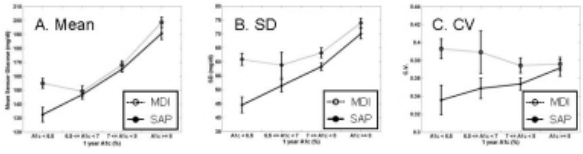
The STAR 3 study demonstrated greater reductions in A1C with sensor-augmented pump therapy (SAP: 8.3 to 7.5%) than multiple daily insulin injections (MDI: 8.3 to 8.1%) at 1 year in type 1 diabetes (P <0.001). Week-long continuous glucose monitoring (CGM) studies were conducted at baseline and 12 mo for comparison of MDI and SAP groups. Changes in soluble CD40 ligand (CD40L), a potential biomarker of oxidative stress, were also compared between the groups. Treatment groups were classified according to 12-mo A1C levels (<6.5%, n=16 SAP/n=3 MDI; 6.5 to <7%, n=33 SAP/n=17 MDI; 7 to <8%, n=124 SAP/n=88 MDI; and ≥8%, n=45 SAP/n=106 MDI). Glycemic parameters including mean sensor glucose (MSG), standard deviation (SD), and coefficient of variation (CV) were compared between SAP and MDI subjects in each A1C cohort. CD40L was measured by a colorimetric sandwich ELISA (R&D Systems, Minneapolis, MN). MSG values at A1C levels ≥6.5% were similar in SAP and MDI groups (Figure, Panel A). However, SD and CV were lower at A1C levels <8% in SAP vs. MDI subjects, and the overall between-groups difference was significant for both SD (P<0.01, Panel B) and CV (P=0.01, Panel C). As A1C increased to ≥8%, the differences between SD and CV in the SAP and MDI groups narrowed. Mean CD40L levels fell over the course of the study by 32.92 pg/ml in the SAP group and rose by 50.43 pg/ml in the MDI group; the between-group difference was not significant (p=0.18). CD40L does not appear to be related to A1C, the change in A1C from baseline, or to glycemic variability (GV). At comparable A1C levels <8%, SAP reduced measures of GV compared to MDI. Based on these results, SAP may be recommended to improve A1C and reduce glycemic excursions.



Supported by: Medtronic, Inc.

924-P

Continuous Subcutaneous Insulin Infusion (CSII) in Type 2 Diabetes: Reductions in A1C, Mean Glucose, and Variability

DAVID RODBARD, HENRY ANHALT, TIMOTHY BAILEY, BRUCE BODE, ROCCO BRUNELLE, STEVEN EDELMAN, JUAN FRIAS, MARK KIPNES, *Potomac, MD, West Chester, PA, Escondido, CA, Atlanta, GA, Carmel, IN, San Diego, CA, San Antonio, TX*

We evaluated the effect of CSII therapy in a 16 week open-label pilot study. 56 insulin pump naïve patients with type 2 diabetes previously treated with A) ≥2 oral agents alone B) oral agents plus basal insulin, or C) oral agents plus Multiple Daily Injection (MDI) insulin therapy were switched to CSII and monitored with Continuous Glucose Monitoring (CGM) at baseline,1,2,3,4, and 16 weeks. There were significant reductions in A1C, mean glucose, SD of glucose within days, hyperglycemia, and percentiles of the glucose distributions. Reductions of A1C and mean glucose were linearly related to baseline A1C with similar relationships irrespective of previous treatment (Fig. 1). Most improvement occurred in the initial 4 weeks. Subjects with baseline A1C 9%-10% showed the most dramatic response (Fig. 2). There was a small increase in risk of non-severe hypoglycemia. Conclusion: Use of CSII rapidly improves glycemic control in patients with T2DM as documented by CGM; these effects are more significant after adjustment for baseline A1C or mean glucose.

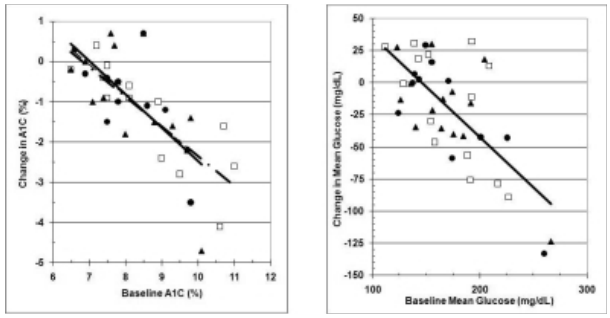


Fig. 1. Prior therapy: Cohort A: Oral agents (closed circles); cohort B: Oral agents + basal insulin (open squares); cohort C: MDI (closed triangles). Left panel: A1C; Right panel: Mean Glucose. All 3 cohorts show the same linear relationship.

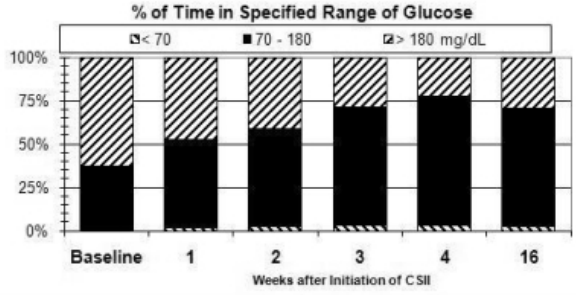


Fig. 2. Changes in glucose distributions in subjects using CSII from Baseline to 16 weeks for subjects with baseline A1C 9–10%: dramatic increase in % of time in the 70–180 mg/dL range and reduction in % of time >180 mg/dL.

925-P

Continuous Subcutaneous Insulin Infusion and Overall Quality of Diabetes Care

AMD ANNALS STUDY GROUP, *Italy*

We investigated the overall quality of care provided to patients with type 1 diabetes (T1DM) and treated with continuous subcutaneous insulin infusion (CSII), as compared with patients treated with multiple daily injections (MDI).

Clinical data were extracted from electronic medical records, and a quality of care summary score was calculated. The score, ranging between 0 and 40, is based on process and outcome indicators relative to HbA1c, blood pressure, LDL-cholesterol and microalbuminuria. Previous studies have documented that the risk to develop a new cardiovascular event was 80% higher in patients with a score <15 and 20% higher in those with a score between 15 and 25, as compared to those with a score >25.

Propensity scores methods were used to compare quality of care received by patients on CSII and those on MDI. Two different control groups were identified, one within the same diabetes center (internal controls), the other from diabetes centers of the same region, but not using CSII (external controls).

Among 24.293 patients with T1DM seen by 195 centers during the year 2009, 1913 (7.9%) were on CSII. The use of CSII varied among the different clinics: in 39% of the centers no patients were on CSII, in the others the percentage ranged between 0.16% and 42.0%. The quality score was of 26.5±8.7 in patients on CSII and 25.0±8.2 in external controls (p<0.0001). In particular, the proportion of patients with a score >25 was of 47.3% and 39.4% for cases and controls, respectively (p<0.0001). Even in comparison with internal controls, patients on CSII showed better quality of care (25.6±8.4 vs. 26.5±8.5; p=0.02). Among centers using CSII, quality of care delivered to patients treated with either CSII or MDI increased with the increase in the number of patients treated with CSII.

In conclusion, the organization of care for patients on CSII ensures better overall quality of care. The attitude to prescribe CSII is also associated with a better overall performance of the diabetes clinics. Within centers adopting CSII, patients on CSII receive a better care than patients on MDI.

Supported by: Associazione Medici Diabetologi (AMD)

For author disclosure information, see page 785.

926-P

Effect of Adjuvant Injected Pramlintide on Closed-Loop Automated Insulin Delivery

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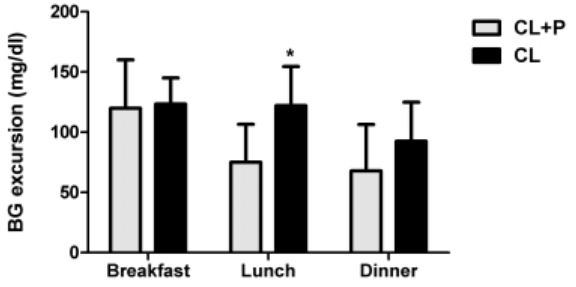
Even under closed-loop conditions, meal-related blood glucose excursions frequently exceed target levels due to delays in insulin absorption. We hypothesized the addition of mealtime pramlintide injections would improve post-prandial glycemia by allowing a better match between glucose and insulin absorption. Using a PID+IFB algorithm, 8 subjects (4 female, age 16-28 y, A1c 7.5±0.7%), were studied for 24 hours on CL control alone (CL) and 24 hours on CL plus pre-meal pramlintide (CL+P), 30 mcg per dose. Target glucose was set at 120 mg/dl; meals were served at 8AM, 1PM, and 6PM, and were identical for both days of study. No pre-meal manual boluses were given. Reference blood glucose excursions, defined as incremental glucose rise from pre-meal to peak, were compared between conditions for each meal. Compared to CL alone, CL+P was associated with a delayed time to glucose peak over all meals (2.5±0.9 vs 1.5±0.4 hr, p<0.0001) and reduced glucose excursions (88±42 vs 113±32 mg/dl, p=0.006). Beneficial effects of pramlintide on glycemic excursions were particularly evident at lunch (75 ± 32 vs 122 ± 33 mg/dl, p=0.03) and dinner (68 ± 39 vs 93 ± 32 mg/dl, p=0.07), as seen in the figure. Pramlintide delayed the time to peak post-prandial glucose levels and reduced the magnitude of prandial glucose excursions. The effects of larger doses of pramlintide are currently being examined.



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927-P

Graphic Assistance with ICU Glycemic Management Helps Eliminate Hypoglycemia

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Glycemic management has become an integral part of ICU care. Management is generally directed by written protocols using single blood glucose (BG) measurements or computerized applications. The large variety of published reports does not stress pattern recognition or analysis of graphic, real time data. We present our 11 year experience applying graphic assistance (GA) built into the electronic medical record (EMR) to guide continuous insulin infusion (CII) in our ICU's. GA adds the dynamic element missing from paper CII protocols.

The GA presents all insulin (units/hr, IV and SC bolus units), BG's, Target BG range (100-150 mg/dl), and nutrition in a real time window. The display is updated automatically as the EMR is updated by the RN. The trends seen with GA help predict the BG response to CII changes. RN's are taught to interpret the GA information so that the rates of change of BG and CII are used in addition to absolute values. Training and experience are required to take advantage of GA, but training is required for any CII system. While GA at first was difficult for some staff, it is now universally accepted.

While our hypoglycemic rate has been low, when the GA was not available our hypoglycemic events increased 40%. With reinstitution of GA, our hypoglycemic rate returned to low levels (0.05% BG's < 40 mg/dl, representing 1% of CII patients; 7.7% BG's < 100 mg/dl), below most published reports. Targeted glycemic control is also well maintained: time to reach target < 6 hrs.; 70% BG's are within target and 93% are within 70-180 mg/dl.

GA assistant can be used with any paper CII protocol providing the dynamic aspects of CII which are incorporated into computerized systems. If an EMR is unavailable, a manual paper plot can serve adequately. GA can also be an adjunct to a computerized system to provide confidence to staff about computer recommendations. GA can be used easily to estimate cumulative CII doses to transition to subcutaneous insulin.

In conclusion, we have found that incorporating the dynamic information with GA in real time assists CII titration minimizing hypoglycemia while achieving BG targets.

928-P

Hybrid Artificial Pancreas Using Prandial Inhaled Insulin and Zone-MPC

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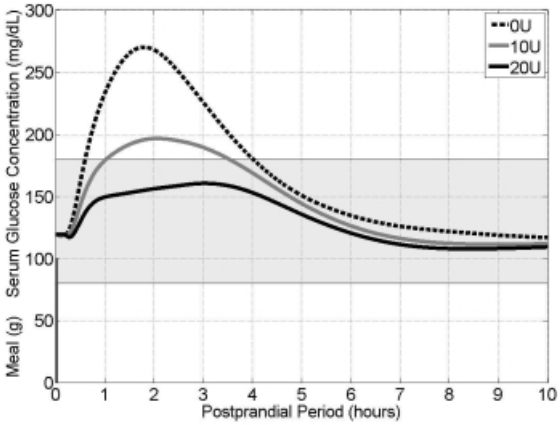
Overcoming postprandial glucose peaks is one of the main challenges in type 1 diabetes when managed with subcutaneous (SQ) insulin. An artificial pancreas (AP) that solely controls insulin delivery via the SQ route can improve overall glucose regulation; however, the postprandial peaks will still be a challenge due to the slow absorption rate of SQ insulin.

A novel hybrid AP is presented that combines rapid-acting Technosphere Insulin (TI) as a means to deliver the first phase of insulin to counter postprandial glucose peaks, while an advanced control design (zone-MPC) that is engineered to regulate glucose to the 80 – 140 mg/dL range controls corrections and basal via SQ. This system was evaluated on a population of 100 *in silico* subjects from the UVa / Padova FDA-accepted metabolic simulator following a meal challenge of 100 g of carbohydrate. The results show that the average postprandial glucose peaks of the subjects who were given 10 U TI and 20 U TI were lower than the control group (no TI) by 60 mg/dL and 86 mg/dL, respectively. Also, in the postprandial period, the average glucose concentrations of the subjects were within the normoglycemia region (80 – 180 mg/dL) for 86% and 100% in case of 10 U TI and 20 U TI, respectively. The average glucose concentration of the control group was within the normoglycemia region for 70% of the postprandial period. Figure 1 shows the average serum glucose concentration in the postprandial period for the cases of no TI, 10 U TI, and 20 U.



These findings suggest that a hybrid approach that combines inhaled insulin for first phase insulin delivery with zone-MPC controlling SQ delivery of corrections and basal insulin can provide improved and safe glucose regulation, even for large meals.

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929-P

Insulin Pump Adjustments and Glycemic Outcomes iin the Adult Cohort of the STAR 3 Study

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STAR 3, a 1-year randomized controlled trial, compared sensor-augmented pump (SAP) to multiple daily injection (MDI) therapy in type 1 diabetes. Adult subjects with high vs. low end-of-study A1C values may have interacted with the pump or adjusted its settings in different ways. At baseline, the mean A1C of 163 adult subjects (age >18) randomized to SAP was 8.3±0.5%, and it decreased by 12 months to 7.5±0.8% (P<0.001). Quarterly attributes of subjects with the lowest and highest A1C values at 1 yr were compared. Overall comparisons between high and low A1C groups were made with a repeated ANOVA model; final-quarter comparisons were made with a general linear model. Subjects with low A1C values trended toward lower total daily doses (TDD) of insulin, more boluses/day, and smaller boluses than those with high A1C values. Low-A1C subjects had fewer sensor glucose readings (SG)

>180 mg/dl and more SG <70 mg/dl (Tables). Changes to basal rate settings, insulin sensitivity, and insulin/carb ratios were similar between groups. Most pump setting adjustments occurred in the first 3 mo. Although not statistically significant, there was a trend toward fewer severe hypoglycemic (SH) episodes in subjects with high A1C (P=0.19). With this initial analysis of STAR 3 data, behaviors concerning bolus insulin delivery appear to be the most important to optimize glycemic outcomes in adult SAP patients.

Table 1. Lowest A1C Quartile (A1C ≤7.0%, n=57)

Attribute	Q1	Q2	Q3	Q4
TDD/kg	0.55	0.58	0.59	0.58
Basal/TDD (%)	0.50	0.51	0.50	0.51
Daily Number of Boluses	5.56	5.52	5.56	5.42
Mean Bolus (U) * §	4.09	4.48	4.48	4.50
SG <70 (%) * §	0.02	0.03	0.03	0.03
SG >180 (%) * §	0.24	0.23	0.22	0.21
Subjects with >0 SH Episodes	2	1	1	0

Table 2. Highest A1C Quartile (A1C >7.7%, n=44)

Attribute	Q1	Q2	Q3	Q4
TDD/kg	0.59	0.61	0.61	0.65
Basal/TDD (%)	0.47	0.48	0.49	0.48
Daily Number of Boluses	5.09	4.88	4.92	4.79
Mean Bolus (U) * §	5.47	5.73	5.72	5.93
SG <70 (%) * §	0.02	0.01	0.02	0.02
SG >180 (%) * §	0.41	0.39	0.38	0.38
Subjects with >0 SH Episodes	3	2	2	2

* P<0.05 for high vs. low A1C quartile, overall (Q1-Q4)
§ P<0.05 for high vs. low A1C quartile, Q4

Supported by: Medtronic, Inc.

930-P

Insulin Pump Adjustments and Glycemic Outcomes in the Pediatric Cohort of the STAR 3 Study

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STAR 3 was a 1-yr trial comparing sensor-augmented pump (SAP) therapy to multiple daily injection (MDI) therapy in type 1 diabetes. Pediatric subjects with high vs. low end-of-study A1C values may have used or adjusted the pump in different ways. At baseline, the mean A1C value of the 78 subjects aged 7-18 yr in the SAP group was 8.3±0.6%; by 12 months A1C decreased to 7.9±0.9% (P<0.001). Quarterly attributes of subjects with the lowest and highest A1C values at 1 yr were compared. Overall comparisons between high and low A1C groups were made with a repeated ANOVA model; final-quarter comparisons were made with a general linear model. Subjects with low A1C values used lower total daily doses of insulin (TDD), more boluses/day, and smaller boluses than those with high A1C values (P<0.05). They had fewer sensor glucose values (SG) >180 mg/dl, but a similar number <70 mg/dl (Tables). Changes to basal rate settings, insulin sensitivity, and insulin/carb ratios were similar between groups. There were more severe hypoglycemic (SH) episodes in subjects with high A1C, but the difference over the entire year was not statistically significant (P=0.061). Most pump setting adjustments occurred in the first 3 mo. This analysis of STAR 3 data suggests that promoting behaviors that allow pediatric SAP patients to give smaller and more frequent insulin boluses may help to optimize glycemic outcomes.

Table 1. Lowest A1C Quartile (A1C ≤7.4%, n=23)

Attribute	Q1	Q2	Q3	Q4
TDD/kg §	0.79	0.87	0.89	0.80
Basal/TDD (%)	0.43	0.42	0.42	0.44
Daily Number of Boluses * §	5.94	6.43	6.69	6.21
Mean Bolus (U) * §	3.48	4.10	4.00	3.97
SG <70 (%)	0.02	0.02	0.02	0.02
SG >180 (%) * §	0.30	0.34	0.32	0.29
Subjects with SH Episode(s)	0	0	0	0

Table 2. Highest A1C Quartile (A1C >8.2%, n=16)

Attribute	Q1	Q2	Q3	Q4
TDD/kg §	0.86	0.92	0.98	0.95
Basal/TDD (%)	0.44	0.46	0.44	0.44
Daily Number of Boluses * §	5.28	4.51	4.69	4.48
Mean Bolus (U) * §	5.25	6.25	7.01	7.68
SG <70 (%)	0.03	0.04	0.04	0.02
SG >180 (%) * §	0.42	0.48	0.48	0.49
Subjects with SH Episode(s)	1	0	2	1

*P<0.05 for high vs. low A1C quartile, overall (Q1-Q4) §P<0.05 for high vs. low A1C quartile, Q4

Supported by: Medtronic, Inc.

931-P

Insulin-Pump Treatment Improves Metabolic Control but Does Not Reduce the Risk of Hospitalization Associated with Acute Complications among Pediatric Patients with Type 1 Diabetes

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Treatment with continuous subcutaneous insulin infusion (CSII) is becoming gradually more popular in children with diabetes. The authors performed a longitudinal observation study assessing the clinical impact of CSII treatment on metabolic control rate and risk of hospitalization due to acute complications of diabetes. The study was performed in a single, pediatric diabetology center over a 10-year period. Initiation of CSII treatment was based on individual decision of the physician. Patients were matched for age and duration of diabetes with the next patient treated with multiple dose injection (MDI). Individual time to hospitalization due to acute complications of diabetes was recorded. Metabolic control was assessed using mean HbA1c. Complete records of 2978 hospital visits of 476 patients were available (239 on MDI and 247 on CSII). Acute visits constituted 15.8% of all hospitalizations (N=461). Median (25-75%) observation time equaled 2 (0.95-3.32) years. Over the analyzed period, the percentage of CSII-treated patients increased steadily from 5.6% in 2000 to 51.4% in 2010. CSII was associated with lower mean HbA1c adjusted for sex and diabetes duration than MDI (7.69+/-1.33 vs. 8.07+/-1.60; p=0.004). Risk of acute hospitalization was similar in both groups (log-rank test p=0.9). In Cox regression model, only HbA1c level remained a significant predictor of acute hospitalization (HR=1.20 95%CI 1.05-1.37 per 1%; p=0.007), with duration of diabetes (p=0.9), sex (p=0.5) and mode of treatment (p=0.6) non-significant. Rate of acute hospitalizations equaled 7.1 in MDI and 7.5 per 100 patient-years in the CSII group (Odds ratio 0.95 95%CI 0.61-1.46). Median (25-75%) duration of hospital stay was shorter in CSII than in MDI group but the difference was not statistically significant: 6 (4-8) vs 7 (3-10) days; p=0.10 with an observed statistical power level of 26%. Concluding, it seems that although CSII treatment does contribute towards significantly lower glycated hemoglobin level, but does not protect pediatric patients with type 1 diabetes from acute complications better than MDI treatment.

932-P

Intensive Insulin Therapy for ICU Patients Using Particle Swarm Intelligence and Predictive Power

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Good glycemic control for ICU patients can reduce the death rate significantly; however, it remains a big challenge because of scarcity of individualized models. To deal with this challenge, a novel approach has been proposed by integrating Particle Swarm Optimization (PSO) into Model Predictive Control (MPC) to indentify the model on-line as well as to design the insulin delivery rate automatically.

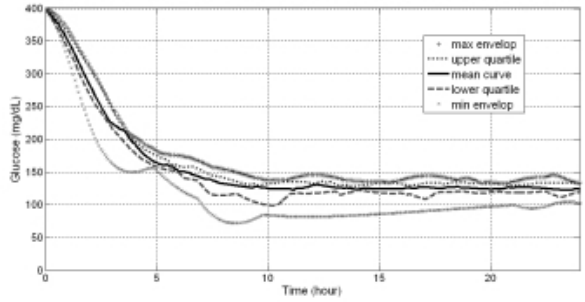
According to the population distribution, ten typical linear dynamic models have been selected and one patient's model could be considered a linear combination of these ten basic models. PSO is used to update the coefficients for the combination every five min, and while MPC is used to design the insulin delivery rate every thirty min based on this combination model from PSO.

Sampling from a multivariate log-normal distribution, 15 virtual subjects based on the Dalla Man et al 2007 model are generated and the proposed method is evaluated on these subjects. All subjects follow a 24-h protocol with the same initial glucose value of 400 mg/dL. As shown in the following figure, the glucose level could be controlled under 200 mg/dL in less than 4 h for all subjects. After 10 hours, glucose concentrations are between 80

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

and 150 mg/dL for all subjects. No hypoglycemia event occur during the 24-h intensive glycemic control trial.



As a model-free full closed-loop method, this novel combination can control the glucose level into a safety range promptly and hence could reduce the risk of death. Due to its simplicity and effectiveness, the proposed method can be an excellent candidate for intensive glycemic control in ICU.

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933-P

No Cardiac Effects Found with Therapeutic and Supratherapeutic Doses of Technosphere® Inhalation Powder: Results from a Thorough QTc Clinical Study

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The cardiac effect of Technosphere Inhalation Powder (TIP), the particle component of Technosphere Insulin Inhalation Powder (Afrezza®), was assessed in a randomized, 4-period crossover, double-blind, double-dummy, placebo- and active-controlled cardiac safety study. Healthy men (n=26) and women (n=22), confined to the clinical unit for 12 days, were dosed with inhaled 40 mg TIP, 20 mg TIP, placebo, and oral 400 mg moxifloxacin ([moxi], active control) in a randomized sequence (3-day interdose washout period).

ECGs were obtained digitally from supine resting subjects for each treatment at: 45, 30, and 15 mins before each dose, and at 5, 10, 15, 20, and 30 mins and 1, 2, 3, 4, 8, 12, and 23 hrs after each dose. ECGs (including QTcI, QTcB, QTcF, QT, PR, QRS, and HR) were read and assessed centrally by ECG core laboratory personnel who were blinded to subject treatment and time. Safety was appraised by evaluation of adverse events (AEs), clinical laboratory values, physical exams, vital signs, 12-lead ECGs, and pulmonary function tests.

The upper 95% confidence bound (1-sided) of the time-matched analysis of the placebo-corrected mean QTcI change from baseline (the primary objective) was well below the 10-ms threshold at all times in both TIP groups. The moxi group met the assay sensitivity criteria (i.e., mean difference of moxi and placebo >5 ms) at 7 time points. Time-averaged analysis of the placebo-corrected mean QTcI change from baseline for TIP showed no significant effect on QTc (-0.5 ms and -0.3 ms for the 20- and 40-mg TIP doses, respectively). The placebo-corrected mean QTcI change from baseline for moxi was +5.5 ms (expected, +5 ms to +10 ms), and the mean change from baseline for placebo was -2.2 ms. The predominant treatment-related AE was cough (54%), which was highest in the TIP groups. Other safety assessments were unremarkable.

This study showed that inhaled TIP did not produce clinically significant effects on heart rate, PR and QRS interval duration, or cardiac morphology. The data also showed that TIP did not affect cardiac repolarization.

Supported by: MannKind Corporation

934-P

Novel Methodology To Determine the Accuracy of Insulin Pumps—Key Components of the Artificial Pancreas System—Illustrated by an Accuracy Analysis of the OmniPod Insulin Pump

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Two new methods were developed to measure the accuracy of insulin pumps controlled automatically by the Artificial Pancreas System (APS©). The APS© enables closed-loop glucose control by automating the communication between a glucose sensor, controller/algorithm, human user interface & an insulin pump. During discussions with the FDA, the Agency requested to re-confirm the accuracy of the FDA approved OmniPod as an integral part of the APS©. The results from this testing illustrate the proposed method:

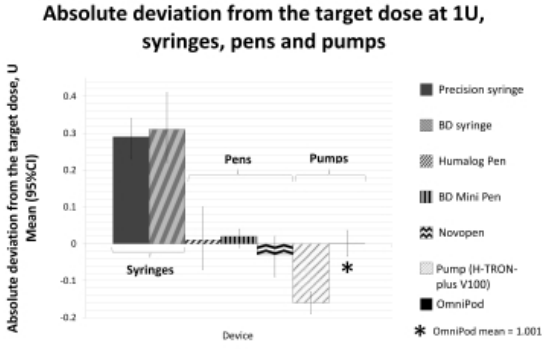
Method 1:we used five OmniPods, a 100uL pipette, digital microscope and imaging software to measure the average bolus delivery on a linear scale for volumes 0.05, 0.1, 0.2, 1 and 6 units (U). The FDA requested further confirmation of the accuracy the minimal delivery dose.

Method 2:two OmniPods, a digital microscope and imaging software were used to measure the volume of a spherical bolus of 0.05U of insulin. (Volume = $4/3\pi r^3$)

Method1: At the target bolus dose of 0.05U the mean delivered dose +/- SD was 0.0497 +/- 0.003U. At 0.1U - 0.0991 +/- 0.005U; at 0.2U - 0.2 +/-0U; at 1U - 1.001 +/- 0.0179U; at 6U - 6.029 +/- 0.037U.

Method 2:At the target bolus dose of 0.05 U, the mean delivered dose +/-SD was 0.05049 +/- 0.0014U. The bench testing results using the two novel methods demonstrated that the OmniPod had a relative error ranging from -0.90% to +0.96% for all measured doses (0.05, 0.1, 0.2, 1, 6U). We also compared accuracy of the OmniPod pump with other insulin injection devices using data acquired by Keith et al (2004).

New assessment methods allow for testing the accuracy of automated insulin delivery and reduce the influence of measurement/human errors. Both methods confirmed a high degree of accuracy for the OmniPod insulin pump, in absolute terms and as compared to other devices.



Supported by: JDRF

935-P

Nursing Satisfaction Survey and Infection Rate Results from Conversion of Insulin Vials to Pens in a Hospital Setting

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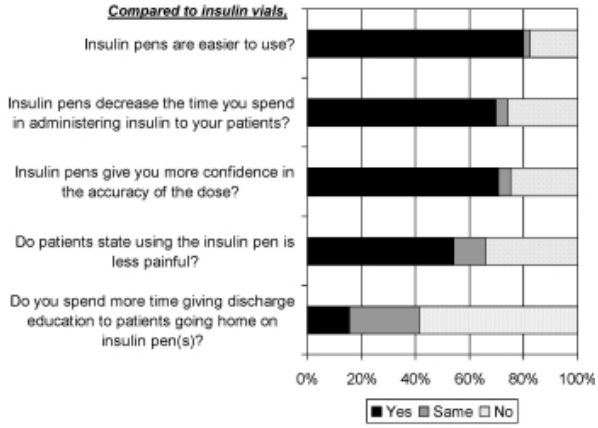
In an effort to reduce potential insulin errors, increase safety, decrease nursing time, and attain tighter glycemic control, TriCity Medical Center (TCMC), a 397-bed community hospital, converted from the use of insulin vials to insulin pens and safety needles in February 2009. Two distinct pens, insulin glargine (Lantus SoloStar®) and insulin lispro (Humalog Kwikpen®) and a single use safety needle (BD Autoshield™) were used. To ensure conversion success, we obtained hospital-wide approval, utilized an overseeing multi-disciplinary Diabetes Task Force, and implemented a comprehensive nursing and hospitalist education program. Bar-coding of the pens were used to ensure the "one patient, one pen match up" rule. One year post-implemenation, a survey was completed by 109 nurses throughout the hospital. The results showed the majority of nurses felt that compared to insulin vials, the pens were easier to use, decreased in nursing time, improved insulin dosing accuracy, reported patients experiencing less injection pain, and decreased discharge education time. Infection rates were evaluated for 1st Quarter 2008 (1Q08) vs. 1st Quarter 2010 (1Q10). For 1Q08 vs. 1Q10, ventilator associated pneumonia was 2.4 vs. 1.0 per 1000 ventilator days; central line associated bloodstream infection was 4.5 vs 1.9 infections per 1000 central line days; and cardiac surgical site infection was 4.3 vs. 1.6

infections per 100 surgeries, respectively. The decrease in infection rates may be attributable to the fact that pen conversion has enhanced the use of our insulin protocols, which may help to minimize insulin errors and provide better overall glycemic control. We feel that conversion to insulin pens has improved the safety of insulin delivery to our hospitalized patients, nursing satisfaction, and overall glycemic control.



936-P

Piloting a Novel Algorithm for Glucose Control in the Coronary Care Unit: The RECREATE (REsearching Coronary REduction by Appropriately Targeting Euglycemia) Trial

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Elevated glucose levels are commonly noted in patients with an acute myocardial infarction (AMI) and are a risk factor for subsequent mortality. A variety of glucose lowering approaches in this population have achieved variable glucose levels and have yielded mixed effects on mortality. We developed a standard, simple, paper-based glucose lowering algorithm and assessed its feasibility and safety in the setting of AMI in an international multicentre randomized controlled trial.

287 participants who presented to hospital with an acute ST segment MI (STEMI) and a capillary glucose level ≥ 8.0 mmol/L were randomly allocated to glucose management with intravenous glulisine (Apidra) insulin using this paper-based algorithm in the coronary care unit (CCU), followed by once daily subcutaneous insulin glargine (Lantus) for 30 days versus locally-defined standard approaches to glucose management. The primary outcome was a difference in mean glucose levels at 24 hours. Participants were followed for clinical outcomes through 90 days.

There were no differences in baseline characteristics or AMI therapies. At 24 hours, the mean glucose level was 1.41 mmol/L (95% CI 0.69, 2.13) lower in the insulin arm compared with the standard therapy arm. Differences in lower glucose levels were maintained at 72 hours and 30 days. There were no differences in hypoglycemia or clinical outcomes between the groups.

The RECREATE pilot study demonstrates that a simple paper-based insulin algorithm can be safely and effectively used to target euglycemia following acute STEMI with minimal hypoglycemia. The RECREATE intravenous insulin algorithm was broadly applicable and easy to implement in this international trial. It is therefore feasible to test this approach globally in a wide variety of clinical settings.

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937-P

Proinsulin-Transferrin Fusion Protein as a Potential Prodrug for Sustained Release of an Active Form of Insulin

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Purpose. The therapeutic potential of proinsulin (ProINS), the single-chain precursor to insulin (INS), has been evaluated in clinical trials. However, due to the low conversion efficiency to INS and low activity of ProINS compared to INS, high doses were required to achieve a biological effect which led to side effects, including myocardial infarction, and withdrawal from clinical trials. The purpose of our studies was to produce and characterize ProINS as a transferrin (Tf) fusion protein in order to make a sustained delivery therapeutic agent.

Methods. His-tagged ProINS-Tf was expressed in HEK293 cells and purified using a Ni-NTA column. Hepatic glucose output assays were performed in rat hepatoma H4IIE cells following 24h treatment. Human ProINS- and INS-specific radioimmunoassay (RIA) was used to quantify concentrations of ProINS-Tf and of converted INS-Tf, respectively, in the *in vitro* cell culture medium. ProINS-Tf and converted INS-Tf was also quantified by RIA in plasma samples following i.v. injection of ProINS-Tf to CF-1 mice *in vivo*.

Results. ProINS-Tf exerted a ~24- and ~6-fold stronger activity (IC_{50}= 52.1±8.48 pM) than ProINS (IC_{50}=1291.3±148.5 pM) and INS (IC_{50}=308.9±19.7 pM), respectively, in inhibiting hepatic glucose production in H4IIE cells. No increased activities were observed when treating cells with equimolar ProINS and Tf as separate proteins. The increased activity was blocked by addition of 1000-fold excess Tf. Following incubation of ProINS-Tf with H4IIE cells, an increase of INS-Tf in the medium was measured using INS-specific RIA, which corresponded with a decrease of ProINS-Tf using ProINS-specific RIA. This conversion to INS-Tf was also blocked by excess Tf. Furthermore, *in vivo* conversion of ProINS-Tf to INS-Tf was observed following i.v. injection of ProINS-Tf in mice.

Conclusion. The conversion and activation of ProINS-Tf to INS-Tf in hepatoma cells suggest the potential of using ProINS-Tf as a hepato-specific hypoglycemic agent. The advantages of ProINS-Tf fusion protein would be the increased plasma half-life due to Tf, and sustained Tf-mediated activation of ProINS-Tf to its active form.

Supported by: NIH Grant GM063647

938-P

The Efficacy and Safety of Basal Insulin in Diabetes Mellitus: A Systematic Review

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Insulin glargine, detemir, and NPH were commonly used as basal insulin in the treatment of diabetes mellitus. However, the advantages and disadvantages of them remain disputable. In order to investigate the efficacy and safety of the 3 kind of insulin and insulin analogues, we collected prospective randomized control trials to compare the different basal insulin in CCTR (2010, issue 4), MEDLINE (1950-2010) and EMBase (1950-2010). Eighteen clinical trials were finally included for a meta-analysis. No significant difference was found between different insulin or insulin analogues in the change of HbA1c from the baseline (glargine versus NPH, overall MD 0.03, 95%CI -0.14~0.21, P=0.69; detemir versus glargine, overall MD 0.04, 95% CI -0.23~0.32, P=0.75; detemir versus NPH, overall MD 0.15, 95%CI -0.02~0.31, P=0.09) and achieving HbA1c≤7.0% rate. Compared with glargine and NPH, insulin determir was associated with relatively lower body weight gain (detemir versus glargine, overall MD -0.43, 95% CI -0.85~0.00, P=0.05; detemir versus NPH, overall MD -0.62, 95%CI -0.66~-0.58, P<0.00001; glargine versus NPH, overall MD -0.44, 95%CI -1.20~0.32, P=0.26). Compared with NPH, insulin glargine, but not determir showed a lower incidence of all hypoglycemia (glargine versus NPH, overall RR0.88, 95%CI 0.80~0.96, P=0.005; detemir versus NPH, overall RR 1.31, 95%CI 0.86~2.01, P=0.21; detemir versus glargine, overall RR 0.98, 95% CI 0.93~1.04, P=0.54), severe hypoglycemia, and nocturnal hypoglycemia events. The final dose of insulin detemir was significant higher than glargine, but not NPH (detemir versus glargine, overall MD 0.11, 95%CI 0.07~0.14, P<0.00001; glargine versus NPH, overall MD 0.09, 95%CI -3.78~3.96, P=0.96; detemir versus NPH, overall MD -2.61, 95%CI -27.11~21.89, P=0.83). In conclusion, the efficiencies of different basal insulin are not of significant difference. However, insulin detemir is distinguished by less body weight gain, but relatively higher insulin dose. Meanwhile, compared with NPH, insulin glargine is associated with lower incidence of hypoglycemia.

939-P

Tight Blood Glucose Control Algorithm for T1DM Based on Disease Dynamics

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An optimally controlled insulin pump can improve insulin therapy by more closely maintaining normoglycemia. Thus the control algorithm to calculate the necessary insulin dose and automate infusion is key to minimizing the short and long and term complications and morbidity of T1DM.

Several control algorithms reported in the literature are "patient-oriented"; meaning that the algorithm must be tailored to work for a specific patient. Patient parameter identification is expensive and time consuming. Uncertainties due to rapid changes during stress and patient habit changes

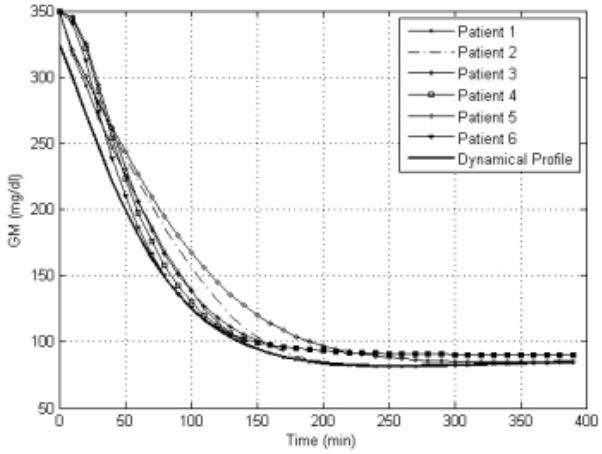
For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

present a 10-30% risk of insulin overdose and hypoglycemia for algorithms like PID or MPC.

This research focuses on a "disease-oriented" algorithm. The natural dynamics of glucose regulation is the only parameter needed to design a High Order Sliding Mode Control Algorithm (HOSMCA). It works based on glucose measurements (GM) from an amperometric sensor, with as much as 5 min sample time. This feature makes the algorithm patient independent. To avoid risk of hypoglycemia, HOSMCA designs an adaptive glucose dynamic profile (DP) based on response to the maximal GM. It regulates the velocity of lowering glucose via optimally minimal insulin dosage. DP can be adjusted to any physician specifications for patient.

In a test of HOSMCA, using 2 different mathematical models to generate *in silico patients (SP);* Bergman Minimal, and Sorensen Models, 6 different SP's were simulated with varying insulin resistance from 0.8 to 10.2 min^{-1}per mU/l. These simulations lasted 400 minutes, and represent postprandial episodes where GM starts at 350 mg/dl. GM for every patient was under 120mg/dl at minute 150 without any hypoglycemic episodes. The realities of pump dynamics and sensor sample rate are considered so that this same system may be used for testing with patients in a clinical/ambulatory setting.



HOSMCA's patient independent GM lowering profiles are essential equivalet in six models using insulin resistance varying from 0.8 to 10.2 min-1per mU/l .

940-P

Treatment Satisfaction in Adults with Type 1 Diabetes Using Mealtime Inhaled Technosphere® Insulin (Afrezza®) in Combination with Insulin Glargine (Lantus®) Versus Insulin Lispro (Humalog®) in Combination with Glargine

RICHARD E. PETRUCCI, MARK PEYROT, RICHARD R. RUBIN, *Valencia, CA, Baltimore, MD*

In this 16-week, randomized, multicenter study, adults with type 1 diabetes used mealtime inhaled Technosphere® Insulin (Afrezza®) in combination with insulin glargine (Lantus®; TI+G; n=61) or insulin lispro (Humalog®) in combination with insulin glargine (L+G; n=65). Secondary study endpoints included Inhaled Insulin Treatment Questionnaire (IITQ) measures of diabetes worries, perceptions of insulin therapy, treatment satisfaction, and treatment preference. Intent-to-treat analysis used mixed models to estimate differences in mean group changes in IITQ scores PRO from baseline to week 16 (adjusted for baseline scores); *t*-tests assessed within-group changes at week 16.

Diabetes worries and treatment preference did not change significantly from baseline to week 16 in either treatment group, with no significant difference between groups in change from baseline. Treatment satisfaction increased significantly in both groups (P<0.05), with no significant difference between groups in change from baseline. Perceptions of insulin therapy improved significantly in the TI+G group only (P<0.001), with greater improvement in the TI+G group than in the L+G group (P<0.002). Insulin perception subscales for convenience, comfort, and ease of regimen adherence showed significant (P<0.01) improvement in the TI+G group, with greater improvement than in the L+G group (P<0.05). In the TI+G group, improvement in treatment satisfaction was significantly (P<0.01) associated with improvement in convenience, comfort, and ease of regimen adherence.

The findings indicate that, compared with patients using injected rapid-acting insulin for mealtime boluses, those using TI for mealtime boluses came to see insulin therapy more positively (more convenient, more comfortable or less painful, easier to adhere to regimen) during the course of the study.

Supported by: MannKind Corporation

941-P

Treat-to-Target Technosphere® Insulin in Patients with Type 1 Diabetes

SATISH K. GARG, WILLIAM C. KELLY, BRANDON J. FRESON, RICHARD E. PETRUCCI, PETER J. RITCHIE, *Aurora, CO, Valencia, CA*

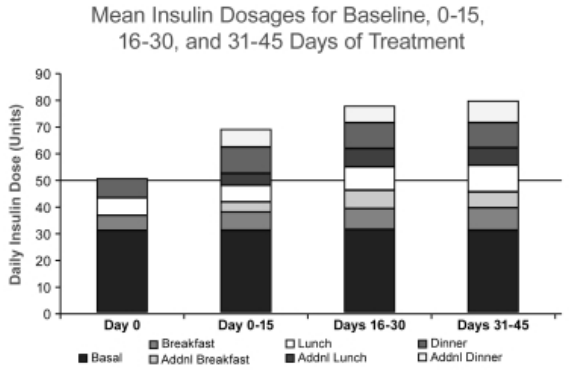
Technosphere Insulin (TI [Afrezza®]) is an ultra rapid acting inhaled insulin reaching maximum blood concentration within 15 mins and results in rapid glucose lowering with a short duration of action (~2-3 hrs).

This single-arm, open-label, treat-to-target pilot study was designed to examine the effects of TI on A1C, postprandial glucose control, and daily insulin requirements in 15 patients with T1DM over 45 days. The study consisted of 4 visits, at 0, 15, 30, and 45 days. All patients were on intensive insulin treatment and wore a continuous glucose monitor (CGM) with real-time display. Patients were instructed to take a second dose of TI if blood glucose (BG) was ≥180 mg/dl 2 hrs after meals.

Baseline patient demographics were mean age 38.3 yrs, diabetes duration 20.1 yrs, BMI 26.4 kg/m^2, total daily insulin dose 52.1 U (basal insulin 31.1 IU, prandial insulin 21.0 U [5.5, 6.3, and 6.7 U at breakfast, lunch, and dinner]); 67% of patients were on insulin pumps and 33% were on multi-dose insulin.

Final mean mealtime TI doses were 8.6, 9.8, and 9.6 U (breakfast, lunch, and dinner). During the study, the mean basal insulin dose remained the same. A second supplemental dose of TI was taken 37.7% of the times 90-120 mins after meals (39% between days 0-15; 36% between days 16-30; 34.6% between days 31-45). Mean supplemental doses at day 45 were 5.9, 6.6, and 7.9 U (Figure). Prandial TI doses increased during the first 30 days before stabilizing. A1C values decreased from 7.86% to 7.47% during the study. There were no changes in CGM values with regard to percent of time with CGM values below, above, and within target range of 60-150 mg/dl.

Supplemental TI improved glucose control in T1DM patients without any increase in time spent with BG <60 mg/dl. A randomized study involving larger numbers of patients is needed.



Mean basal dose remained ~ 31 U/day throughout the study. Bolus dose increased 2 fold through day 15 and 2.5 fold through days 31-45. Premeal TI dose remained similar with an increase of ~30 TI postprandially (Addnl Bolus). Subjects advised to take Addnl Bolus at 2 hours postmeal if SMBG >180 mg.

Supported by: MannKind Corporation

942-P

Usefulness of Insulin Glargine in Japanese Hemodialysis Patients with Diabetic Nephropathy

EITARO TANAKA, MASAO TOYODA, HIROKI SATO, MASAAKI MIYAUCHI, TOMOYA UMEZONO, DAISUKE SUZUKI, *Isehara, Japan*

Since insulin glargine (a recombinant insulin) has no distinct peak hypoglycemic effect, improvement of QOL and a decrease in the frequency of hypoglycemic episodes can be expected by switching hemodialysis patients from NPH to insulin glargine. Therefore, the purpose of this study was to examine the outcome when Japanese hemodialysis patients with diabetic nephropathy were switched from NPH to insulin glargine, and to investigate the efficacy of insulin glargine.

In hemodialysis patients who were on treatment with basal-bolus therapy with NPH or pre-mixed insulin therapy, therapy was switched from neutral protamine hagedorn insulin (NPH)NPH or the pre-mixed preparation to insulin glargine. Changes of HbA_1c, the daily insulin dose, and the frequency

of hypoglycemic episodes were examined by comparison between the time of switching and 3 months later.At 3 months after switching, there was significant improvement of HbA_1c compared with the level at the time of switching (HbA_1c7.1±1.0%→HbA_1c6.3±0.7%, p=0.0013), while there was no significant change of the daily insulin dose. The frequency of hypoglycemic episodes also showed a statistically significant decrease.It is possible for insulin glargine to improve HbA_1c without increasing the frequency of hypoglycemic episodes in Japanese hemodialysis patients with diabetic nephropathy if it is used appropriately. This leads to better QOL as well as safer/more favorable glycemic control. It may be necessary to conduct a similar comparative study in Western patients who have different levels of dietary carbohydrate intake and other differences from Japanese patients.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—PHARMACOLOGIC TREATMENT OF DIABETES OR ITS COMPLICATIONS

[***See also: Presidents Posters 408-PP to 416-PP, page A113.***]

Guided Audio Tour: Pharmacologic Treatment of Diabetes—Clinical Diabetes *(Posters 943-P to 950-P), see page 15.*

943-P

Estrogen Prevents Pioglitazone-Induced Apoptosis in Osteoblasts

HUI SHENG, JINGJING QU, BEI XU, WENJUN LI, CHUNJUN SHENG, XIAOYUN CHENG, YONGCHUN YU, G.E. ZHANG, LING QIN, SHEN QU, *Shanghai, China, Hong Kong, China*

Thiazolidinediones (TZDs), as insulin sensitizers, are used in clinics for type 2 diabetes patients. Recent studies showed that TZDs exert bone damage, which is characterized by inhibiting bone formation. Our previous studies showed that TZDs induced osteoblasts apoptosis *in vitro* and *in vivo* models, indicating that osteoblasts apoptosis is one of the important mechanisms in this pathophysiology. Clinical data showed older diabetic women are more susceptible to TZDs-induced bone loss, implying estrogen may have protective effects. This study aims to investigate the effects of estrogen on pioglitazone-induced osteoblasts apoptosis.

Primary rat calvaria osteoblasts and mice MC3T3-E1 osteoblasts were used and treated by 17β-estradiol and pioglitazone hydrochloride (Pio). Osteoblasts apoptosis was tested by flow cytometry and Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. Glycogen synthase kinase 3beta (GSK3β) was assayed by Western blot. siRNA for GSK3 β were used for underlying mechanism exploration.

Pio induced osteoblasts apoptosis in a dose-dependent manner, and the apoptosis rate increased from 4.5% in control group to 12.2%, 18.2%, 25.5%, in 5uM, 10uM and 20uM Pio- treated groups. Simultaneous treatment with Pio and 17β-estradiol prevented ostoeblasts apoptosis, the apoptosis rate decreased to 15%, 10.4%, and 6% after 17β-estradiol treatment (0.001nM, 0.01nM, 0.1nM) in 10uM Pio group. Western blot results showed that Pio induced osteoblasts apoptosis with activation of GSK3β, and 17β-estradiol addition reduced the activity of GSK3β. siRNA for GSK3β could also improve Pio-induced osteoblasts apoptosis. The similar results were also confirmed in primary rat ostoeblasts.

Estrogen could prevent Pio-induced osteoblasts apoptosis *in vitro* study. GSK3β plays an important role in Pio-induced osteoblasts apoptosis. This study could at least partly explain the clinical observation that older diabetic women are more susceptible to TZDs-induced bone loss.

Supported by: Pujiang Program (09PJ1410300,10PJ1408400) and NSFC (30900698,81070238)

944-P

Combination Treatment with Metformin and Statins Shows Enhanced Effect on Reducing Risk for Prostate Cancer

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Treatment with metformin (METF) and statins have shown promise for cancer prevention trials. This study compared prostate cancer (PCa) risk associated with METF and sulfonylureas (SU), two predominating hypoglycemic agents in patients with T2DM in the Veteran Administration Health Care System (VAHCS). Further, to better inform future trial design, whether the effect of METF on PCa incidence was modified by statin use was examined. The study cohort consisted of 5042 male patients seen in VAHCS who were diagnosed for T2DM, without cancer diagnosed prior to the baseline, prescribed with either METF or SU as the exclusive hypoglycemic medication for ≥180 days between FY1999-FY2005, and with no missing baseline covariates. Mean follow-up was ~ 5 yrs. Cox proportional hazard analyses were conducted to assess the hazard ratio (HR) of PCa incidence due to METF and/or statins, where propensity scores of METF and statin use were adjusted as inverse probability weights to account for imbalance in baseline covariates across medication groups. All variables associated with PCa (age, race/ethnicity, comorbidity, smoking, BMI, HbA1C, LDL and duration of diabetes) were accounted for.

	HR	p-val		HR
METF (no statin)	1.58	<0.0001	METF (with statin)	0.78
Statin (no METF)	0.54	<0.0001	Statin (with METF)	0.27
Interaction (METF and Statin)	0.49	<0.0001		

We explored mechanisms and dose effects of METF and statins. Higher mean LDL was associated with increased PCa incidence. A longer proportion of time on higher doses of statins was correlated with reduced PCa incidence. METF max daily dose >1000mg was assoc with lower PCa incidence (HR .45, p=0.0004). Higher baseline HbA1C was associated with decreased risk of PCa.This apparent paradox may reflect the possibility that subjects with greater insulin resistance benefit more from METFstatins or have lower androgen levels. In summary, in the diabetic population with high prevalence of dyslipidemia, the effect of METF and statin use on PCa incidence may be enhanced by one another. The independent effect of METF requires further investigation including accounting for dose, and metabolic and hormonal characteristics.

945-P

The Effects of Glycaemic and Cardiovascular Risk Therapy on Clot Structure and Fibrinolysis in Subjects with Type 2 Diabetes

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Subjects with diabetes have denser fibrin networks with increased resistance to fibrinolysis, representing one mechanism for increased atherothrombosis risk in this population. Although therapeutic agents can affect clot structure, no studies have been conducted to investigate this in diabetes. We analysed, for the first time, the effects of various therapies on clot structure and fibrinolysis in subjects with diabetes.

Clot structure was assessed in 875 participants of the Edinburgh Diabetes Study (mean age 68±0.3 years, 450 males) using a dynamic turbidimetric assay. We report clot final turbidity (FT), a measure of clot density, clot formation time, a predictor of ischemic events and fibrinolysis speed, an indicator of lysis potential.

Insulin treatment in men was associated with higher FT compared with subjects not on this treatment (0.38±0.02 and 0.33±0.005 au, respectively; p<0.05), whereas statin therapy caused reduced FT (0.35±0.008 and 0.39±0.02 au, respectively; p<0.05). Women on metformin with no ischemic history had quicker clot lysis than subjects not on this therapy (838±33 and 751±28 sec, respectively; p<0.05), and antiplatelet therapy was associated with enhanced clot formation time (610±19 and 718±63 sec, respectively; p<0.05). Metformin and antiplatelet therapy had no effect on clot structure parameters in men.

In multivariable analysis, both metformin and antiplatelet treatment were associated with a less thrombotic fibrin network in women. In men, however, insulin therapy had a deleterious effect on clot structure with the reverse evident in those taking statins, further confirming our findings.

In conclusion, a less thrombotic clot structure is observed with metformin therapy in women and statin use in men, contributing to the cardioprotective properties of these agents. In contrast, insulin treatment is associated with deleterious effects on clot structure in men only, consistent with higher risk of ischemic events in insulin-treated subjects. This study shows gender differences in the interactions between fibrin structure and various therapies in diabetes, which may have future clinical implications.

946-P

Pioglitazone Treatment Reduces Myocardial Steatosis and Prevents Diabetic Cardiomyopathy in Diabetic Mice

DESIREE ABDURRACHIM, KLAAS NICOLAY, JEANINE J. PROMPERS, *Eindhoven, The Netherlands*

Myocardial triglyceride (MTG) accumulation is thought to contribute to the development of diabetic cardiomyopathy (DCM). The effect of pioglitazone on controlling DCM is still not clear. In this study, we investigated the effect of pioglitazone on MTG levels and cardiac function in a diabetic mice using magnetic resonance spectroscopy and imaging, respectively.

Measurements were performed in db/db mice (n=9) and control db/+ mice (n=8) at 7 and 13 weeks. After measurements at 7 weeks, 4 db/db mice

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

were treated with pioglitazone (37.4±3.1 mg/kg/day) admixed in chow for 6 weeks. Systolic and diastolic cardiac function were determined from the left ventricular ejection fraction (EF) and peak filling rate (PFR), respectively.

At 7 weeks, db/db mice were hyperglycemic compared with controls, while plasma TG levels were similar. MTG levels were higher in db/db mice (Fig. 1), while EF and PFR were still normal (Fig. 2). At 13 weeks, plasma glucose was further elevated in untreated db/db mice and plasma TG was also higher than in controls. MTG content remained higher than in controls and was accompanied with a decrease in PFR, while EF was unaltered. In pioglitazone-treated db/db mice, blood glucose and plasma TG levels were significantly lower than in untreated db/db mice. MTG levels were significantly reduced, while PFR remained normal.

Our findings suggest that pioglitazone treatment in an early stage of diabetes prevents the development of DCM, possibly by reducing lipotoxic effects by diverting fatty acids to adipose tissue.

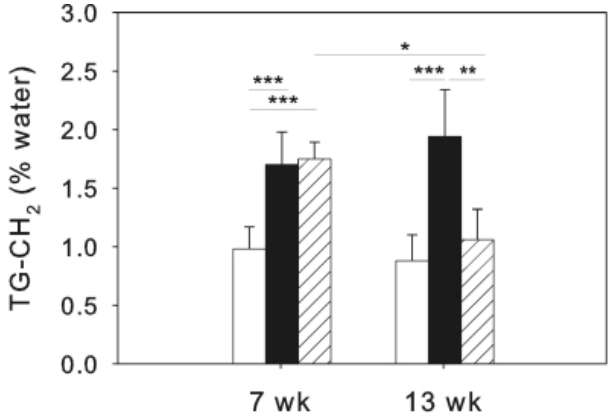

Figure 1. Myocardial TG (MTG) levels (white bars: db/+, black bars: untreated db/db, hashed bars: pioglitazone-treated db/db; *p<0.05, **p<0.01, ***p < 0.001).

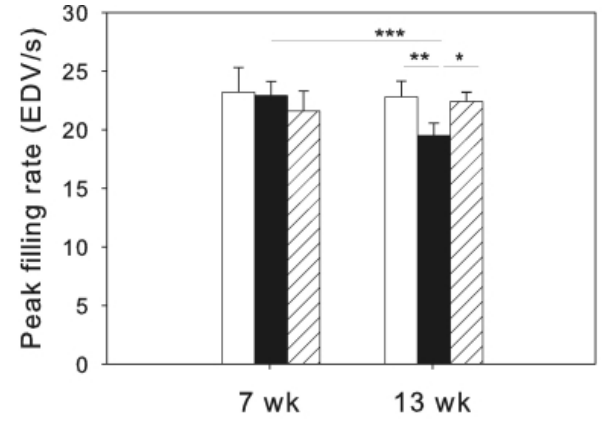

Figure 2. Peak filling rate (PFR) (white bars: db/+, black bars: untreated db/db, hashed bars: pioglitazone-treated db/db; *p<0.05, **p<0.01, ***p < 0.001).

947-P

Efficacy of an Amlodipine/Olmesartan Medoxomil Algorithm on BP Control in Patients (Pts) with Type 2 Diabetes Mellitus (T2DM) and Hypertension Uncontrolled on Previous Antihypertensive Monotherapy

SHAWNA D. NESBITT, THOMAS W. LITTLEJOHN, ALI SHOJAEE, JEN-FUE MAA, *Dallas, TX, Winston-Salem, NC, Parsippany, NJ*

A prespecified subgroup analysis was conducted of pts with T2DM in a prospective, open-label dose-titration study assessing the efficacy of an amlodipine/olmesartan medoxomil (AML/OM) regimen in pts uncontrolled on antihypertensive monotherapy (SBP ≥140 mmHg [≥130 mmHg for pts with T2DM] and ≤180 mmHg; DBP ≤110 mmHg). Without washout, pts started on AML/OM 5/20 mg and up-titrated every 4 weeks (wks) for 20 wks to AML/OM 5/40 mg, AML/OM 10/40 mg (to achieve seated (Se)BP <120/70 mmHg), AML/OM 10/40+ hydrochlorothiazide (HCTZ) 12.5 mg and AML/OM 10/40+HCTZ 25 mg (to achieve SeBP <125/75 mmHg). The primary efficacy endpoint was the cumulative percent of pts achieving SeSBP goal <140 mmHg (<130 mmHg for pts with T2DM) by Wk 12. Of 999 pts, 192 (19.2%) had T2DM with mean (±SD) baseline $HbA1_c$ of 6.8±0.8%. The primary endpoint was achieved by 57.9% of pts with T2DM and by 80.1% of pts without T2DM. Other BP goals and mean SeBP changes from baseline in Table.

	Baseline SeBP (±SD; mmHg)	Mean Change (±SE) in SeBP at Wk 12 (mmHg)	Patients Achieving SeBP Goal* by Wk 12 (%)	Mean Change (±SE) in SeBP at Wk 20 (mm Hg)	Patients Achieving SeBP Goal* by Wk 20 (%)
With T2DM	150.8±11.3/89.1±8.9	-20.8±1.1/ -11.6±0.5	50.0	-24.2±1.2/ -13.1±0.7	65.3
Without T2DM	154.3±8.5/92.6±8.4	-22.0±0.5/ -12.0±0.3	76.4	-27.4±0.6/ -14.8±0.4	89.4

*Cumulative goal <140/90 mmHg (<130/80 mmHg T2DM). *P*<0.0001: all SeBP changes vs baseline

An ABPM substudy showed that BP reductions were maintained throughout the 24-hr dosing interval. Treatment emergent adverse events (TEAEs) occurred in 100/192 (52.1%) and drug-related (DR) TEAEs in 47/192 (24.5%) of T2DM pts.TEAEs occurred in 429/807 (53.2%) and DR-TEAEs in 208/807 (25.8%) of pts without T2DM. The majority of TEAEs were mild-to-moderate. This well-tolerated, treat to goal treatment algorithm allowed a large percentage of patients with T2DM and hypertension uncontrolled on monotherapy to safely achieve BP control by Wk 12 and 20.

Supported by: Daiichi Sankyo, Inc.

948-P

Pharmacodynamics of Basal Insulins NPH, Glargine and Detemir in Type 2 Diabetes Mellitus: Effects of Adiposity

FRANCESCA PORCELLATI, PAOLA LUCIDI, PAOLO ROSSETTI, PAOLA CANDELORO, ANNA MARINELLI ANDREOLI, PATRIZIA CIOLI, RAFFAELA FEDE, GEREMIA B. BOLLI, CARMINE G. FANELLI, *Perugia, Italy*

The role of adiposity of Type 2 diabetes (T2DM) on pharmacodynamics (PD) of basal insulins NPH, detemir (Det) and glargine (Gla) is not known. To examine the question, we studied the relationship between PD and body mass index (BMI), in 18 subjects with Type 2 diabetes (age 60±7 yrs, BMI 29.1±3.2 kg/m^2, A1C 7.5±0.6%, treatment insulin±oral hypoglycemic agents [mean±SD]). PD results (glucose infusion rate over 32h [$GIR_{0\text{-}32\ h}$, $AUC_{0\text{-}32}$]) were generated by a randomized, single-blind, cross-over study using the euglycemic clamp (100 mg/dl) for 32 h after s.c. injection of 0.4 U/kg at 22.00 h of either NPH or Gla or Det, after 1-week treatment with each insulin, and analyzed according to BMI. Based on BMI status (<29 and >29 kg/m^2, i.e. below and above the median BMI of the overall group), GIR was greater in people with BMI <29 kg/m^2 compared to those with BMI >29 kg/m^2 although statistical significance was achieved only with Det (1564±649 and 598±604 mg/Kg, respectively, p=0.03) and not with NPH (1282±532 and 1058±859 mg/Kg) and glargine (1668±807 and 1408±563 mg/Kg), (both p>0.2). A multiple regression analysis after correcting for age and duration of diabetes revealed a statistically significant inverse correlation between BMI and GIR only with Det (r= -0.68, p=0.003), but not with Gla (r= -0.41, p= 0.11) and NPH (r= -0.37, p= 0.15). In addition, a positive correlation was found between BMI and endogenous glucose production (EGP) with NPH and Det (r= 0.66, p=0.005 and r= 0.62, p=0.011, respectively) but not with Gla (r= 0.35, p=0.17). As expected, PD of basal insulins in T2DM is inversely correlated with adiposity, likely because of greater insulin resistance in BMI >29 kg/m^2. However, among the three insulins examined, Det exhibits the lowest PD action and weakest effect in restraining EGP as adiposity increases, as compared to NPH and Gla. PD of Gla (mediated by greater suppression of EGP) is less affected by adiposity as compared to NPH and to greater extent, Det. These findings may explain, at least in part, the need for higher doses of Det as compared to Gla in clinical trials in obese T2DM when the two basal insulins are titrated to same target A1C.

949-P

Diabetes in Pregnancy: A Meta-Analysis of the Safety of Insulin Glargine Compared with NPH Insulin

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Studies of insulin glargine in pregnancy are of small numbers of women. We aimed to provide quantitative estimates of perinatal outcomes in women treated with insulin glargine versus NPH insulin during pregnancy. A formal literature search (PubMed to October 2010) identified observational studies

and clinical trials of diabetes pregnancies (preexisting or gestational diabetes) that included ≥ 15 women on each insulin. Data on a total population of 702 women were extracted and synthesized (Review Manager 5.0.25) using standard statistical procedures from the 8 studies meeting the selection criteria. Maternal outcome measures including mean third trimester A1C and incidence of hypoglycemia, preeclampsia, and cesarean section were similar for the 2 insulins (Table), though with wide confidence intervals particularly for hypoglycemia. Similarly, neonatal outcomes were not different (Table), but some events, including low Apgar score and respiratory distress syndrome, were too few to give useful estimates. In conclusion, published studies of insulin glargine versus NPH insulin in pregnancy give no signal of concern across a range of perinatal outcome measures. However, because quantitative estimates of difference for individual measures have large uncertainties, accumulation of larger data sets is now warranted.

Outcome	Studies/ Women (n/n)	Odds Ratio or Mean Difference	95% CI
Maternal			
Mean A1C in 3rd trimester (%, glargine–NPH)	6/538	-0.01	-0.07, 0.05
Maternal hypoglycemia	5/472	1.01	0.27, 3.77
Pre-eclampsia	8/702	0.55	0.23, 1.32
Cesarean section	6/608	1.04	0.72, 1.52
Neonatal			
Gestational age at birth (weeks, glargine–NPH)	7/611	0.09	-0.43, 0.61
Birth weight (g, glargine–NPH)	7/601	13	-19, 45
NICU admission	6/581	0.79	0.45, 1.38
Apgar score < 7 at 5 min	4/323	1.36	0.26, 7.06
Macrosomia (> 4000 g)	4/355	1.20	0.71, 2.02
Large for dates (> 90th percentile)	4/381	1.05	0.68, 1.63
Congenital malformation	5/508	0.78	0.39, 1.59
Respiratory distress syndrome	6/549	1.62	0.82, 3.21
Neonatal hypoglycemia	7/650	0.99	0.63, 1.56
Hyperbilirubinemia	6/586	0.93	0.49, 1.79

CI, confidence interval; A1C, hemoglobin A_{1c}; NICU, neonatal intensive care unit

Supported by: sanofi-aventis

950-P

Cancer and All-Cause Mortality: Meta-Analysis of Randomised Clinical Trials of Metformin

METFORMIN TRIAL LISTS' COLLABORATION, RICHARD STEVENS, JULIE MCLELLAN, BEN CAIRNS, RAGHIB ALI, CLARE BANKHEAD, ANGELYN BETHEL, FRANCESCA CROWE, ANDREW FARMER, SIAN HARRISON, JENNIFER HIRST, RAFAEL PERERA, ANNETTE PLUDDEMANN, PETER ROSE, PHILIP HOME, STEVEN KAHN, AMBADY RAMACHANDRAN, ANJA SCHWEIZER, GIANCARLO VIBERTI, RICCARDO CAMISASCA, RURY HOLMAN, *Oxford, United Kingdom, Newcastle, United Kingdom, Seattle, WA, Egmore, India, Basel, Switzerland, London, United Kingdom*

Observational studies and laboratory data have suggested that metformin may reduce cancer risk by as much as 30%. We examined incident cancer and all-cause mortality in previously conducted randomised controlled trials (RCTs).

RCTs of metformin versus active glucose-lowering therapy or placebo/usual care were identified by systematic review. Inclusion criteria included adult humans, ≥500 patients, follow-up ≥1 year. Data on cancer incidence and all-cause mortality were extracted from published papers, or otherwise by contacting investigators. For two RCTs cancer incidence data was not available and cancer mortality data was used as a surrogate. Summary relative risks (RR), 95% confidence intervals (CI) and I-squared statistics for heterogeneity were calculated by fixed effects inverse variance meta-analysis.

Of 2,126 abstracts identified, 55 publications described 12 RCTs meeting our criteria. RRs for cancer were available from 7 RCTs (4 from publications, 3 from investigators) for a total of 371 cancers during >47,000 person-years follow-up. RRs for mortality were available from 11 RCTs (10 from publications, 1 from investigators) for a total of 555 deaths during >64,000 person-years.

Summary RRs for incident cancer in patients randomised-metformin versus any comparator were 1.10 (95% CI 0.88-1.37; I-squared=39%) across all trials, 1.03 (95% CI 0.81-1.32; I-squared=28%) in a subgroup analysis of active-comparator trials and 1.47 (95% CI 0.85-2.55; I-squared=50%) in a subgroup analysis of placebo/usual care comparator trials. Summary RRs for all-cause mortality were 0.94 (95% CI 0.79-1.12; I-squared=20%) across all trials, 0.97 (95% CI 0.77-1.23; I-squared=0%) in a subgroup analysis of active comparator trials and 0.90 (95% CI 0.69-1.17; I-squared=61%) in a subgroup analysis of placebo/usual care comparator trials.

Meta-analysis of currently available RCTs does not support the hypothesis that metformin lowers cancer risk. Eligible trials also showed no significant effect of metformin on all-cause mortality. However, limitations include heterogeneous comparator types and absent cancer data from 5 trials.

Supported by: Diabetes UK

Guided Audio Tour: Pharmacologic Treatment of Diabetes—Diabetes Complications *(Posters 951-P to 957-P), see page 13.*

951-P

Topical Clonidine for Treatment of Painful Diabetic Neuropathy: A Randomized Double Blind Phase IIb Clinical Trial

JAMES N. CAMPBELL, MARK S. KIPNES, MICHAEL C. ROWBOTHAM, KARIN L. PETERSEN, BRUCE C. STOUCH, MARGARET KELLY, CLAUDIA M. CAMPBELL, KERRIE BRADY, WILLIAM K. SCHMIDT, *Baltimore, MD, San Antonio, TX, San Francisco, CA*

One of the leading complications of diabetes is a painful, length-dependent neuropathy that preferentially affects the feet (painful diabetic neuropathy, PDN). We hypothesized that the signals for pain may arise at least in part from sensitized/hyperactive cutaneous nociceptors, and that this abnormal signaling may be reduced by local administration of the alpha-2 adrenergic agonist, clonidine, in a topical gel formulation. There are no FDA approved topical prescription therapies for PDN. Subjects with PDN were randomized to receive 0.1% topical clonidine gel (n=89) or corresponding placebo gel (n=90) applied t.i.d. to their feet for 12 weeks. Subjects entered daily diary ratings of their average pain (0 to 10 numeric pain rating scale, NPRS). The baseline pain level was carried forward to week 12 (BOCF) for subjects who terminated early. A trend was apparent indicating a greater decrease in the mean pain level at week 12 compared to baseline in the clonidine treated group (-2.3) compared to the placebo group (-1.7; between group Δ=0.6, p=0.07). It was hypothesized *a priori* that the efficacy of clonidine would require expression of functional nociceptors in the skin. Accordingly, this was measured during the screening period in each subject by determining the relative painfulness of 0.1% topical capsaicin (over-the-counter) applied to the pre-tibial area for 30 minutes. Topical clonidine had no efficacy over placebo in subjects who reported no pain to the capsaicin stimulus. However, in those subjects who felt any level of pain to the capsaicin stimulus, clonidine was significantly superior to placebo (Δ=0.9, p<0.05). If the NPRS rating of the capsaicin stimulus was ≥2, the mean change in pain at week 12 was -2.5 for active compared to -1.4 for the placebo (Δ=1.1, p=0.01). Other factors such as measures of large fiber function, duration of disease, and disease severity did not predict clonidine efficacy. These results suggest that topical clonidine gel, applied topically to the area of pain, significantly reduces the level of pain in subjects with preserved nociceptors in the affected skin.

952-P

Gliclazide Improves Myocardial Dysfunction of Obese Rats after Ischemic Injury

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Several studies have discovered that the SUR1-regulated cation ($NC_{Ca\text{-}ATP}$) but not K_{ATP} channels are upregulated in ischemic astrocytes, and block of SUR1 with SUs reduced cerebral edema and infarct volume. Recent patch-clamp studies also found similar SUR-1 regulated non-selective cation channel (NSC_{Ca}) in myocardial cells, but the effects of blocking NSC_{Ca} by SUs on ischemic myocardium have not been reported. The aim of the study was to evaluate the effects of gliclazide on myocardial infarct size, post-ischemic cardiac function and arrhythmia in obese rats with cardiac ischemia-reperfusion (I/R) injury. Diet-induced obese rats were divided into 2 groups. SU group and Control group rats were given gliclazide (1 mg/kg) or saline lavage Q12h for 48 hours. All the rats were subjected to myocardial I/R injury by Isoprenaline (100mg/kg) injection subcutaneously 24 hours after first lavage. ECG was recorded and all the arrhythmias were analyzed with arrhythmia severity index (ASI). At the end of 24 hours after I/R injury, hemodynamic parameters were measured with an electromanometer. The hearts slides were stained with TTC and the infart-size was calculated with Image-Pro Plus 6.0. Blood glucose was only slightly declined during study. The mortality was 63.64% (14/22) in control group and 45.45% (10/22) in SU group (NS). The severity of arrhythmia was lighter in SU group (ASI: 2.14±1.83 vs. 4.00±2.85, p<0.05). Gliclazide administration reduced myocardial infarct size (32.7%±9.1% vs. 48.6%±12.8%, p<0.05) and improved diastolic function as the left ventricle end-diastolic pressure (LVEDP) was lower and maximum

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

rate of decrease of LVP(-(dp/dt)max) was higher in SU group. Our findings indicate that NSC_{Ca} channels are in involved in development of myocardial dysfunction and arrhythmias, and that targeting SUR1 may provide a new therapeutic approach to ischemic cardiac injury.

	Control group (n=22)	SU group (n=22)
LVSP (mmHg)	120.92±13.53	138.12±24.86
IVEDP (mmHg)	6.86±2.42	2.51±3.77*
+(dp/dt)max (mmHg/s)	2192.4±1461.7	3678.9±1751.9
-(dp/dt)max (mmHg/s)	-1663.6±1097.2	-2834.8±1007.2*

Hemodynamic performance of obese rats after I/R injury

Supported by: Innovative Research Grant for Chinese University students

953-P

Safety and Effectiveness of Metformin in Patients with Diabetes and Heart Failure: Systematic Review

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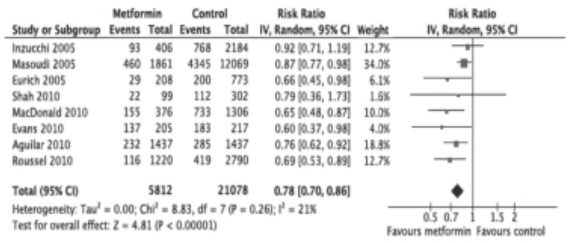
Despite ongoing concerns, metformin is commonly used in patients with type-2 diabetes (DM) and heart failure (HF). Therefore, we updated our earlier systematic review of metformin in patients with DM and HF published in 2007.

A comprehensive search (multiple electronic databases until December 2010, hand-searches, contact with experts) for controlled studies of metformin evaluating outcomes (mortality, hospitalizations) in patients with DM and HF was conducted. Studies without a control group were excluded. Two reviewers independently identified citations, extracted data, and evaluated quality using the Downs and Black instrument. Adjusted risk estimates were abstracted and pooled using random effects generic inverse variance weighting (Cochrane Review Manager 5.0). Heterogeneity assessed using I^2 statistic.

Our search yielded >12,000 citations but only 8 cohort studies met our inclusion criteria (inter-rater agreement = 0.85); no RCTs were identified. Most (5 of 8) studies were published in 2010 (not included in our 2007 review), and were of good quality (median score > 16). Metformin was associated with reduced mortality compared to controls (mostly sulfonylurea therapy) in all 8 studies; achieving statistical significance in 6 studies (Figure). Pooled risk estimates indicate metformin was associated with reduced mortality (pooled risk estimates 0.78, 0.70-0.86; P<0.001; Figure), although there was modest heterogeneity (I^2=21%). Metformin was also associated with a small reduction in all-cause hospitalization (pooled estimate 0.92, 0.87-0.98, I^2=0%, P=0.01).

The totality of available evidence indicates that metformin is safer and more effective than other treatments in patients with DM and HF. Given recent FDA labeling changes for metformin in HF, clinicians should consider metformin as the treatment of choice for those with DM and HF.



* Study risk ratios represent published multivariate adjusted risk estimates. The pooled estimate reflects the overall risk estimate of metformin compared to controls after multivariate adjustment for age, sex, comorbidities, drug therapies, +/- clinical data as reported in original publications.

954-P

Characteristics of Patients with Ketosis-Prone Diabetes (KPD) Presenting with Acute Pancreatitis: Implications for the Natural History and Etiology of a KPD Subgroup

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There is a lack of systematic, longitudinal information regarding the characteristics and natural history of patients who present with concomitant acute pancreatitis (AP) and diabetic ketoacidosis (DKA). We analyzed a large (n=813), multiethnic cohort of patients with ketosis-prone diabetes (KPD) followed prospectively from the time of the index DKA with repeated clinical, metabolic, and β-cell functional reserve measures. We compared KPD patients whose index DKA was associated with AP (N=57) to those whose index DKA was not associated with AP (N=756). The AP group had higher levels of serum amylase (3.7 vs. 0.2 X upper limit of normal (ULN), P<0.0001), lipase (10.8 vs. 0.3 X ULN, P<0.0001), and triglycerides (1272.0 vs. 218.9 mg/dL, P=0.001), and lower serum bicarbonate (9.6 vs. 11.7 mEq/L, P=0.03) than the non-AP group at admission. The AP group had later onset of diabetes (37.4 vs. 33.2 y, P=0.01), shorter duration of disease (34 vs. 73 months, P=0.0003) and fewer prior DKA episodes (0.5 vs. 2.1, P<0.0001). The AP group also had greater β-cell secretory reserve at baseline and higher fasting C-peptide (FCP) levels 6 months after the index DKA (2.7 vs. 1.7 ng/dL, P=0.03). Using the validated "Aβ" classification scheme for KPD, 86% of the AP patients were β+ (with preserved β-cell functional reserve), compared to 60% of the non-AP patients. Within the AP group, those with a history of alcoholism had milder indices of pancreatic inflammation than those without alcoholism, and demonstrated better long-term β-cell functional reserve (FCP at 6 months 3.3 vs. 1.5 ng/dL, P<0.05). We conclude that: 1) despite greater severity of illness at the time of the index DKA (evidence of worse intraabdominal inflammation, more severe acidosis), KPD patients presenting with AP have a greater capacity for β-cell functional recovery, with a higher likelihood of belonging to a "β+" KPD category; 2) novel etiologies of combined exocrine and endocrine pancreatic damage may underlie the pathogenesis of autoantibody-negative KPD patients who present with idiopathic, non-alcoholic pancreatitis.

955-P

KIOM-VN118 Inhibits AGEs/RAGE Binding in Mouse Mesangial Cells and Improves Renal Function and Pathology in the Spontaneously Diabetic Torii (SDT) Rats

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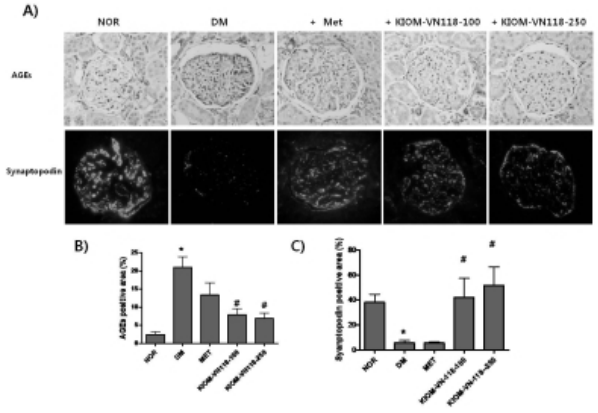
Advanced glycation end products (AGEs) have been implicated in the development of diabetic complications. KIOM-VN118, the 80% ethanol extract of herb, inhibits the formation of AGEs *in vitro*. In this study, we determined the effects of KIOM-VN118 on AGEs and receptor for AGEs (RAGE) binding in glomerular mesangial cells (GMCs) and on development and progression of diabetic nephropathy in the spontaneously diabetic Torii (SDT) rats. Human RAGE overexpressed GMCs were cultured in AGEs-BSA labeled with Alexa 488 and KIOM-VN118 and AGE/RAGE binding was measured using fluorescence (Ex. 485 nm/Em. 528 nm). To check the renal function, SDT rats were treated with KIOM-VN118 (100 and 250 mg/kg, n=7/group) once a day orally for 16 week. Inhibition of AGEs/RAGE binding by KIOM-VN118 gradually increased in a dose-dependent manner. KIOM-VN118 reduced histologic renal damage, AGEs and CML levels in urine (p<0.05 vs. DM group), and albuminuria in SDT rats. In the renal cortex, KIOM-VN118 reduced expression of TGF-β1 and AGEs, collagen deposition, and podocyte apoptosis. In conclusion, KIOM-VN118 may provide a potential therapeutic approach for prevention of diabetic nephropathy.



Effect of KIOM-VN118 on AGEs and synaptopodin expression in glomerulus of renal cortex in Torri rats with type 2 diabetes. Paraffin sections of kidney immunolabeled with AGEs and synaptopodin (A). AGEs and synapotodin immunostaining was quantified (B and C, *P<0.01 vs. NOR; #P<0.01 vs. DM, n=7).

Supported by: Korea Institute of Oriental Medicine [K10040]

956-P

Effect of Glucagon Like Peptide-1 Agonist on Neointimal Formation after Balloon Injury in Rats

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It is well established that enhancement of glucagon like peptide (GLP)-1 reduces glucose levels and preserves pancreatic beta-cell function in patients with type 2 diabetes. However, its potential efficacy against restenosis after balloon injury has not been explored. The present study investigated the effect of intraperitoneal (IP) injection or direct infusion of GLP-1 agonist containing virus into vessel, in reducing occurrence of restenosis in carotid artery after balloon injury. Sprague-Dawley rats were grouped into three (n = 10 per group): control (normal saline IP), exenatide IP (1 μg/kg per day) with control virus (rAd-bGAL) transfusion, and normal saline IP with GLP1 agonist containing virus (rAd-GLP-1) transfusion. Exenatide or normal saline were given intraperitoneally from 1 week before to 2 weeks after carotid injury. After three weeks of treatment, exenatide IP and rAd-GLP-1 transfusion caused a significant reduction in intima-media ratio (IMR) and rAd-GLP-1 was more potent in this aspect. This effect was accompanied by improved glucose homeostasis, decreased circulating levels of high-sensitivity C-reactive protein (hsCRP) and increased adiponectin level. Moreover, IMR was correlated significantly with levels of hsCRP, TNFα, and monocyte chemoattractant protein-1. *In vitro* evidence with vascular smooth muscle cells (VSMCs) demonstrated that proliferation and migration were decreased significantly after rAd-GLP-1 treatment. In addition, treatment of rAd-GLP-1 decreased monocyte adhesion in VSMCs. The current findings suggest that exenatide IP or direct infusion of rAd-GLP-1 has protective properties against restenosis after balloon injury and therapeutic implications for treating macrovascular complications of diabetes.

957-P

Results of a Randomized Trial To Evaluate a Novel RAGE Inhibitor in Patients with Diabetic Nephropathy

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Purpose: Studies have shown that Advanced Glycation Endproducts (AGEs) and Receptor for AGEs (RAGE) play an important role in the pathogenesis of diabetic nephropathy (DN). Inhibiting RAGE may provide a promising therapeutic target for the prevention and treatment of DN. Primary objective of this study is to evaluate the efficacy of PF-04494700 administered for 6 months to subjects with type 2 diabetes and persistent albuminuria.

Methods: A Phase 2a efficacy and safety study was conducted to assess the effects of the PF-04494700 treatment taken once daily for up to 6 months vs. placebo, in 110 subjects with type 2 diabetes and persistent albuminuria, defined as a urinary albumin/creatinine ratio (UACR) of 60-1800 mg/g. Primary efficacy evaluation was the change in UACR from baseline to end of treatment (Month 6). Safety/tolerability was assessed throughout the conduct of the study. Subjects were required to have controlled stable blood pressure, and were treated with maximally tolerated stable dose of an angiotensin converting enzyme inhibitor (ACE-I) or an angiotensin II receptor blocker (ARB).

Results: PF-04494700 did not demonstrate a statistically significant reduction over placebo at Month 6 in UACR, a measure of proteinuria. Estimated mean percent change from baseline to Month 6 was -22.81% for the PF-04494700 group and -27.71% for the placebo group (p=0.69). There was no evidence of a treatment difference for other efficacy measures (estimated glomerular filtration rate, serum creatinine), potential markers of RAGE inhibition, or exploratory biomarkers of Alzheimer's Disease.

Conclusions: Therapy with PF-04494700 vs placebo did not produce any difference in any of the efficacy measures, potential markers of RAGE inhibition or in exploratory biomarkers. Treatment with PF-04494700 for 6 months in subjects with type 2 diabetes and persistent albuminuria was generally safe and well-tolerated. Overall incidence and severity of treatment-emergent adverse events were similar for the PF-04494700 group and placebo.

Guided Audio Tour: Pharmacologic Treatment of Diabetes—Insulin Therapies *(Posters 958-P to 965-P), see page 13.*

958-P

The Failure of Insulin Glargine To Maintain Basal Glucose Control in T1DM: The Dawn and the Afternoon Phenomena

DAWN CLARK, ALLEN KING, GARY WOLFE, *Salinas, CA*

Once-daily insulin glargine (IG) is indicated for basal insulin replacement in T1DM. It usually provides a level 24 h action. The dawn phenomenon (DP) is common and requires not a level, but an increased morning action. Afternoon phenomenon (AP), a rising glucose prior to IG injection, is observed in ~ 25% and is due to < 24 hour action in some or to the lack of appropriate pre-lunch bolus insulin. With continuous glucose monitoring (CGM), we studied both phenomena by periodic meal omissions.

The subjects' (n=37) IG (2100–2200 h) was titrated to a 24 hour CGM basal glucose target >4 hr post-meal and at meal times by daily alternate meal omission to <130 mg/dl but <10%, <70 mg/dl. After 2 days of a constant glargine dose, the mean 24 hr basal glucose was reconstructed by cut and pasting the omitted meal periods. The DP and the AP were assessed by 0200 - 1000 hr and 2000 – 1500 h glucose, respectively.

The mean (SD) age was 44 (17) years, duration of diabetes, 12 (10) years and Hb A1c, 7.41 (0.74) %. By CMG, 31 (81%) demonstrated a >10 mg/dl and 20 (54%), >30 mg/dl glucose increase with the DP. The mean 0200H glucose, 119 (62), was significantly both clinically and statistically, different ($p < 0.001$) from the 1000 h, 172 (91) mg/dl. The 2000 – 1500 h difference, the AP, was >10 in 16 (43%) and >30 mg/dl in 11 (30%) of the subjects, respectively.

By omitting breakfast we demonstrated that the average T1DM patient has a clinically significant increase in morning glucose that is not controlled by IG. As previously reported, the AP occurs in ~ 30% of subjects and our results suggest it is probably due to waning IG effect and not due to the lunch meal or bolus since both were omitted.

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959-P

Novel Insulin Infusion Protocol: Subcutaneous Administration of Long-Acting Insulin during Insulin Infusion Prevents Rebound Hyperglycemia

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Intravenous (IV) insulin infusion is widely used in the inpatient setting for optimizing glucose control in patients with diabetic ketoacidosis (DKA) and post-operative states (post-op). However, there are no clear standards for optimally transitioning patients from IV to subcutaneous (SC) administration of insulin, and rebound hyperglycemia is frequently observed after discontinuation of IV insulin.

In this study, we evaluated whether daily SC administration of long-acting insulin simultaneously with IV insulin could prevent rebound hyperglycemia. Twenty-four diabetic patients (Type 1 and 2), either in DKA or post-op, were recruited for this study. They were randomized to receive the standard University of Colorado Hospital IV insulin infusion protocol (control group, n=17) or IV insulin plus SC glargine or detemir, given daily in a dose of 0.25U/kg of body weight (intervention group, n=7). Eight patients were treated for DKA and sixteen patients were kidney or liver transplant recipients. After the IV insulin infusion was discontinued, point of contact glucose measurements were obtained to adjust SC insulin doses as needed. The patients were followed for 12 hours after discontinuation of IV insulin. The number of rebound hyperglycemic values (above 180mg/dl) during three consecutive 4-hour periods was compared between the control and interventional groups.

Rebound hyperglycemia was frequent in the control group: 17 episodes in the first 4-hour period, 17 episodes in the second and 12 episodes in the third. In contrast, among patients who received daily SC injections of either glargine or detemir, the rate of rebound hyperglycemia was significantly diminished:3 episodes in the first 4 hours, 5 in the second and 0 in the third period. There were no differences between glargine and detemir. We observed 3 hypoglycemic readings (< 70 mg/dl) in the control and 1 in the interventional group.

We conclude that daily administration of SC long-acting insulin during IV insulin infusion is a novel, safe, and effective method of preventing rebound hyperglycemia, thus improving transition of diabetic patients from IV to SC insulin.

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

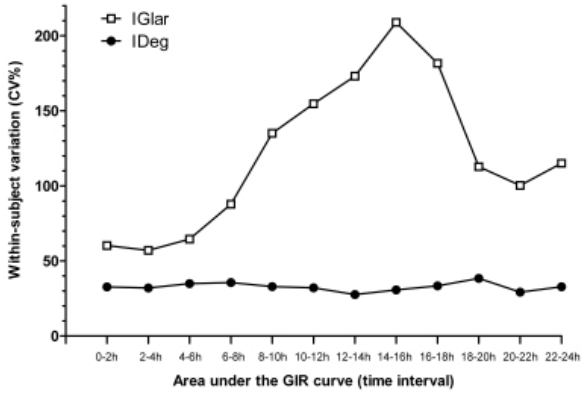
960-P

The Pharmacodynamic Variability of Insulin Degludec Is Consistently Lower Than Insulin Glargine over 24 Hours at Steady State

TIM HEISE, LIDIA HERMANSKI, LESZEK NOSEK, ANDRE FELDMANN, SØREN RASMUSSEN, HANNE HAAHR, *Neuss, Germany, Soeborg, Denmark*

Insulin degludec (IDeg; formerly named SIBA) has been shown to have a lower within-subject pharmacodynamic (PD) variability than insulin glargine (IGlar) under steady-state conditions (Heise et al. Diabetologia 2010;53(Suppl.1):S387).

This post-hoc analysis investigated whether the lower within-subject variability of IDeg was consistent over 24 hours. PD variability was investigated in 54 subjects with type 1 diabetes who underwent a 24h euglycemic glucose clamp on the 6th, 9th and 12th day of treatment with 0.4 U/kg of IDeg or IGlar once daily. Within-subject coefficients of variation (CVs) were derived from a linear mixed regression model that reduced the influence of extreme values observed with IGlar. The consistency of variability over time was analyzed with successive log-transformed endpoints for the area under the glucose infusion rate curve (AUC_{GIR}) in 2h intervals. Overall, IDeg demonstrated lower within-subject variability for total $AUC_{GIR,0\text{-}24h}$ (CV 23 vs. 72%, p<0.0001), for GIR_{max} (21 vs. 53%, p<0.0001) and for the fluctuation around the mean GIR value over 24h (31 vs. 62%, p<0.001). The lower within-subject variability of IDeg was consistent over time (CVs of 33% for $AUC_{GIR,0\text{-}2h,}$ 32% for $AUC_{GIR,10\text{-}12h}$ and 33% for $AUC_{GIR,22\text{-}24h;}$ see figure) whereas the variability of IGlar was higher and increased substantially after 8h postdosing (CVs of 60% for $AUC_{GIR,0\text{-}2h,}$ 155% for $AUC_{GIR,10\text{-}12h}$ and 115% for $AUC_{GIR,22\text{-}24h}$). In conclusion, the within-subject variability for IDeg is consistently lower than IGlar over 24 hours, which may be due to the slow release of IDeg monomers from soluble multi-hexamers that form after sc injection. IDeg's lower within-subject variability is thought to contribute to the lower risk of hypoglycemia observed in clinical studies.



961-P

Dosing Formulas in T1DM Treated by Multiple Daily Insulin Doses (MDI) Determined by Structured Continuous Glucose Monitoring (CGM)

ALLEN KING, DAWN CLARK, GARY WOLFE, *Salinas, CA*

Previous dosing formula studies of CGM-titrated T1DM subjects were confined to pump-treated patients. MDI treated T1DM patients may differ because the basal analog action is different than pump delivered pre-programmable basal action of rapid acting insulin.

MDI treated T1DM subjects on an isocaloric, 50% carbohydrate diet were placed on CGM. The basal insulin, glargine at 2000-2100 h, was titrated from daily CGM downloads to a basal glucose of < 130 mg/dl but not > 10% of glucose readings < 70 mg/dl. Pre-meal lispro was titrated to a 2-4th h post-meal glucose to ± 20% of the pre-meal. The basal rate was studied by serial meal omissions and results were not accepted until ≥ 2 days of a constant basal dose. The variables of weight (Wt, kg), total daily dose (TDD), total basal dose (TBD), and insulin to carbohydrate ratio (ICR) were analyzed. The correction factor was not independently studied. The resulting formulas were determined by the linear regression with the slope forced through y = 0 intercept.

The mean (SD) age of the 36 subjects was 44.0 (17) years; HbA1c of 7.4 (0.7) %; weight of 80.2 (16.7) kg; and 38% female. The mean basal 0200 h glucose, 119 (62), was significantly (p < 0.001) different from the 1000 h, 172 (91) mg/dl. Because of this pronounced dawn phenomenon, morning target basal glucose could not be achieved with glargine without pre-dawn or afternoon hypoglycemia. The resulting formulas (correlation coefficients) were: wt X 0.23 = TBD (0.53), TDD X 0.33 = TBD (0.86) and 99/TBD = ICR (0.84).

The dawn phenomenon prevented better morning basal glucose control in most patients resulting in a lower (yet highly correlated) TBD/TDD ratio than in pump treated (0.33 vs. 0.41). The slope-derived X of X/TBD = ICR was slightly lower than pump-treated (99 vs.113) patients and probably reflects the reduced TBD dosage. These results may help in estimating and evaluating insulin dosing in MDI-treated T1DM patient.

Supported by: Eli Lilly and Company

962-P

Glycemic Control in the ICU at a County Hospital—A Tale of Two Protocols

HYUNAH EOM, TYLER AGUINALDO, *Tracy, CA, San Jose, CA*

Purpose: The purpose of this study is to compare the efficacy and safety of two different insulin drip protocols, both with moderate glycemic targets, to traditional sliding scale insulin (SSI) in the ICUs in a county hospital.

Methods: A retrospective chart review at Santa Clara Valley Medical Center, San Jose, CA. A conventional insulin drip (CID) protocol used a single blood glucose (BG) measurement to determine the change in insulin drip rate. A nomogram-based insulin drip (NID) protocol used two consecutive BG measures to determine the change in insulin drip rate.

Results: The CID and NID protocols had similar efficacy in terms of percent of time in the target BG range, mean AM BG, and time to reach the BG target. Both insulin drip protocols were far superior to patients treated with SSI in terms of efficacy. The CID protocol demonstrated significantly more hypoglycemic events (BG <70mg/dL) and more severe hypoglycemic events (BG<40mg/dL) than the NID protocol. Patients on SSI had fewer hypoglycemic events than either insulin drip protocols.

Results	Sliding Scale (n=49)	CID Protocol (n=11)	NID Protocol (n=55)	P-value SS vs CID	P-value SS vs NID	P-value CID vs NID
Time on protocol Hours	3048	649	2776	n.s.	n.s.	n.s.
Mean hours/ patient (±SD)	62.2±48.6	59.0±24.5	50.5±33.7	n.s.	n.s.	n.s.
% Time BG in target range (±SD)	20.0%±22	63.4%±22	67.7±21	<0.001	<0.001	n.s.
% Pts achieved BG <160 mg/dL	65.3%	100%	98.2%	<0.001	<0.001	n.s.
Time to BG <160 mg/dL (hrs) (±SD)	23.9±23.8	7.6±3.9	6.2±3.9	<0.05	<0.001	n.s.
Mean AM BG (mg/dL) (±SD)	207±61	164±60	166±75	<0.05	<0.01	n.s.
Hypoglycemic events (<70 mg/dL)	3 (1 patient)	11 (7 patients)	13 (13 patients)	<0.001	<0.01	<0.001
Severe hypoglycemic events (<40 mg/dL)	0	3 (2 patients)	0	<0.01	n.s.	<0.01

Conclusion: We conclude that a nomogram based insulin drip protocol with a moderate blood glucose target is similarly effective to a conventional insulin drip protocol, and results in fewer total and severe hypoglycemic events. Although much less effective at controlling hyperglycemia than insulin drip protocols, traditional sliding scale insulin results in less hypoglycemic episodes than either insulin drip protocol.

963-P

Mechanism for the Differential Effect of the Long-Acting Insulin Analog Detemir on Weight in Patients with Type 2 Diabetes

BEN SHELDON, NAJLAA ALSINI, SUNIL ZACHARIAH, FARIBA SHOJAEE-MORADIE, CAROLINE BODINHAM, DENISE ROBERTSON, JIMMY BELL, LOUISE THOMAS, HUBERT VIDAL, EMMANUELLE MEUGNIER, RICHARD H. JONES, A.M. UMPLEBY, DAVID RUSSELL-JONES, *Guildford, United Kingdom, London, United Kingdom, Lyon, France*

Insulin detemir (detemir) seems to lack insulin's usual propensity to cause weight gain. This single-centre, 24-week, randomized parallel-group trial attempted to elucidate the mechanisms. Twenty-two type 2 diabetic subjects (14M, 8F, aged 60.4 ±8.1 y), BMI 32.3 ±3.6 kg/m2) (mean±SD) were titrated for 8 weeks with NPH insulin (NPH) and then randomized to receive either

detemir or NPH for 16 weeks. Whole-body fat distribution by MRI, hepatic and muscle fat by MRS, resting energy expenditure (REE), energy intake (by 7 day food diary), weight change, glycaemic control, hypoglycaemic episodes, fasting metabolites and hormones were measured after 8 weeks and after the 16-week treatment period. In a sub-set, basal and stimulated lipolytic activity in a subcutaneous fat tissue biopsy was compared between NPH (n=5) and detemir (n=7). Weight change over the treatment period was –0.62 ± 0.84 kg with detemir and +2.19 ± 1.03 kg with NPH (p=0.049). There was no difference in HbA1c, number of hypoglycemic episodes, REE, energy intake, total, visceral or subcutaneous adipose tissue. There was a trend for an increase in tibialis intramuscular lipid with NPH (p=0.064) that was not seen with detemir. Fasting non-esterified fatty acids (NEFA) decreased significantly with detemir compared to NPH (p=0.046). Basal lipolysis in the fat biopsies also showed a significant reduction with detemir compared to NPH over the treatment period (p<0.04). Skeletal muscle biopsies were taken in a sub-set to study the effects of NPH (n = 5) and detemir (n = 5) on the regulation of gene expression during the 16-week treatment period using microarrays. Preliminary data suggest differential effects on sets of genes related to mitochondria and electron transfer chain and to vascular remodeling and endothelial function. Detemir caused less weight gain in patients with type 2 diabetes patients compared to NPH. The decrease in basal NEFA levels and basal lipolysis suggests that detemir improves fasting insulin sensitivity. We hypothesise that that this may be due to a greater hepatoselective action of detemir reducing overinsulinisation of adipose tissue and skeletal muscle.

964-P

Characteristics of Remission Patients with Newly Diagnosed T2DM in Intensive Therapy

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According to our previous study, some newly diagnosed type 2 diabetes mellitus patients can maintain euglycaemia without hypoglycemic agents after 2-week intensive insulin therapies by continuous subcutaneous insulin infusion (CSII). But the others didn't respond well to the treatment.

To determine patients who would most likely to benefit from this treatment, a retrospective study was conducted. 136 patients [89M/47F, age 49.8±10.1 yrs, A1C 11.1±2.1%] with newly diagnosed T2DM were enrolled into this study. After intensive therapy, 27 patients failed to remain euglycaemia. The characteristics at baseline of remission and non-remission patients were compared in Table1. Data are median±IQR unless '♦' indicated(mean±SD).

There were no differences in DM family history, BMI, WHR (waist-to-hip ratio), FPG, PPG, HbA1c, Tch, TG, LDL-C and AIR/AUC_{IVGTT} between two groups. But both HOMA-β and HOMA-IR in the remission group were higher than those in the non-remission group. This indicated the better compensatory function of β-cell, rather than the first phase insulin secretion, was more important for the prognosis. In addition, the sex ratio and age were different between groups. Male and younger patients seem to have a more favorable outcome. Besides, lower level of HDL-C was seen in the remission patients.

In conclusion, sex, age, the level of HOMA-β, HOMA-IR HDL-C were related to the prognosis of intensive insulin therapy by CSII. Patients with better compensatory function of β-cell would be more likely to recover.

	Non-remisson group	Remission group	p-value		Non-remisson group	Remission group	p-value
male /Female	13/14	76/33	0.03	AUC□pmol□	51.1±49.4	56.9±48.8	0.14
Age ♦	53.7±10.4	48.8±9.8	0.02	AIR□pmol/L/min□	-8.5±16.9	-10.6±23.9	0.35
DM family history(Y/N)	12/15	49/60	0.96	HOMA-B	13.33±13.42	18.85±26.53	0.01
BMI	23.7±4.1	25.0±4.3	0.156	HOMA-IR	2.79±2.21	3.76±2.38	‹0.01
WHR ♦	0.93±0.05	0.94±0.07	0.54	TC (mmol/L)	5.6±2.3	5.9 ±1.7	0.82
FPG(mmol/L)	12.4±4.4	11.1±5.6	0.18	TG (mmol/L)	1.67±1.47	1.7±0.9	0.91
PPG(mmol/L)	17.5±8.0	16.9±7.4	0.65	HDL-C(mmol/L)	1.2±0.3	1.1±0.3	0.01
GSP(mg /L) ♦	584.4±149.6	545.4±183.6	0.33	LDL-C(mmol/L)	3.9±1.7	4.1±1.6	0.57
A1C(%) ♦	11.5±1.6	11.0 ±2.1	0.19				

965-P

Human Hyaluronidase Coinjection Consistently Accelerates Prandial Insulin Pharmacokinetics (PK) and Glucodynamics (GD) across Studies and Populations

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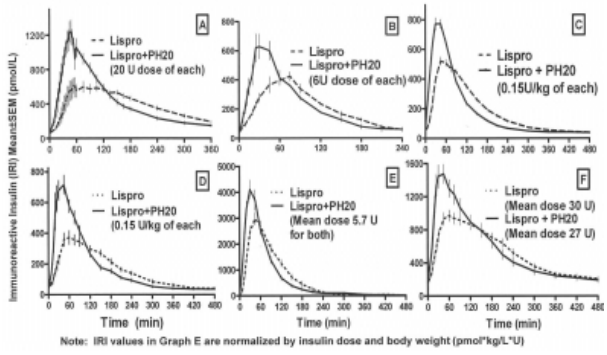
Recombinant human hyaluronidase (rHuPH20) is FDA-approved as an adjuvant to increase the dispersion and absorption of other injected drugs. When coinjected with prandial insulins, rHuPH20 accelerated the absorption and action of both regular human insulin and rapid acting insulin analogs, and reduced postprandial glycemic excursions in patients with diabetes. To assess the consistency of these effects across studies and populations we have compared the effect of rHuPH20 on PK and GD parameters for insulin lispro obtained across 6 separate studies, 4 in healthy volunteers (HV) and 1 in type 1 diabetes (T1DM) and 1 in type 2 diabetes (T2DM), as summarized below. A consistent ultrafast profile was observed with greater and earlier peak exposure, twice the PK exposure in the first hour and half the exposure after 2 hours. Insulin action in the first hour is also doubled and after 4 hours it is halved. PK results are graphed below. In conclusion, rHuPH20 consistently accelerated rapid acting insulin exposure and action across multiple studies and populations.

Study (Graph)	$\Delta AUC_{INS\,0\text{-}1h}$	ΔC_{INSmax}	Δt_{INSmax}	$\Delta AUC_{INS>2h}$	$\Delta G_{0\text{-}1h}$	$\Delta G_{0\text{-}2h}$	$\Delta G_{>4h}$
Proof of Concept HV, n=12 (A)	+155%	+90%	-49 min	-31%	+102%	+52%	-29%
Dose-finding HV, n=12 (B)	+77%	+63%	-20 min	-72%	+80%	+42%	-24%
Variability HV, n=20 (C)	+106%	+62%	-16 min	-53%	+77%	+38%	-49%
Comprehensive Analog HV, n=14 (D)	+191%	+110%	-26 min	-71%	+108%	+48%	-45%
TIDM Meal n=21 (E)	+54%	+35%	-18 min	-57%	na	na	na
T2DM Meal n=21 (F)	+116%	+74%	-31 min	-24%	na	na	na

AUC=area under curve, INS=insulin, h=hour, max=maximum, t=time, C=concentration, G=total glucose infused (obtained in euglycemic clamp studies), na=not applicable.



Guided Audio Tour: Pharmacologic Treatment of Diabetes—GLP-1 Receptor Agonists *(Posters 966-P to 973-P), see page 15.*

966-P

Pilot Study on the Effect of Liraglutide on Retinal Microvascular Function in Type 2 Diabetic Patients

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GLP-1 receptor agonists have been introduced in the treatment of T2DM. Beside their metabolic effects, GLP-1 agonists were shown to address vascular pathways and to modulate endothelial function.

This two arm, parallel study, included 42 well controlled patients with T2DM (22 male, age: 56.6±6.1 years; duration of diabetes: 5.3±4.9 years; HbA1c : 6.3±0.4 %; mean±SD). Main inclusion criteria were: pretreatment with metformin on a stable dosage, HbA1c < 7.0%, age 30 – 65 years, no retinopathy. Patients were randomized to receive additional liraglutide in a stepwise escalating dosage from 0.6 mg to 1.8 mg or remained on metformin monotherapy. After 8 weeks (1.2mg) and after 12 weeks (1.8 mg) retinal capillary blood flow was assessed using a retinal laser doppler scanner at 670 nm (Heidelberg Retina Flowmeter, Heidelberg Engineering) at baseline and 20 seconds after flicker light stimulation. In addition, venous blood was taken for the measurement of HbA1c and asymmetric- dimethylarginin (ADMA).

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

HbA1c levels declined from 6.3±0.4 to 5.8±0.3 % (p<0.05) during liraglutide treatment, and remained unchanged in the control group. The microvascular response to flicker light increased by 7.9 ± 4.2 % after 8weeks and by 3.9±3.8% after 12 weeks of liraglutide treatment (mean±SEM; p=0.09). In the control group, the microvascular response declined by -1.3±5.8 % and by -3.7±7.9 % (n.s.), respectively. Liraglutide treatment reduced ADMA levels from 392±16 to 365±20 nmol/L at 8 weeks and to 347±14 nmol/l (p<0.05) at 12 weeks of treatment. ADMA levels were significantly lower after treatment with liraglutide and metformin compared with metformin monotherapy (347±14 vs. 401±22 nmol/L; p<0.05). No association was observed between the change in HbA1c levels and the retinal microvascular response or ADMA levels.

This pilot study support the assumption of endothelial effects of liraglutide beyond glucose control. The clinical impact of the improved endothelial function has to be validated in confirmatory studies with vascular endpoints.

Supported by: Novo-Nordisk Germany

967-P

The Effect of Disease Stage, Indicated by Number of Previous Oral Antidiabetic Agents, on the Response to Liraglutide in Type 2 Diabetes

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The optimal timing of clinical initiation of GLP-1 receptor agonists in the treatment cascade in type 2 diabetes is still debated. This analysis aimed to evaluate difference in efficacy of using liraglutide early (add-on to patients on ≤1 oral antidiabetic agent [OAD]), or later (add-on to ≥2 OADs) in the natural history of T2D. In this context, a pooled analysis of 26-week data from 7 randomised phase 3a and 3b clinical trials (n=4625) was conducted to examine the effect of placebo or liraglutide (1.2 or 1.8 mg). Patients were stratified according to previous treatment status: diet/exercise or add-on to one OAD (Early), versus add-on to ≥2 OADs (Late). The mean duration of diabetes was 6 years in the early and 9 years in the late group. Subjects presented here were all continued on their pre-trial OADs throughout the trials. Change in A1c from baseline was significantly greater in patients treated early vs late for all groups (Table). A significantly higher proportion of patients receiving liraglutide 1.8 mg early reached A1c target <7% than those treated late (Table). Beta-cell function was assessed by HOMA-B and proinsulin:insulin ratio. There was a significantly better improvement in HOMA-B among patients treated early vs late with liraglutide 1.8 mg. Thus, using liraglutide in patients who were treatment naive or previously on only 1 OAD demonstrated better responses compared to add-on to 2 OADs, suggesting that use of liraglutide early in the disease may provide greater clinical benefits and potential improvement in beta-cell function.

Table: Change in endpoints by early vs late treatment (as indicated by number of previous OADs) after 26 weeks of treatment

		LS means		Difference Early vs Late (95% CI)	*p* value
		EARLY N=987	LATE N=495		
Change in A1c from baseline (%)	Liraglutide 1.8 mg	-1.55	-1.18	-0.36 (-0.52, -0.20)	*p*<0.0001
	Liraglutide 1.2 mg	-1.38	-0.82	-0.56 (-0.92, -0.19)	*p*=0.0027
	Placebo	-0.46	0.09	-0.55 (-0.87, -0.22)	*p*=0.0010
Change in HOMA-B from baseline (%)	Liraglutide 1.8 mg	41.3	23.8	17.5 (5.7, 29.2)	*p*=0.0037
	Liraglutide 1.2 mg	36.3	26.4	9.9 (-12, 31.8)	*p*=0.3740
	Placebo	1.4	-6.4	7.8 (-14.9, 30.5)	*p*=0.5018
Change in proinsulin:insulin from baseline	Liraglutide 1.8 mg	-0.11	-0.06	-0.05 (-0.1, 0.0)	*p*=0.0535
	Liraglutide 1.2 mg	-0.08	-0.05	-0.03 (-0.14, 0.09)	*p*=0.6504
	Placebo	0.02	0.01	0.01 (-0.07, 0.09)	*p*=0.8130
Change in HOMA-IR from baseline	Liraglutide 1.8 mg	-0.92	-0.94	0.02 (-0.81, 0.85)	*p*=0.9569
	Liraglutide 1.2 mg	-0.94	-1.04	0.10 (-1.55, 1.75)	*p*=0.9074
	Placebo	1.15	-0.18	1.34 (-0.17, 2.84)	*p*=0.0813
		EARLY	LATE	OR (95% CI)	*p* value
Proportion of subjects reaching A1c <7% (%)	Liraglutide 1.8 mg	72	49	2.76 (1.75, 4.34)	*p*<0.0001
	Liraglutide 1.2 mg	61	41	2.28 (0.74, 7.03)	*p*=0.1526
	Placebo	14	9	1.78 (0.69, 4.58)	*p*=0.2311

968-P

Cardioprotective Effect of the GLP-1 Receptor Agonist Lixisenatide on Ischemia-Reperfusion-Induced Injury in the Isolated Rat Heart

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Endogenous glucagon-like peptide 1 (GLP-1) is an incretin peptide secreted from intestinal L-cells in response to food intake. It stimulates insulin release from the pancreas when blood glucose levels are elevated. In addition, there is some evidence that GLP-1 may also have beneficial cardiovascular effects. Therefore, we examined the acute effect of lixisenatide, a novel synthetic GLP-1 receptor agonist, on cardiac function in isolated Langendorff-perfused rat hearts during regional ischemia and reperfusion in comparison to native GLP-1 (GLP-1_{7-36} amide) and liraglutide. This involves transient occlusion of the left anterior descending (LAD) coronary artery for 45 minutes followed by a reperfusion period of 120 minutes allowing simultaneous recording of left ventricular pressure, contractility, heart rate and coronary flow. Infarct size was determined by planimetry. Administration of lixisenatide at 0.3 nM starting 10 minutes prior to and during reperfusion significantly reduced myocardial infarct-size by 36% (p=0.0028 vs vehicle control). Native GLP-1 or liraglutide (both also at 0.3 nM) showed an infarct-size reduction of 32% (p=0.0071 *vs* vehicle control) and 29% (p=0.0159 *vs* vehicle control), respectively. The observed cardioprotective effect was not associated with a significant change in cardiac hemodynamics, particularly coronary flow. However, all GLP-1 receptor agonists stimulated myocardial glucose uptake during recovery from regional ischemia, suggesting a direct cardiac effect. Thus, we show for the first time that the novel GLP-1 receptor agonist, lixisenatide, protects against myocardial ischemia-reperfusion injury in isolated rat hearts. This finding may represent a novel therapeutic benefit and supports the rationale to study lixisenatide in a cardiovascular outcome trial.

969-P

Exenatide Once Weekly: Sustained Improvement in Glycemic Control and Weight Loss through 3 Years

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In a 30-week controlled trial (DURATION-1), the once-weekly formulation of the GLP-1 receptor agonist exenatide (exenatide QW) elicited a more robust glucose lowering effect than the BID formulation of exenatide (ΔA1C: -1.9% vs. -1.5%), coupled with similar weight loss, in patients with type 2 diabetes on a range of background therapies. The controlled period of the trial was followed by an open-ended, open-label period in which all patients either continued exenatide QW treatment or switched from exenatide BID to exenatide QW. Approximately 66% (n=194) of the 295 ITT patients completed 3 years of treatment (baseline [mean±SD]: A1C 8.2±1.0%; FPG 167±44 mg/dL; weight 101±18 kg; duration of diabetes 7±5 y; therapy at screening: diet/exercise [15%], MET [33%], MET+SFU [29%], MET+TZD [9%]). Significant A1C improvement (LS mean [95%CI]) was observed with 3 years of treatment (-1.6% [-1.7, -1.4]), resulting in a mean±SE A1C of 7.0±0.1% (57% achieved A1C ≤7.0%). Significant improvements in FPG (-33 mg/dL [-39, -28]) and weight (-2.3kg [-3.4, -1.2]) were also observed. Furthermore, 3 years of treatment was associated with the following changes in cardiovascular risk markers: systolic blood pressure (-2.1 mmHg [-4.5, 0.2]), total cholesterol (-9.9 mg/dL [-15.5, -4.3]), LDL cholesterol (-7.0 mg/dL [-11.8, -2.1]), and triglycerides (-12% [-18, -6]; geometric LS mean % change). Nausea (predominantly mild) was the most common adverse event with exenatide QW during the initial controlled period (27%), and decreased over time (16% from week 30-156). Injection site pruritus and erythema were infrequent (<5%) from week 30-156 (vs. 18% and 7%, respectively, in the controlled period). Treatment-emergent events leading to withdrawal from week 30-156 were also infrequent (<4%). No major hypoglycemia was observed; minor hypoglycemia in this treatment period occurred predominantly with concomitant SFU. To conclude, exenatide QW elicited a robust and sustained improvement in glycemic control in patients with type 2 diabetes on an array of background treatments. Importantly, this effect was associated with improvements in broader cardiometabolic measures, including body weight and lipids.

970-P

Exenatide Exerts a Potent Anti-Inflammatory Action

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In view of our previous report that exenatide induces a decrease in plasma C- reactive protein concentrations independently of weight loss, we have now tested the hypothesis that it may exert an anti-inflammatory effect in patients with type 2 diabetes. Twenty four patients were prospectively randomized to be injected subcutaneously with either exenatide 10 μg daily (n=12, mean age: 53.8±4.2 years; mean BMI: 39.1±2.3kg/m^2; mean HbA1c:8.2±0.4%) or placebo (n- 12, mean age: 55.6±3.3 years; mean BMI: 38.1±1.9kg/m^2; mean HbA1c:8.6±0.4%) for 12 weeks. Fasting blood samples were obtained at 0, 3, 6 and 12 weeks. Blood glucose fell from 139±17 to 110±9mg/dl and HbA1c from 8.6±0.4 to 7.9±0.6% (P<0.05). There was a significant reduction in ROS generation, the mRNA expression of JNK-1 and TLR-4 in MNC by 18±8%, 20±11% and 16±7%, respectively (P<0.05 for all), and the plasma concentrations of MCP-1, MMP-9 and SAA by 18±8%, 20±11% and 16±7%, respectively (P<0.05 for all). In order to examine the possibility that these actions may be exerted acutely, we examined whether a single injection of exenatide would exert an acute anti-inflammatory effect. Blood samples were collected at 0, 2, 4 and 6h. The injection of exenatide resulted in a significant reduction of pro-inflammatory mediators, JNK-1 and TLR-4 at 2h by 15±4% and 23±7%, respectively (P<0.05 for all). This reduction was transient and coincided with the known pharmacokinetic peak of exenatide at 2h after an injection. We conclude that exenatide exerts an anti-inflammatory effect at the cellular and molecular level and that this may contribute to a potentially beneficial anti-atherogenic effect. **ADA-Funded Research**

971-P

Effect of Exenatide BID on Kidney Function and Adverse Events in Clinical Trials

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Exenatide (EXE) is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise for glycemic control in type 2 diabetes mellitus. EXE is metabolized and excreted via the kidney. This post-hoc analysis assessed the effect of EXE on kidney function in 6 placebo (PBO)-controlled trials (4-6 month duration) of EXE 10 mcg BID. Potential clinically important (PCI) renal function values for BUN and serum creatinine (SCr) are defined as: BUN >45 mg/dL; SCr >1.6 mg/dL (male), >1.4 mg/dL (female). Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were used to estimate glomerular filtration rate (eGFR), with analyses performed on subjects with baseline eGFR <120.

Baseline eGFR was similar between groups (MDRD: EXE 85±16 mL/min, PBO 86±16 mL/min; CKD-EPI: EXE 92±16 mL/min, PBO 92±16 mL/min). The change from baseline was similar between groups (MDRD: EXE 5.0±50 mL/min, PBO 5.7±54 mL/min; CKD-EPI: EXE 2.2±40 mL/min, PBO 1.2±41 mL/min).

At studies' endpoint, there were no clinically meaningful changes from baseline in BUN (EXE -0.3±3.7 mg/dL, PBO 0.3±4.1mg/dL) or SCr (EXE 0.01±0.13 mg/dL, PBO: 0.00±0.11 mg/dL) for either group. Proportion of subjects with elevation of BUN (EXE 16%, PBO 17%) or elevated SCr (EXE 5%, PBO 5%) values were similar between groups. Proportion of subjects with PCI elevated BUN (EXE 0.4%, PBO 0.2%) or PCI elevated SCr (EXE 1.3%, PBO 1.2%) values were similar between groups.

Comparison of the percent of subjects with decreased or increased kidney function using the MDRD equation, showed no significant differences between EXE and PBO (EXE 14% decreased, 14% increased, 72% no change; PBO 12% decreased, 13% increased, 75% no change). Similar results were obtained using the CDK-EPI equation (EXE 11% decreased, 10% increased, 79% no change, PBO 10% decreased, 10% increased, 80% no change). Fewer EXE subjects experienced kidney adverse events (EXE 0.7%, PBO 1.0%) and no acute kidney adverse events were noted in EXE (EXE 0%, PBO: 0.1%).

This posthoc analysis did not show an effect of EXE or PBO on kidney function in subjects with normal or near-normal eGFR.

Supported by: Amylin Pharmaceuticals and Eli Lilly and Company

972-P

Clinical Characteristics and Outcomes in Patients with Type 2 Diabetes (T2D) Adding Insulin Glargine to Exenatide or Exenatide to Insulin Glargine in a US Managed Care Setting

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Few studies have addressed the real-world efficacy or treatment persistence of insulin glargine (GLA) and exenatide (EX) in combination. Using a national US insurance claims database, a retrospective study was conducted in T2D patients aged ≥18 who added EX to GLA (EX+GLA) or GLA to EX (GLA+EX) from 2006-09 and had continuous health plan coverage 6-month pre- (baseline) and 1-yr post-index (follow-up). 422 patients were included, with the majority (67%) in the EX+GLA cohort (mean age 53.9 yrs; 52.3% male) and 33% in the GLA+EX cohort (mean age 54.2 yrs; 58.2% male). The EX+GLA cohort had lower A1C than the GLA+EX cohort at baseline.

A significant reduction in A1C was observed in both cohorts at follow-up. Average daily dose of glargine was 36.1 units in the GLA+EX and 43.4 units in the EX+GLA group. The mean number of hypoglycemic events increased slightly from baseline but remained low in the EX+GLA and GLA+EX cohorts (0.25 to 0.75 and 0.17 to 0.57 events per patient per yr, respectively). Improved lipid profiles were observed at follow-up in both cohorts. Only small proportions of patients stayed on both drugs at the end of 1-yr follow-up (EX+GLA: 11% and GLA+EX: 9.9%) but more patents stayed on glargine than exenatide in both cohorts (EX+GLA: 43.6% vs. 21.0%; GLA+EX cohorts: 44.0% and 23.6%). This real-world study demonstrated that combination use of GLA and EX in T2D patients with poor glycemic control was associated with significant reductions in A1C without increasing hypoglycemia.

	EX+GLA (n=281)			GLA+EX (n=141)		
	Baseline	Mean change at end of follow-up	*P*-value	Baseline	Mean change at end of follow-up	*P*-value
HbA1C, mean ± SD	8.4 ± 1.5	-0.4 ± 1.5	<0.0001	8.9 ± 1.6	-0.9 ± 1.6	<0.0001
HDL-C, mg/dL, mean ± SD†	41.7 ± 12.0	-2.2 ± 10.7	0.0665	41.7 ± 15.9	1.1 ± 12.3	0.53
LDL-C, mg/dL, mean ± SD†	92.7 ± 35.7	-15.2 ± 36.9	0.0003	84.5 ± 36.1	-6.8 ± 29.4	0.12
TG, mg/dL, mean ± SD†	211.4 ± 168.0	-18.5 ± 91.5	0.0699	206.7 ± 171.9	-59.3 ± 169.8	0.02

†For lipids subset, n= 92-95 for EX+GLA and n=55 for GLA+EX

Supported by: Study funding and editorial support provided by sanofi-aventis US.

973-P

Weight Change in Placebo- and Exenatide (BID)-Treated Subjects with Type 2 Diabetes on Insulin Glargine: Effects of Sex, Diabetes Duration, Baseline A1C, and Insulin Dose

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A 30-week, double-blind, placebo (PBO)-controlled study of exenatide (EXE) added to insulin glargine (IG) ± oral agents in type 2 diabetes (T2D) (A1C 7.1-10.5%) demonstrated improved glycemic control, weight (wt) loss and low risk of hypoglycemia. Data were used to examine wt change and the following clinical variables: baseline A1C, T2D duration, IG dose, and sex. 259 subjects (mean age 59 y, wt 94 kg, A1C 8.4%, T2D duration 12 y, IG dose 48 U [0.51 U/kg]) were randomized to EXE 10μg BID+IG (n=137) or PBO+IG (n=122). IG dose was decreased by 20% if A1C ≤8% or maintained if A1C >8%; at 5 weeks, IG was titrated in all subjects to achieve fasting glucose of <100 mg/dL (EXE+IG: 0.66 U/kg vs. PBO+IG: 0.71 U/kg, at study's endpoint).

At endpoint, PBO+IG subjects gained wt while EXE+IG subjects lost wt. EXE+IG-treated subjects had a significant wt reduction compared to PBO+IG in both baseline A1C ≤8% and >8% groups with a greater difference in wt in those with a baseline A1C>8%. PBO+IG-treated subjects had wt gain in the baseline A1C >8% but not the ≤8% group. EXE+IG subjects with T2D duration ≥10 y, but not <10 y, lost more wt than PBO+IG. There was a positive correlation between total IG dose and wt change in the EXE+IG and PBO+IG groups. Significantly greater wt loss with EXE+IG vs PBO+IG was consistent independent of sex or baseline IG dose.

EXE added to optimized IG is consistently associated with wt loss across a range of clinical variables compared to optimized IG (PBO) alone. IG dose change was associated with wt change.

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

Change in weight at Endpoint from BL (kg)

Baseline Variable	EXE+IG	PBO+IG	Difference	p
All	-1.78	0.96	-2.74	<.001
A1C≤8%	-1.97	-0.08	-1.89	0.031
A1C>8%	-1.56	1.45	-3.01	<.001
T2D duration <10 years	-0.92	0.72	-1.64	0.075
T2D duration ≥10 years	-2.28	0.99	-3.27	<.001
IG dose ≤0.5 U/kg	-1.62	0.71	-2.34	0.001
IG dose >0.5 U/kg	-1.72	1.30	-3.02	<.001
Men	-1.55	1.27	-2.81	<.001
Women	-1.92	0.55	-2.47	0.002

Estimates and p-values are from separate mixed models on each subgroup. Data presented as LS Mean.

Supported by: Amylin Pharmaceuticals and Eli Lilly and Company

Guided Audio Tour: Pharmacologic Treatment of Diabetes—DPP-4 Inhibitors *(Posters 974-P to 981-P), see page 15.*

974-P

Effect of a Novel Xanthine-Based DPP-4 Inhibitor (BI 14361) on Infarction Size and Cardiac Function in Rats after Myocardial Ischemia-Reperfusion

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Dipeptidyl peptidase (DPP)-4 inhibition has been reported to have beneficial effects on myocardial ischemia. Mechanisms behind these effects could include the involvement of stromal cell-derived factor (SDF)-1α with subsequent increased recruitment of circulating stem cells and/or incretin receptor-dependent pathways improving tissue repair. The objective of this study was to evaluate the cardiac effects of the novel, linagliptin-like, xanthine-based DPP-4 inhibitor BI 14361 in a rat ischemia-reperfusion injury (I/R) model.

Rats were divided into 3 groups: sham, I/R, and I/R plus BI 14361 (n=10–12 per group). BI 14361 was given once daily starting 2 days before I/R. I/R was induced by ligation of the left anterior descending coronary artery for 30 min. Echocardiography was performed after 5 days and cardiac catheterization after 7 days.

BI 14361 significantly reduced the absolute infarction size (–27.8%; p<0.05), the proportion of infarcted tissue relative to the total area at risk (–18.5%; p<0.05), and the extent of myocardial fibrosis (–31.6%; p<0.05). BI 14361 also significantly increased the accumulation of stem/progenitor cells as characterized by CD34-, CXCR4-, and C-kit-expression and immunoreactivity for active SDF-1α in the infarcted myocardial tissue. Left ventricular ejection fraction was similar in all I/R groups after 7 days; however, DPP-4 inhibition reduced infarct size and fibrotic remodeling, and increased the density of stem cells in infarcted areas by blocking the degradation of SDF-1α.

In summary, although the evidence for DPP-4 inhibition as a new therapeutic strategy for myocardial ischemia is still limited, the findings of this study suggest that further long-term studies are warranted to determine whether the effects of BI 14361 translate into long-term functional improvement.

Supported by: Boehringer Ingelheim

975-P

Mechanisms of the Antihyperglycemic Effect of Sitagliptin in Patients with Type 2 Diabetes (T2D)

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The antihyperglycemic effect of DPP4 inhibitors is thought to be mainly due to potentiation of insulin secretion *via* GLP-1. To assess the mechanism of chronic DPP4 inhibitor treatment, we administered a mixed meal (MM) with 2 glucose (G) tracers (6,6D_2-G infused, D_1-G ingested) to 47 T2D patients (pts) (age=56±7 yrs [mean±SD], BMI=29.9±4.2 kg/m^2, HbA_{1c}=7.4±0.8%) and 7 age- and BMI-matched controls (C); pts were re-studied after 6 weeks of double-blind, randomized treatment with sitagliptin (*sita*, 100 mg/day, n=25) or placebo (*plb*, n=22). Changes from baseline (D) in fasting G (-17±16 *vs* 1±32 mg/dl, p<0.01) and G area-under-curve (AUC) (-10.7±0.7 *vs* +1.8±10.7 g·dl^{-1}·5h, p<0.0001) were greater with *sita* than *plb*, respectively, in parallel with a lower appearance of oral G (DAUC=-64±165 *vs* +26±108 mg·kg^{-1}·5h, p=0.01), and a trend to greater suppression of endogenous G output (DAUC=-33±81 *vs* -7±74 mg·kg^{-1}·5h, p=0.1). Insulin sensitivity, significantly lower at baseline in pts *vs* C (271±42 ml·min^{-1}·m^{-2} *vs* 389±27, p<0.0001), improved by 11% after treatment (D=30±30 *vs* 3±41 ml·min^{-1}·m^2, *sita vs plb,* p<0.01), while total insulin secretion was unchanged. Baseline β-cell G sensitivity (β-GS), lower in pts *vs* C (32[30] pmol·min^{-1}·m^{-2}·mM^{-1} *vs* 98[115], p=0.0002), improved with *sita vs plb* (+19[29] *vs* 5[21], p=0.01). Glucagon and total GIP AUCs decreased (p=0.03 and 0.01, respectively) with *sita vs plb*, while total GLP-1 response was maintained.

At baseline and follow-up, the G response to MM was matched by isoglycemic (iso-G) IV G infusion. As expected, the difference in β-GS (MM minus iso-G) was larger in C than pts (67[91] *vs* 17[22], p=0.0004). Interestingly, *sita vs plb* increased β-GS with *both* MM and iso-G (p=0.01 and p=0.002, respectively), but the relative difference was unchanged from baseline.

We conclude that chronic *sita* treatment improves glycemic control by lowering appearance of oral G, postprandial G release and glucagon response. Insulin sensitivity and β-cell G sensitivity also improve. While reversal of glucose toxicity may at least partly contribute to these findings, the results are consistent with potentiation of active GLP-1 effects on glucagon and β-cell function.

976-P

One Year of Sitagliptin Treatment Does Not Result in Exocrine Pancreatic Pathology in Mice

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DPP4 inhibitors such as sitagliptin (SIT) are approved for use in human type 2 diabetes. A study in transgenic HIP rats with marked overexpression of human islet amyloid polypeptide (hIAPP) suggested that SIT, administered for 12 weeks, was associated with ductal metaplasia and pancreatitis. To determine whether longer term (52 weeks) treatment of transgenic mice with more physiological production of hIAPP is similarly associated with exocrine pancreas pathology, we analyzed pancreata from hIAPP transgenic and non-transgenic mice fed a high fat diet alone (control), with SIT, metformin (MET), SIT+MET or glyburide (GLY) as a secretagogue control. Pancreas sections were examined in a blinded manner for necrosis, fibrosis, inflammatory cell infiltrate, hemorrhage or ductal abnormalities in the exocrine pancreas. Abnormalities were graded as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe).

As there was no difference in the findings between genotypes, data are pooled (Table). No exocrine hemorrhage or ductal abnormalities were observed. All treatment groups exhibited mild to moderate periductal fibrosis and inflammatory cell infiltrates. Mild, focal necrosis was only observed in 2 mice (one control non-transgenic, one SIT non-transgenic). However, hemorrhage was observed in islets from two mice treated with SIT (both non-transgenic); but was not observed in any other treatment group, including SIT+MET. There were no statistically significant differences among the features noted for any treatment and/or genotype group.

Treatment	Control			Sitagliptin (3.1 g/kg in diet)			Metformin (1 g/kg in water)			Sitagliptin + Metformin			Glyburide (50 mg/kg in diet)		
N=	30			32			32			37			27		
Grade	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2
Hemorrhage	30	0	0	32	0	0	32	0	0	37	0	0	27	0	0
Ductal Changes	30	0	0	32	0	0	32	0	0	37	0	0	27	0	0
Necrosis	29	1	0	31	1	0	32	0	0	37	0	0	27	0	0
Fibrosis	17	12	1	19	13	0	26	6	0	27	10	0	18	9	0
Inflammatory Cell Infiltration	18	10	2	23	8	1	27	5	0	26	10	1	21	5	1

In summary, long-term sitagliptin therapy alone or in combination with metformin is not associated with adverse effects on the exocrine pancreas. Further, there is no interaction between hIAPP genotype and treatment to result in exocrine pancreas pathology.

Supported by: Merck

977-P

Short-Term Treatment of GS-9667 in Combination with Sitagliptin Improves Glucose and Lipid Homeostasis in ZDF Rats

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GS-9667, a novel partial agonist of the A_1 adenosine receptor, inhibits adipose tissue lipolysis, lowers circulating free fatty acid (FFA) levels and improves insulin sensitivity in diet-induced models of insulin resistance. The present study was undertaken to compare the anti-diabetic effects of GS-9667 with that of sitagliptin. Zucker Diabetic Fatty (ZDF) rats were treated

with Vehicle, GS-9667 (10 mg/kg, S.C., twice daily), sitagliptin (30 mg/kg, P.O., once daily) alone or in combination for 5 consecutive days. Fasting plasma glucose (FPG), insulin, FFA, Triglycerides (TGs) and Glucagon-like peptide-1 (GLP-1) were measured before and after treatment. An oral glucose tolerance test (OGTT) was also performed at the end of the treatment. FPG levels were significantly lowered by GS-9667 (-38 ± 3%), sitagliptin (-21 ± 6%) or combination (-44 ± 5%) at the end of the study as compared to pre-treatment values. Insulin levels were lower in GS-9667 (-15 ± 12% decrease) and combined (-44 ± 8%) groups but these changes were not significant. GS-9667 significantly lowered FFA levels (-29 ± 4%) and in combination with sitagliptin (-34 ± 7%) while sitagliptin did not have a significant effect on FFA levels. TGs were significantly decreased in GS-9667 (-43 ± 4%) and combination (-57 ± 3%) groups, but no significant change with sitagliptin alone treatment. GLP-1 levels were significantly increased in sitagliptin (5.0 ± 1.0 pM) and combination (4.7 ± 0.6 pM) groups. During OGTT, four groups have similar glucose disposal and insulin response regardless the difference in baseline levels. Compared to the sitagliptin group, GS-9667 + sitagliptin further significantly increased GLP-1 levels to 14.2 ± 3.8 pM during OGTT. Summarized, the glucose lowering effects of GS-9667 and sitagliptin are comparable whereas FFA and TG were decreased only with GS-9667. GLP-1 increase by sitagliptin was further enhanced with GS-9667 in response to the glucose load. In conclusion, combination of GS-9667 with sitagliptin results in enhanced beneficial effects on glucose and lipid homeostasis than each of the agent alone.

Supported by: Gilead Sciences, Inc.

978-P

Linagliptin Offers a New Therapeutic Approach for ARB-Resistant Diabetic Nephropathy

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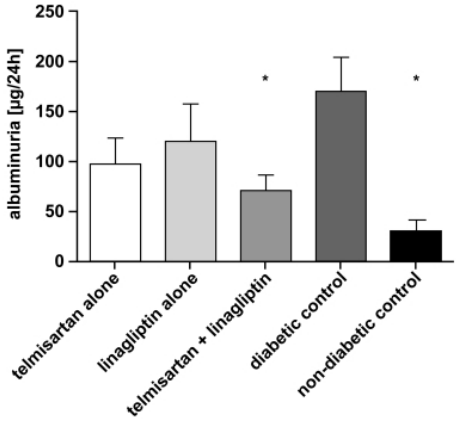
The need for an improved treatment for diabetic nephropathy is greatest in patients who do not adequately respond to angiotensin receptor blockers (ARBs). This study investigated the effect of the novel dipeptidyl peptidase (DPP)-4 inhibitor linagliptin, alone and in combination with the ARB telmisartan, on the progression of diabetic nephropathy in diabetic eNOS knockout mice, a new model closely resembling human pathology.

Sixty-five male eNOS knockout C57BL/6J mice were divided into 4 groups after receiving intraperitoneal high-dose streptozotocin: telmisartan (1 mg/kg), linagliptin (3 mg/kg), linagliptin+telmisartan (3+1 mg/kg), and vehicle. Fourteen mice were used as non-diabetic controls. After 12 weeks, urine and blood were obtained and blood pressure measured.

Glucose concentrations were increased and similar in all diabetic groups. Telmisartan alone reduced blood pressure by 5.9 mmHg vs diabetic controls (111.2±2.3 mmHg vs 117.1±2.2 mmHg; mean±SEM; n=14 each; p=0.071). Combined treatment significantly reduced albuminuria compared with diabetic controls (71.7±15.3 µg/24h vs 170.8±34.2 µg/24h; n=12–13; p=0.017), whereas the effects of single treatment with either telmisartan (97.8±26.4 µg/24h; n=14) or linagliptin (120.8±37.7 µg/24h; n=11) were not statistically significant. Linagliptin, alone and in combination, led to significantly lower plasma osteopontin levels compared with telmisartan alone where values were similar to diabetic controls. Plasma TNF-α concentrations were significantly lower in all treatment groups than with vehicle.



In conclusion, linagliptin significantly reduced urinary albumin excretion in diabetic eNOS knockout mice that were refractory to ARB. Linagliptin may offer a new therapeutic approach for patients resistant to ARB treatment.

Supported by: Boehringer Ingelheim Pharmaceuticals, Inc.

979-P

The DPP-4 Inhibitor Linagliptin Is Weight Neutral in the DIO Rat but Inhibits the Weight Gain of DIO Animals Withdrawn from Exenatide

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Linagliptin is a novel DPP-4 inhibitor for the treatment of type 2 diabetes, which is currently in late stage clinical development. This study assessed the effect of linagliptin (3mg/kg po, once daily for 28 days) either alone or in combination with a low dose of exenatide (3µg/kg/day sc) on body weight, carcass composition and relevant plasma markers of obese female Wistar rats fed a high-fat cafeteria diet (DIO) rats for approximately 20 weeks. Linagliptin had no effect on body weight, daily food intake, plasma glucose, insulin or carcass fat in DIO rats compared to vehicle-treated controls and did not augment the effect of a low dose of exenatide (delivered via a subcutaneously implanted osmotic minipump), when dosed in combination.

In a follow on study (21 days duration), a high dose of exenatide (30µg/kg/day sc) was shown to reduce body weight (6%; $p<0.001$) and body fat (16% $p<0.05$) in DIO rats compared to vehicle-treated controls. Carcass protein ($p=0.8$) and water ($p=0.7$) were not affected. In DIO rats where the osmotic minipump delivering exenatide was removed (Day 10) and replaced by an osmotic minipump delivering saline, weight regain was observed such that the body weight of these animals was not significantly different to controls ($p=0.239$) after 21 days. In contrast, linagliptin (3mg/kg po) reduced weight regain after withdrawal of exenatide such that a significant difference from controls was evident ($p<0.05$). This weight regain was characterized principally by fat deposition and linagliptin-treated animals put on 10.6% less fat than vehicle-treated counterparts during exenatide withdrawal ($p=0.07$).

These data demonstrate that linagliptin, has no weight reducing effect per se in untreated DIO rats or in DIO rats treated with exenatide but in DIO rats where weight loss has been induced by a high dose of exenatide and then withdrawn, linagliptin reduces or delays subsequent weight regain. Linagliptin may, therefore, be of value in controlling weight rebound during intermittent courses of treatment with exenatide.

980-P

Sitagliptin and Metformin Decrease Plasma Glucose by Complementary Mechanisms in Treatment-Naïve Patients with Type 2 Diabetes Mellitus

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Patients with T2D often require combination therapy to achieve glycemic targets and the use of agents with complementary effects may enhance therapeutic benefit. The mechanisms by which sitagliptin (SITA) and metformin (MET) lower plasma glucose were assessed in a randomized, placebo (PBO)-controlled, 4-period crossover study in 18 drug-naïve patients with T2D. Subjects received either SITA (100 mg, AM Days 1 and 2), MET (500 mg AM and PM Day 1 and 1000 mg AM Day 2), SITA+MET (as above) or PBO. Patients ate a standard meal 2 hrs post-dose on Day 2. As reported previously, compared with PBO, SITA, MET, and SITA+MET reduced 2-hr post-meal glucose by 31, 40, and 74 mg/dL, respectively. Relative to PBO, SITA increased 4-hr post-meal active GLP-1 2.2-fold without increasing total GLP-1 while MET increased total and active GLP-1 1.5- and 1.7-fold, respectively; however, SITA+MET increased active GLP-1 3.4-fold. New analysis (see table) shows differences from PBO for incremental post meal 4-hr weighted mean serum insulin, C-peptide and plasma glucagon (LS mean [95% CI]):

	Serum insulin (µIU/ml)	Serum C-peptide (ng/ml)	Plasma Glucagon (pg/ml)
SITA	3.1 (-12.1, 18.2)	0.2 (-0.4, 0.7)	-4.9 (-10.6, 0.8)
MET	-10.4 (-25.6, 4.7)	-0.7 (-1.3, -0.1)	11.7 (5.9, 17.5)
SITA + MET	-22.3 (-37.1, -7.4)	-1.2 (-1.7, -0.6)	0.8 (-4.9, 6.6)

While SITA trended towards an increase in β-cell sensitivity (SITA/PBO = 1.26 [95% CI = 0.87, 1.83]), MET and SITA+MET increased β-cell sensitivity significantly (MET/PBO = 1.67 [1.15, 2.41]; SITA+MET/PBO = 1.71 [1.19, 2.46]). In summary, SITA+MET resulted in greater increase in active GLP-1 and greater decrease in plasma glucose, serum insulin and serum C-peptide than

For author disclosure information, see page 785.

either alone and SITA neutralized an increase in glucagon observed with MET alone. This suggests that SITA and MET have distinct mechanisms of action which combine to reduce plasma glucose more than either alone in patients with T2D.

981-P

Comparison of the Direct and Indirect Antioxidant Effects of DPP-4 Inhibitors: The Anti-Inflammatory and Vasodilatory Potential of Linagliptin

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Dipeptidyl peptidase (DPP)-4 inhibitors are a novel class of drugs for the treatment of type 2 diabetes (T2DM). Preliminary evidence suggests that these agents may confer antioxidant effects that could have beneficial effects on cardiovascular disease, a serious complication of T2DM. This study compared the direct and indirect antioxidant effects of the DPP-4 inhibitors linagliptin, alogliptin, vildagliptin, saxagliptin, and sitagliptin, which differ in their molecular origins and structures.

Antioxidant effects were determined in isolated human leukocytes using phorbol ester-, lipopoly saccharide (LPS)-, and zymosan A-induced oxidative burst (NADPH oxidase activation) using chemiluminescence and fluorescence assays. Indirect antioxidant effects of a therapeutic dose of linagliptin (~3 mg/kg/d added to food) were also tested in a rat model of nitroglycerin-induced nitrate tolerance. Direct vasodilatory effects were measured by isometric tension recordings in isolated rat aortic ring segments.

Linagliptin (IC_{50} ~5 μM) was the most efficient inhibitor of oxidative burst in isolated human leukocytes in response to NADPH oxidase activation by LPS and zymosan A; linagliptin (2 μM) maximally suppressed leukocyte adhesion to endothelial cells in the presence of LPS. In vivo, linagliptin ameliorated nitroglycerin-induced endothelial dysfunction and also reduced the formation of reactive oxygen species in isolated cardiac mitochondria and oxidative burst in whole blood from nitrate-tolerant rats. Finally, linagliptin had the most potent direct vasodilatory effect (EC_{50} ~25 μM) in isolated vessels compared with the other DPP-4 inhibitors tested (EC_{50}>100 μM).

These observations suggest that linagliptin has pleiotropic antioxidant and vasodilatory properties that are not shared (or at least only to a minor extent) by other agents in this class, which may be due to the chemical differences between these agents. Further studies are needed to explore whether these antioxidant properties translate into beneficial effects in patients with T2DM.

Supported by: Boehringer Ingelheim Pharmaceuticals, Inc.

Guided Audio Tour: Pharmacologic Treatment of Diabetes—Novel Therapies—SGLT2 Inhibitors *(Posters 982-P to 989-P), see page 13.*

982-P

Single Doses of LX4211, a Dual Inhibitor of SGLT1 and SGLT2, Improve Parameters of Glycemic Control and Increase GLP-1 and PYY in Patients with Type 2 Diabetes (T2D)

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LX4211 is a dual inhibitor of sodium-glucose co-transporters, SGLT1/SGLT2, designed to block glucose (G) absorption in the GI tract via SGLT1 inhibition and renal G reabsorption via SGLT2 inhibition. This study compared the PK and PD of a liquid and solid formulation of LX4211 in T2D. PD endpoints included biomarkers hypothesized to reflect 1) inhibition of SLGT1 including total and active GLP-1, PYY; 2) inhibition of SGLT2, 24-hr urinary G; and 3) cumulative effect on glycemic parameters including fasting plasma G (FPG), mean plasma G (MPG) and insulin. After a 14-day washout (wo) of metformin, patients received single 300mg oral doses of LX4211 before breakfast as two (2) 150mg tabs, six (6) 50mg tabs, or 300mg solution in a randomized sequence using an open-label, Latin Square crossover design, with a 5-day wo between doses. PK and PD endpoints were assessed on days -1 (baseline [BL] untreated control), 1, 6, and 11.

		2x150mg		6x50mg		300mg liquid	
	BL	Dose Day	Change from BL	Dose Day	Change from BL	Dose Day	Change from BL
FPG (mg/dL)[#]	183.0	166.0	-17.0[b]	167.2	-15.8[b]	165.0	-18.0[b]
MPG (mg/dL)*	201.9	174.9	-27.0[a]	171.0	-30.9[a]	171.5	-30.4[a]
Insulin (μIU·hr/mL)**	563.5	480.4	-83.1[a]	492.9	-70.6[a]	462.7	-100.8[a]
Total GLP-1 (pmol·hr/L)**	85.3	99.2	13.9[c]	100.3	15.0[a]	99.5	14.2[c]
Active GLP-1 (pmol·hr/L)**	42.3	49.5	7.2[b]	51.1	8.8[c]	45.3	3.0
Total PYY (pmol·hr/L)**	387.8	484.5	96.7[b]	511.6	123.8[a]	505.1	117.3[a]
24-hr urinary G (g)[#]	17.3	73.1	55.8[a]	77.5	60.2[a]	84.8	67.5[a]

[a]P<0.001
[b]P<0.05
[c]P<0.01
[#]2 hrs post dose
*Hrs 2-13 after dosing
**Mean AUC for the day

PK and PD were similar between LX4211 formulations, with favorable changes noted in indices of glycemic control including reduction of FPG, MPG, and insulin. LX4211 significantly increased total and active GLP-1, PYY, and urinary G excretion. AEs were infrequent. The ability of single doses of LX4211, a dual SGLT1/SGLT2 inhibitor, to significantly increase GLP-1 and PYY, and rapidly lower FPG and MPG, is consistent with the hypothesis that SGLT1 is a desirable drug target in addition to SGLT2. Further study of LX4211 as a potential treatment for diabetes is warranted.

983-P

TS-071, a Novel, Potent and Selective SGLT2 Inhibitor, Improves Glycemic Control and Preserves Pancreatic β-Cell Mass in Diabetic Mice

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TS-071 (TS) is a novel sodium-dependent glucose co-transporter 2 inhibitor, which is under clinical development for type 2 diabetes (T2DM). TS increases urinary glucose excretion and provides insulin-independent reduction of hyperglycemia in vivo. In this study, we examined the effects of chronic TS treatment on glycemic control and β-cell injury in two models of T2DM. Eleven-week-old db/db mice were given orally either vehicle (VEH) or TS for 8 weeks. At the end of the study, TS (3 mg/kg QD) significantly decreased plasma glucose (PG), glycated hemoglobin (GHb) and triglyceride (TG) [fasting PG (mg/dL): VEH 796±36 vs. TS 535±22, P<0.001; GHb(%): VEH 9.5±0.3 vs. TS 6.9±0.2, p<0.001; fasting plasma TG (mg/dL): VEH 87±14 vs. TS 47±5, p<0.05]. TS significantly restored the insulin-positive β-cell to total islet area (VEH 21.5±1.6% vs. TS 31.8±2.3%, p<0.01) and normalized α-cell/β-cell distribution pattern in islets (α-cell / β-cell ratio: VEH 0.31±0.04 vs. TS 0.16±0.03, p<0.05). Next, ICR mice were made diabetes by high-fat diet (HFD) feeding and 100 mg/kg streptozotocin (STZ). HFD/STZ mice were given orally VEH, TS (1-10 mg/kg QD) or a DPP-4 inhibitor, sitagliptin (SITA, 100 mg/kg BID) for 12 weeks. TS and SITA significantly decreased GHb (ΔGHb (%): VEH = 0.33±0.4, TS 1 mg/kg = -0.12±0.3, TS 3 mg/kg = -0.61±0.3, TS 10 mg/kg = -1.09±0.1*, SITA = -1.09±0.3*, *p < 0.05 vs. VEH). SITA inhibited plasma DPP-4 activity up to 90% and increased plasma insulin. TS decreased fed PG without stimulating insulin secretion. At the end of the study, significant reduction in pancreatic insulin content from VEH-treated HFD/STZ mice was observed compared with normal mice. Both TS (10 mg/kg) and SITA significantly restored pancreatic insulin contents (μg/g·pancreas: VEH = 29.3±4.9, TS 1 mg/kg = 38.8±3.8, TS 3 mg/kg = 43.0±4.6, TS 10 mg/kg = 53.5±5.7**, SITA = 55.1±10.3*, *p < 0.05, **p < 0.01 vs. VEH). The head-to-head comparison of TS with SITA showed that TS was equally effective as SITA on β-cell injury in HFD/STZ mice.The β-cell preservation effect of TS may be mediated by relief of glucotoxicity and a reduction of insulin secretory demand.

984-P

Characterization of Urinary Tract Infections in the Setting of Pharmacologically Induced Glucosuria

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Type 2 diabetes mellitus (T2DM) predisposes patients to urinary tract infections (UTI). While glucose added to urine has been reported to increase *E. coli* growth *in vitro*, epidemiological data do not consistently show an association between glucosuria and UTI. Controlled clinical trials with dapagliflozin (DAPA), an SGLT2 inhibitor that improves glycemia in patients with T2DM via dose-dependent urinary glucose excretion, offer an opportunity to test this hypothesis. Two analysis methods are described here that use pooled data from 12 randomized studies (12-24wk). Active, directed questioning was used at each visit to identify possible UTI. In the broadest analysis, 65 prespecified MedDRA-preferred terms (PT) were used, including signs and symptoms suggestive of UTI (e.g. dysuria) plus diagnoses of infection of the urinary tract. For a more specific analysis, 9 PT relating only to diagnosed infection were used. Rates of events suggestive of UTI and more definitive events of diagnosed UTI were similar to placebo (PBO) with DAPA 2.5mg and higher with 5 and 10mg (Table). Narrowing the analysis from suggestive to diagnosed UTI reduced the observed event rate. Most UTI did not recur in the 12-24wks, and patients with a history of recurrent UTI were more likely to have an event during the study than those without a prior history. Urine cultures were obtained in ~1/2 of the suggestive events, and ~2/3 of these cultures were positive. The majority of events were mild to moderate and few patients discontinued or interrupted treatment as a result. UTI in the DAPA groups were qualitatively similar to those in the PBO group and the general T2DM population with respect to pathogens, complications and response to antibiotics. Pyelonephritis was infrequent in all groups (PBO- 1; DAPA 2.5mg- 2; DAPA 5mg- 1; DAPA 10mg- 0). In summary, DAPA (≥5mg) was accompanied by an increased risk of UTI with the actual event rate dependent on the data capture method.

		DAPA (mg/d)			
		PBO	**2.5**	**5**	**10**
	N	1393	814	1145	1193
Events Suggestive of UTI(%) 65PT	Total	4.5	4.2	7.3	6.5
Diagnosed UTI(%)	Total	3.7	3.6	5.7	4.3
9PT	Women	6.6	5.8	9.6	7.7
	Men	1.0	1.4	1.6	0.8

Supported by: AstraZeneca and Bristol-Myers Squibb

985-P

Characterization of Genital Infections in the Setting of Pharmacologically Induced Glucosuria

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Dapagliflozin (DAPA), a selective inhibitor of the sodium glucose cotransporter 2 (SGLT2), improves glycemia by inducing dose-dependent urinary glucose excretion in patients with type 2 diabetes mellitus (T2DM). Urinary glucose may provide a favorable growth environment for otherwise commensal genital microorganisms and could increase the risk for genital infection (GenInf). Controlled clinical trials of DAPA offer an opportunity to evaluate this risk. Two analysis methods are described here using pooled data from 12 randomized studies (12-24wk). Active and directed questioning was performed at each visit to identify possible GenInf. In the broadest analysis 45 MedDRA-preferred terms (PT) were used and included nonspecific signs and symptoms suggestive of GenInf (e.g. pruritus) as well as diagnosed cases (e.g. vaginal infection). A more specific analysis relating only to diagnosed GenInf was performed using a combination of 19 PT. Events suggestive of GenInf and more definitive events of diagnosed cases were higher with all DAPA doses (2.5 to 10 mg/d) vs. Placebo (PBO). No clear dose relationship for rates of GenInf with DAPA was apparent. Most patients with GenInf experienced only 1 event. Narrowing the analysis from suggestive events to diagnosed GenInf reduced the observed event rate. Most events of GenInf were mild to moderate and few subjects discontinued study drug treatment as a consequence of a GenInf event. GenInf were handled according to standard of care and antifungal or antimicrobial treatment was used in 68% to 88% of events of GenInf in the DAPA groups and 92% in the PBO group. The majority of treated GenInf responded to a single course of treatment. These results suggest that treatment with DAPA is accompanied by an increased risk for GenInf with the actual event rate dependent on the method used for data capture.

		DAPA (mg/d)			
		PBO	**2.5**	**5**	**10**
	N	1393	814	1145	1193
Events Suggestive of GenInf (%) 45 PT	Total	2.1	5.8	7.0	7.0
Diagnosed GenInf (%)	Total	0.9	4.1	5.7	4.8
19 PT	Women	1.5	5.8	8.4	6.9
	Men	0.3	2.4	2.8	2.7

Supported by: AstraZeneca LP and Bristol-Myers Squibb Company

986-P

Dapagliflozin Added-On to Pioglitazone Reduces HbA1c and Mitigates Weight Gain with Low Incidence of Hypoglycemia in Type 2 Diabetes

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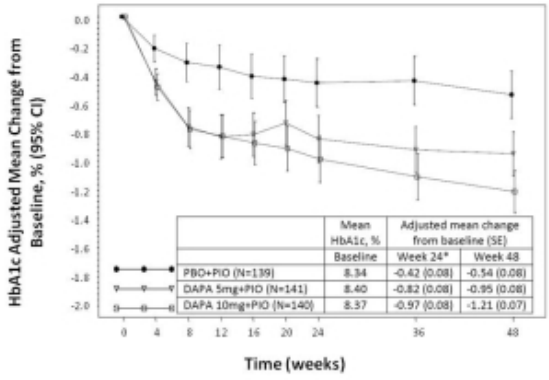
Dapagliflozin (DAPA), an SGLT2 inhibitor, has been shown to improve glycemic control in type 2 diabetes (T2DM) alone or added-on to metformin, sulfonylurea or insulin. This is the first report of DAPA in combination with pioglitazone (PIO). Primary objective was HbA1c change from baseline with DAPA+PIO vs placebo (PBO)+PIO at week 24 in T2DM inadequately controlled on PIO alone (HbA1c ≥7.0-≤10.5%). Following run-in periods of 2 weeks (those on previous PIO, 48%) or 12 weeks (those starting PIO, 52%), patients on PIO ≥30mg were randomized to DAPA 5 or 10mg or PBO QD plus open-label PIO. Mean baseline demographics: age 53.5yr; duration T2DM 5.5yr; HbA1c 8.4%; FPG 165mg/dL, weight 86kg. Significant mean reductions occurred in HbA1c (Figure), FPG, and 120-min PPG, at week 24 and maintained through week 48 in both DAPA groups (Table). DAPA attenuated the PIO-induced weight gain (Table). Discontinuations were low and similar in DAPA and PBO groups. Through 24 weeks: 3 patients on DAPA 5mg reported minor hypoglycemia episodes; events suggestive of genital infection were reported in 7.1-7.8% on DAPA vs 2.9% on PBO; events suggestive of UTI occurred in 3.6-7.8% on DAPA vs 5.8% on PBO. In conclusion, DAPA+PIO was effective, well tolerated, and mitigated the weight gain of PIO without increasing hypoglycemia risk.



*The primary analysis at week 24 was based on ANCOVA model using LOCF data, all remaining data used repeated measure analysis

	Week 24 (LOCF)			Week 48*		
	PBO+PIO (n=139)	DAPA 5mg+PIO (n=141)	DAPA 10mg+PIO (n=140)	PBO+PIO (n=139)	DAPA 5mg+PIO (n=141)	DAPA 10mg+PIO (n=140)
Δ FPG, mg/dL	-5.5 (2.9)	-24.9 (2.9)†	-29.6 (2.9)†	-13.1 (3.6)	-22.8 (3.2)	-33.1 (3.0)
Δ 120-min PPG, mg/dL	-14.1 (6.4)	-65.1 (6.3)†	-67.5 (6.4)†	-25.4 (7.1)	-60.4 (5.9)	-80.9 (5.7)
Δ Weight, kg	1.64 (0.28)	0.09 (0.28)†	-0.14 (0.28)†	2.99 (0.41)	1.35 (0.38)	0.69 (0.36)

Adjusted mean change from baseline (SE); *see footnote in figure; †p-value<0.001

Supported by: Bristol-Myers Squibb Company and AstraZeneca LP

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

987-P

Dapagliflozin Selectively Inhibits Human SGLT2 Versus SGLT1, SMIT, SGLT4 and SGLT6

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Dapagliflozin, an SGLT2 inhibitor that reduces renal glucose reabsorption and may potentially provide an insulin-independent therapy for the treatment of Type 2 diabetes, is 3000-fold selective for human SGLT2 vs. human SGLT1 based on *Ki* values. However, the inhibition of other SGLT family members by dapagliflozin has not been reported to date. SMIT (SLC5A3), SGLT4 (SLC5A9) and SGLT6 (SLC5A11) were stably expressed in CHO cells and the inhibition constants (*Ki*) for both phlorizin and dapagliflozin have been generated. In CHO cells stably expressing human SGLT4, sodium-dependent ^{14}C- α-methyl glucopyranoside (AMG) uptake was assessed at concentrations ranging from 0.5-10mM. Sodium-dependent ^{14}C-myo-inositol uptake in CHO cells expressing recombinant SMIT or SGLT6 was determined at concentrations ranging from 0.1-500μM. The uptake was carried out at 37°C for 2hr in presence of phlorizin at 50-500μM or dapagliflozin at 0.5-500μM. The *Km* values for the respective substrates and the *Ki* values for the inhibition by phlorizin and dapagliflozin for the different isoforms are described below.

Common Name	SGLT1	SGLT2	SMIT	SGLT4	SGLT6
System Name	SLC5A1	SLC5A2	SLC5A3	SLC5A9	SLC5A11
Substrate/*Km*(mM)	1.62±0.6	1.32±0.38	0.08±0.008	1.6 10^{-3}±2 10^{-4}	0.088±0.012
Phlorizin/*Ki*(μM)	0.164±0.01	0.05±0.00	150±40	5.5±0.9	13.0±0.5
Dapagliflozin/*Ki(μM)*	0.61±0.18	2.10^{-4}±6.10^{-5}	14±2	3.3±0.7	0.81±0.12

Both SMIT and SGLT6 were found to transport myo-inositol with *Km* values of 80 and 88μM, respectively. In the present study, dapagliflozin showed *Ki* values of 14 ± 2, 3.3 ± 0.7 and 0.81 ± 0.12μM vs, SMIT, SGLT4 and SGLT6 respectively. We have demonstrated that dapagliflozin is highly selective for human SGLT2 and the inhibition constants for dapagliflozin vs. SGLT1, SMIT, SGLT4 and SGLT6 are 3000, 70000, 16500 and 4050-fold lower than for SGLT2. Phlorizin is 250-fold less potent than dapagliflozin at SGLT2, and is 3-fold, 3000-fold, 110-fold and 260-fold selective vs. SGLT1, SMIT, SGLT4 and SGLT6, respectively. This selectivity profile for dapagliflozin suggests that off-target effects due to the inhibition of these SGLT transporters are unlikely.

Supported by: AstraZeneca LP and Bristol-Myers Squibb Company

988-P

Long-Term Efficacy of Dapagliflozin as Add-On to Metformin (MET) in T2DM Inadequately Controlled with MET Alone

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Dapagliflozin(DAPA), a selective SGLT2 inhibitor, reduces hyperglycemia in an insulin-independent manner by increasing renal glucose elimination. Short-term Wk24 treatment effects were previously reported for this randomized, double-blind, placebo(PBO)-controlled trial (MB102014)[n=546] of DAPA added to metformin(MET) in T2DM inadequately controlled with MET alone [1° endpoint, HbA1c at Wk24]. We report here extended treatment results at Wk102. Patients(pts) 18–77y, HbA1c 7–10%, received DAPA 2.5, 5, 10mg or PBO, plus open-label MET(≥1500mg/d). Wk102 exploratory endpoints included changes from baseline(BL) in HbA1c, FPG and weight. Overall 71.2% of pts completed the study; fewer on PBO(63.5%) than on DAPA(68.3–79.8%), due mainly to more on PBO discontinuing for lack of efficacy. All DAPA groups showed greater mean reductions from BL in HbA1c and FPG *vs* PBO at Wk102 (Table), similar to effects seen at Wk24 and maintained throughout the trial. More pts achieved HbA1c<7% at Wk102 on DAPA(20.7–31.5%) than on PBO(15.4%). Adverse events(AEs), serious AEs and AEs leading to discontinuation were balanced across all groups. Events suggestive of genital infection(GenInf) were reported in 11.7%, 14.6%, 12.6%(DAPA 2.5, 5, 10mg) and 5.1%(PBO) of pts, with 1 discontinuation due to GenInf. Events suggestive of urinary tract infection(UTI) were reported in 8.0%, 8.8%, 13.3%(DAPA 2.5, 5, 10 mg) and 8.0%(PBO), with 1 discontinuation due to UTI. No event of pyelonephritis was reported. In summary, compared to PBO, DAPA added to MET over 102 wks showed greater and sustained improvements in glycemic control, clinically meaningful weight reduction, and no increased risk of hypoglycemia in T2DM inadequately controlled with MET alone.

Wk102 Results

Adj. Mean Δ From BL (SE)*	PBO +MET	DAPA 2.5mg +MET	DAPA 5mg +MET	DAPA 10mg +MET
HbA1c, %	0.02 (0.11)	-0.48 (0.10)	-0.58 (0.10)	-0.78 (0.09)
FPG, mg/dL	-10.4 (3.6)	-19.3 (3.2)	-26.5 (2.8)	-24.5 (2.7)
Body weight, kg	-0.7 (0.5)	-2.2 (0.5)	-3.4 (0.4)	-2.8 (0.4)
% Pts with ≥1 hypoglycemia event†	5.8	3.6	5.1	5.2

*Longitudinal repeated measures analysis. Excludes post-rescue data.
†Includes post-rescue data.

Supported by: Bristol-Myers Squibb, AstraZeneca

989-P

Efficacy and Safety of BI 10773, a New Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitor, in Type 2 Diabetes Inadequately Controlled on Metformin

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SGLT-2 inhibition is a novel insulin-independent glucose-lowering target in type 2 diabetes (T2D). The aim of this double-blind, placebo-controlled 12-week study was to assess the efficacy and safety of 5 doses of BI 10773, a potent SGLT-2 inhibitor in T2D inadequately controlled on metformin. A total of 495 subjects (mean baseline HbA_{1c} 7.9%, age 58 yrs, male 51%, BMI 31.4 kg/m^2) were randomized to BI 10773 (1mg, 5mg, 10mg, 25mg, or 50mg qd), or placebo (PBO), or open-label sitagliptin 100mg (SITA), added to metformin, for 12 weeks. Primary endpoint was change in HbA_{1c} from baseline to week 12. Significant and dose-dependent reductions in HbA_{1c} vs PBO were shown with BI 10773 with a maximum PBO-subtracted lowering of ~0.7% with the 10mg and 25mg doses, whereas SITA lowered HbA_{1c} by ~0.6% vs PBO. Significant reductions in FPG and body weight vs PBO were observed in all BI 10773 groups except 1mg. A maximum PBO-corrected reduction in systolic BP of ~6 mmHg was seen with BI 10773 25mg. Frequency of adverse events (AEs) was similar in all groups (BI 10773: 38.5%, PBO: 36.6%, SITA: 35.2%). The most frequently reported AEs in the BI 10773 groups vs PBO were urinary tract infection (UTI) (3.1% vs 2.8%) and pollakiuria (2.5% vs 1.4%). Genital infections were reported on BI 10773 (2.5%) and SITA (1.4%) but not PBO. Rates of hypoglycemia were similar between groups. Thus BI 10773 resulted in dose-dependent reductions in HbA_{1c}, FPG, body weight and was well tolerated with slightly increased frequency of genital infections but not UTIs vs PBO.

		ΔHbA$_{1c}$, % from baseline	ΔHbA$_{1c}$, % vs PBO	ΔFPG, mg/dL	ΔBody Weight, kg
BI 10773	PBO	0.15(0.08)	-	4.75(3.48)	-1.16(0.31)
	1mg	-0.09(0.08)*	-0.24(0.10)*	-1.70(3.49)	-1.55(0.31)
	5mg	-0.23(0.08)‡	-0.39(0.10)‡	-15.84(3.45)§	-2.28(0.31)†
	10mg	-0.56(0.08)§	-0.71(0.10)§	-22.14(3.49)§	-2.74(0.31)‡
	25mg	-0.55(0.08)§	-0.70(0.10)§	-26.83(3.47)§	-2.56(0.31)‡
	50mg	-0.49(0.08)§	-0.64(0.10)§	-27.91(3.46)§	-2.85(0.32)§
SITA	PBO	0.13(0.10)	-	5.31(3.75)	-1.16(0.31)
	100mg	-0.45(0.10)§	-0.58(0.12)§	-12.18(3.73)†	-0.84(0.31)

All data are mean(SE). *p<0.05, †p≤0.01, ‡p≤0.001, §p≤0.0001 vs PBO

Supported by: Boehringer Ingelheim Pharmaceuticals, Inc.

Guided Audio Tour: Pharmacologic Treatment of Diabetes—Novel Therapies I *(Posters 990-P to 997-P), see page 13.*

990-P

Bile Acid Sequestrant Colestilan Improves Peripheral Insulin Sensitivity in High-Fat Fed ApoE*3 Leiden Mice

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Colestilan, a bile acid sequestrant (BAS), has been used for the treatment of hypercholesterolemia in Japan since 1999. Interestingly, recent studies have demonstrated that BAS also improves hyperglycemia in diabetic animals as well as in type2 diabetic patients. However, the mechanism of the glucose-lowering effect of BAS remains unknown. In this study, we evaluate the effect of colestilan on insulin resistance in high-fat fed hyperlipidemic apoE*3 Leiden (E3L) mice and to investigate the underlying mechanism of its action.

E3L mice were treated with either a high-fat diet or a high-fat diet containing 1.5% w/w colestilan for 8 weeks. Colestilan decreased body weight (-18.4%), visceral fat (-65.5%) and plasma cholesterol (-37.5%) and triglyceride (-26.9%) levels, whereas food intake was increased. Although colestilan increased hepatic lipid synthesis and fecal lipid excretion, lipid content in liver was not changed. Blood glucose and plasma insulin were decreased (-20.6%,-37.7%) with colestilan treatment, and hyperinsulinemic euglycemic clamp analysis demonstrated improved insulin sensitivity, especially in peripheral tissue. Respiratory exchange ratio (RER) was elevated after treatment with colestilan, indicating colestilan-induced catabolism of carbohydrates. By using kinetic analysis we foud that colestilan increased the fractional catabolic rate of plasma glycerol and free fatty acids, and increased [3H]-FFA-derived radioactivity in cholesterol and phospholipid (+258.9%,+127.3%) in bile.

We conclude that colestilan improves peripheral insulin sensitivity in high-fat fed E3L mice by decreasing visceral obesity via an increased flux of free fatty acid from adipose tissue to the liver for the synthesis and excretion of biliary lipid.

991-P

The Effect of Chronic 11β-Hydroxysteroid Dehydrogenase-1 Inhibition on Glucose Metabolism in Response to Stress Hormones

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Cortisol is a hormone that can potently regulate carbohydrate metabolism. Significant cortisol production occurs within the liver, where 11β-hydroxysteroid dehydrogenase-1 (HSD) converts cortisone to cortisol. Since cortisol can increase hepatic glucose production (HGP) through transcriptional effects on glucoregulatory enzymes, chronic inhibition of HSD may have regulatory effects on HGP. The aim of this study was to determine how chronic HSD inhibition affects the hepatic response to metabolic stress. Dogs with previously implanted arterial, portal and hepatic vein catheters were treated for 7d with an HSD inhibitor (HSDi; n=6) or placebo (PBO; n=6). ^{3}H-glucose and d4-cortisol were infused from -140 min (the latter, when converted to d3-cortisol, provides an index of HSD activity). After a basal sampling period (-40 to 0 min), a 240 minute experimental period followed in which somatostatin was infused to inhibit insulin and glucagon secretion, and these hormones were replaced intraportally at 2x and 5x basal amounts, respectively. At the same time, epinephrine was infused peripherally to raise the plasma levels of the hormone to 6x basal. The plasma glucose level in HSDi was matched to that in PBO by peripheral infusion of glucose. Chronic HSD inhibition did not change arterial plasma cortisol levels. However, hepatic d3-cortisol production was completely inhibited (23±2 vs 0±0 ng/kg/min). During the stress hormone challenge, the glucose infusion rate required to maintain similar glycemia (160 mg/dl) was greater in HSDi compared to PBO (2.0±1.0 vs 0.3±0.2 mg/kg/min; P<0.05), which was accounted for by reduced net hepatic glucose output (NHGO; 0.2±0.4 vs 1.3±0.3 mg/kg/min; P<0.05) and increased whole body glucose utilization (3.2±0.7 vs 2.2±0.1 mg/kg/min; P<0.05). Furthermore, the reduction in NHGO resulted primarily from a fall in net hepatic glycogenolysis (change from basal of 1.4±0.4 vs 0.7±0.2 mg/kg/min; P<0.05). These data suggest that chronic inhibition of HSD leads to reduced hepatic glucose output in response to a stress hormone challenge, thereby making it an attractive therapeutic target in the treatment of type 2 diabetes mellitus.

992-P

WITHDRAWN

993-P

LY2599506, a Novel Glucokinase Activator (GKA), Improves Fasting and Postprandial Glucose in Patients with Type 2 Diabetes Mellitus (T2DM)

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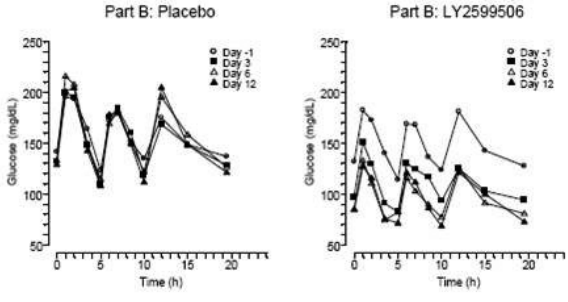
LY2599506 (licensed from Prosidion) is an orally-administered GKA. GKAs lower the plasma glucose threshold for insulin release and may modulate other hormonal and hepatic mechanisms of glucose homeostasis. This Phase 1 study was conducted in 3 parts. In Part A, healthy subjects (n=9) received ~50 mg LY2599506 or placebo four times daily (QID) for 7 days. In Part B, T2DM patients (n=18) underwent dose-titration of LY2599506 or placebo QID for 13 days; in Part C, T2DM (n=11) received twice-daily (BID) and QID LY2599506 dosing for 13 days each in a 2-period crossover design. Planned LY2599506 dose levels were 50, 100, 200, and 300 mg, titrated at 3 day intervals using blood glucose (BG) threshold of 60 mg/dL (Part B) and 80 mg/dL (Part C). Standardized meals at breakfast, lunch, dinner, and bedtime were administered to characterize blood glucose, insulin, glucagon and glucagon-like peptide-1 responses. Mean HbA1c in T2DM was 7.4%, mean diabetes duration was 7 years, and 80% were on stable metformin therapy at baseline. Mild or moderate hypoglycemia was frequent due to dose titration and managed with food/drink. No severe hypoglycemia occurred under conditions of the study, even with dosing at bedtime. QID dosing of LY2599506 achieved a relatively flat 24-h exposure profile. BG was lowered at both fasting and postprandial (PP) time points (Figure). Under ambulatory conditions with dose reduction for BG <80mg/dL, the maximum tolerated daily dose of LY2599506 ranged from 60-530 mg/day. BID dosing was slightly less effective in controlling BG following lunch than QID dosing. Insulin/glucose ratios were increased at fasting and PP time points, but absolute PP insulin levels were not increased. No significant effects on glucagon were observed. LY2599506 was well tolerated and improved glycemic control in T2DM.



For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

994-P

Ebselen, a Glutathione Peroxidase Mimetic, Prevents Fasting Hyperglycemia, Loss of Insulin Secretion, Increases β-Cell Mass, and Preserves Intranuclear MafA and PDX-1 in ZDF Rats

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We have shown that β-cell-specific overexpression of the antioxidant glutathione peroxidase (GPx) nearly normalizes glycemia in diabetic db/db mice. To ascertain whether this finding can be translated to use of oral drugs, we examined whether ebselen (a GPx mimetic clinically used in humans) treatment of diabetic ZDF rats would affect hyperglycemia. ZDF rats were treated with placebo (control group) or 128 mg/kg ebselen orally per day from 6 to 12 weeks of age. No other anti-hyperglycemic treatment was given. Ebselen prevented fasting hyperglycemia (ebselen = 120 ± 11 vs. control = 293 ± 21 mg/dl; p<0.001) and glucose intolerance (OGTT) and restored glucose-induced insulin secretion from isolated islets (ebselen basal = 71 ± 9, 16.7mM stimulation = 187 ± 45μU/mL; n=5, p<0.05; with no significant response in the control group, n=5). There were no differences in body weight at 12 weeks. Compared to 6 week old untreated controls, β-cell mass at 12 weeks increased 2-fold in control rats and 4-fold in ebselen-treated rats (p<0.05). Apoptotic nuclei were less evident in the 12 week old ebselen-treated ZDF rats compared to the control group. β-cell replication in the ebselen-treated and control 12 week old rats was minimal with no differences. In untreated controls, intranuclear expression of MafA and PDX-1 (two critically important regulators of insulin gene expression) were present at 6 weeks but not at 12 weeks. Ebselen treatment preserved MafA and PDX-1 intranuclear expression in 12 week old animals. Ebselen also prevented intraislet accumulation of 4-HNE and 8-OHdG expression (oxidative stress markers) that were present in non-treated, diabetic ZDF rats. In summary, ebselen prevented fasting hyperglycemia and glucose intolerance and restored insulin secretion, increased beta cell mass and insulin granulation, and preserved intranuclear PDX-1 and MafA. Thus, ebselen is an oral treatment candidate to preserve beta cell function in humans with impaired glucose tolerance and type 2 diabetes.

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995-P

Acute Glucose Fluxes Following a Single Dose of Dapagliflozin

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Dapagliflozin (Dapa) is a potent (Ki=0.2 nM), selective SGLT2 inhibitor (3000-fold vs SGLT1) which reduces renal glucose reabsorption and may provide an insulin-independent mechanism for type 2 diabetes treatment. Dapa reduces hyperglycemia acutely in male ZDF rats without hypoglycemia. To examine the impact of acute Dapa on glucose fluxes, diabetic male ZDF rats (Obese) and normoglycemic lean littermates (Lean), 11 wk of age, were dosed with vehicle (Veh) or Dapa at either 0.5 or 1.0 mg/kg, and studied over a 2 hr period. 3-^{3}H-glucose infusion was used to determine whole body glucose fluxes. Arterial plasma glucose levels were decreased and stabilized between 30 and 90 min in Obese ZDFs following both Dapa doses, while Veh levels were unchanged. Lean Dapa glucose levels were reduced insignificantly. There was a small significant decline in plasma insulin with 1.0 mg/kg Dapa treatment in Lean rats 90-120 min post-dose with no change in Obese ZDF vs Veh. Urine glucose loss was dose-dependently increased in both the Obese and Lean ZDFs with Dapa. Glucose production (Ra) was elevated in the Obese vs Lean ZDFs prior to treatment. In Lean rats, Dapa treatment was associated with a dose-dependent increase in Ra; 1.0 mg/kg induced a significant increase (9.8±0.5 mg/kg-min; p<0.001) vs Veh Lean (6.5±0.4 mg/kg-min). By comparison, in Obese ZDFs, the 0.5 mg/kg dose had no impact on Ra, whereas 1.0 mg/kg increased Ra (13.5±0.6 mg/kg-min; p<0.01) vs Veh. Baseline glucose utilization rate (GUR=Ra-urine glucose loss) was elevated in the Veh Obese group vs Veh Lean. Dapa decreased GUR in Lean at 0.5 mg/kg, and diminished GUR in a non-dose-dependent manner in Obese ZDF rats vs Veh. In conclusion, acute Dapa treatment was associated with an increase in glucose production in both Lean and Obese male ZDF rats at the1.0 mg/kg dose. These data demonstrate that acute Dapa treatment increases endogenous glucose production and decreases plasma glucose in hyperglycemic rats to levels that are similar to normal rats, and doesn't decrease further with increased Dapa dosage. No reduction in glucose is observed in normoglycemic rats, further demonstrating the potential for a minimum glucose set-point with Dapa treatment.

996-P

Evaluation of GSK1292263, a Novel GPR119 Agonist, in Type 2 Diabetes Mellitus (T2DM): Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Single and Multiple Doses

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GPR119 receptor agonists increase glucose-sensitive insulin secretion and circulating gut hormones in animal models of T2DM. GSK1292263 was investigated in 2 randomized, placebo-controlled studies with (i) drug-naïve T2DM patients and patients washed off prior anti-diabetic medications (NCT01119846), and (ii) T2DM patients on metformin monotherapy (NCT01128621). Safety, tolerability, PK and PD of GSK1292263 were evaluated when administered as single (25-800mg; n=45) or multiple doses (100-600mg/day for 14 days; n=96); sitagliptin 100mg/day for 14 days was used as a comparator. Subjects taking GSK1292263 or placebo alone for 14 days were co-dosed with 100mg sitagliptin on day 14. An oral glucose tolerance test (OGTT) and 24h profiles of glucose, insulin, C-peptide, glucagon, GLP-1, GIP and PYY were used to assess PD.

All doses of GSK1292263 were generally well tolerated (no SAEs). The most common drug-related AEs were generally mild and similar in subjects administered GSK1292263, placebo or sitagliptin. GSK1292263 AUC and Cmax were less than dose-proportional over the range of doses evaluated. Food increased the systemic exposure of GSK1292263. Steady state was observed after ~4 days of dosing, consistent with the mean half-life range of ~12-18h. Co-administration of single-dose sitagliptin with steady-state GSK1292263 did not alter the PK of either drug.

Following single doses of GSK1292263, there was a dose-dependent decrease in glucose AUC (0-3h) during the OGTT. After 14 days, GSK1292263 did not reduce $AUC_{glucose}$ (0-24h) when administered alone or when co-dosed with metformin or sitagliptin. There was an increase in circulating gut hormone levels during the prandial periods, especially for PYY. Combination with sitagliptin resulted in increased plasma active GLP-1 concentrations, but lower total GLP-1, GIP and PYY concentrations. Sitagliptin alone reduced $AUC_{glucose}$ (0-24h).

This suggests that GPR119 agonism does not provide clinically meaningful glycemic improvement in T2DM patients, and efficacy is not increased when co-dosed with metformin or sitagliptin.

Supported by: GlaxoSmithKline

997-P

WITHDRAWN

Guided Audio Tour: Pharmacologic Treatment of Diabetes—Novel Therapies II *(Posters 998-P to 1005-P), see page 15.*

998-P

TS-071, a Novel and Selective SGLT2 Inhibitor, Improved Glycemic Control and Decreased Body Weight in 12-Week Study of Japanese Patients with Type 2 Diabetes Mellitus

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Renal sodium-glucose co-transporter 2 (SGLT2) inhibition is known as a new approach for the treatment of type 2 diabetes mellitus (T2DM). TS-071 is a novel, orally bioavailable, and highly selective SGLT2 inhibitor. This was a randomized, double-blind, placebo-controlled, parallel group 12-week study in Japanese patients with T2DM.

A total of 236 T2DM patients were randomized into 0.5, 2.5 or 5 mg-QD of TS-071 or placebo (PBO). Baseline mean HbA1c in each group was about 7.91–8.17 %. HbA1c decreased significantly and dose-dependently, differences from PBO were -0.43, -0.70 and -0.82 % in 0.5, 2.5 and 5 mg groups respectively. Both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) decreased significantly. Differences from PBO in FPG were -14.6, -25.9 and -27.9 mg/dL, and those in PPG at 2-hours after meal-test were -36.1, -43.0 and -57.3 mg/dL in 0.5, 2.5 and 5 mg groups respectively. Body weight (baseline about 65 - 70 kg) significantly decreased in 2.5 and 5 mg groups compared to PBO. Differences in body weight change compared to PBO were -1.8 kg (about 3 % of total body weight) in both 2.5 and 5 mg groups respectively. There was a trend to modestly systolic blood pressure reductions without relevant change in pulse in 2.5 and 5 mg groups.

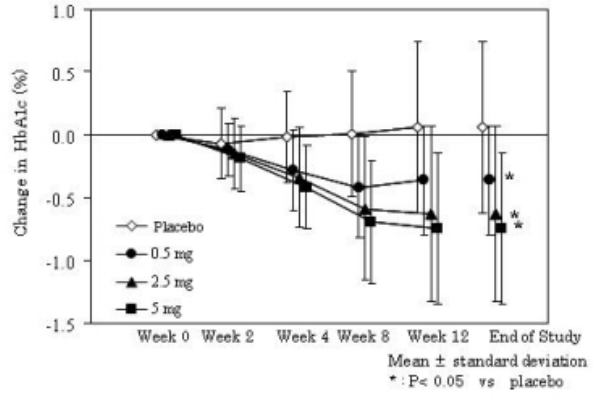

Figure 1. Time-Course of Changes in HbA1c

No major or serious safety concern was observed in all TS-071 groups. No hypoglycemia (less than 70 mg/dL blood glucose level) was observed. Six pollakiuria or urine output increase were observed in 2.5 and 5 mg groups however all events were mild in severity. There were no clinically meaningful changes in serum creatinine or cystatin C, electrolytes.

TS-071 significantly improved HbA1c and other glycemic parameters, induced body weight reduction, and was safe and well tolerated.

999-P

Canagliflozin, a Novel Inhibitor of Sodium Glucose Co-Transporter 2 (SGLT2) Improves Glycemic Control and Reduces Body Weight in Japanese Type 2 Diabetes Mellitus (T2DM)

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Efficacy and safety of a novel, selective SGLT2 inhibitor, Canagliflozin (CANA, TA-7284/JNJ-28431754) as monotherapy in Japanese subjects with T2DM were investigated in a multi-center, randomized, double-blind, placebo-controlled, dose-ranging study. Following a 4-week run-in period, a total of 383 patients (age 57 yrs, HbA1c 8.09%, FPG 165.6 mg/dL, body weight 69.37 kg, BMI 25.70 kg/m^2, at baseline) were randomized to receive CANA 50, 100, 200, 300 mg or matching placebo (PBO) once daily for 12 weeks. HbA1c at Week 12 was significantly decreased in all CANA treatment groups vs. PBO. HbA1c reduction in CANA groups was greater in those patients with baseline HbA1c ≥ 8.0%. Fasting plasma glucose and 2-hours PPG (meal tolerance test) were significantly reduced with CANA treatments. Body weight was reduced by up to 3.19 kg in CANA groups and by 0.78 kg in PBO group. CANA significantly lowered systolic and diastolic blood pressure.

Change from Baseline at Week 12 (LOCF), LS Mean (SE)	50 mg (n=82)	100 mg (n=74)	200 mg (n=75)	300 mg (n=75)	PBO (n=75)
HbA1c (%)	-0.61 (0.06)	-0.80 (0.06)	-0.79 (0.06)	-0.88 (0.06)	+0.11 (0.06)
FPG (mg/dL)	-24.7 (2.1)	-33.1 (2.2)	-36.1 (2.2)	-38.3 (2.2)	-3.0 (2.2)
BW(kg)	-1.98 (0.17)	-2.51 (0.18)	-2.39 (0.18)[1)]	-3.19 (0.18)	-0.78 (0.18)
SBP (mmHg)	-5.8 (1.2)	-7.1 (1.2)	-9.3 (1.2)[1)]	-8.7 (1.2)	-1.2 (1.2)
DBP (mmHg)	-2.2 (0.8)	-3.9 (0.9)	-5.1 (0.8)[1)]	-4.2 (0.8)	-0.9 (0.9)

1) n=76

Thirty five to 49% of patients reported at least one adverse event (AE) and there was no statistical difference in the incidence among the treatment groups. All AEs were mild to moderate in intensity. The most frequently reported AE was nasopharyngitis. AEs related to genital infections were reported in 1 to 2 female patients in each of CANA treatment group and none in PBO. Urinary tract infection was not reported. Pollakiuria was reported in 1 patient each in CANA 50 mg, 100 mg and 300 mg groups. CANA, as monotherapy was generally well tolerated and effective in improving glycemic control and reducing body weight in Japanese T2DM patients.

1000-P

TS-071, a Novel, Potent and Selective SGLT2 Inhibitor, Induces Weight Loss and a Reduction in Adipocyte Size in Diet-Induced Obese Rats

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We have discovered a novel sodium-dependent glucose co-transporter 2 (SGLT2) inhibitor, TS-071 (TS), which is currently under clinical development for the treatment of type 2 diabetes (T2DM). TS is a potent SGLT2 inhibitor with an IC_{50} value of 2.26 nM, and exhibits 1765-fold selectivity for inhibition of SGLT2 over SGLT1. TS competitively inhibited SGLT2 activity with a Ki value of 1.10 nM. The aim of this study is to evaluate the effect of TS on urinary glucose excretion, body weight and metabolic parameters in diet-induced obese (DIO) rats. We also examined the effects of TS on the white adipose tissue mass and the adipocyte size in visceral and subcutaneous fat. Sprague-Dawley rats were made obesity by free access to high-sucrose/high-fat diet for 11 weeks and were given orally either vehicle (VEH) or TS (3 and 10 mg/kg) once daily for 4 weeks. TS significantly increased urinary glucose excretion (VEH = 3.1±0.2 mg/day, TS 3 mg/kg = 2548±144 mg/day***, TS 10 mg/kg = 4938±261 mg/day***, ***$p < 0.001$ vs. VEH) and reduced body weight gain (% change from baseline body weight: VEH = 10.5±1.6%, TS 3 mg/kg = 5.9±0.8%*, TS 10 mg/kg = 2.2±0.9%***, *$p < 0.05$, ***$p < 0.001$ vs. VEH). In addition, TS (10 mg/kg) significantly improved hyperinsulinemia, hypertriglyceridemia and hyperleptinemia in DIO rats. In the pair-feeding experiment, TS (10 mg/kg) induced the marked body weight loss (% change from baseline body weight: VEH 8.9±1.1% vs. TS -1.3±0.7%, $p < 0.001$). TS significantly reduced the white adipose tissue mass in both visceral fat (VEH 89.9±7.0 g vs. TS 66.5±4.2 g, $p < 0.05$) and subcutaneous fat (VEH 96.8±5.4 g vs. TS 67.8±7.7 g, $p < 0.05$). The distribution of the visceral adipocyte size in TS-treated DIO rats was similar to that in lean rats, and TS significantly reduced the average adipocyte size (VEH 9904±883 μm^2 vs TS 7249±282 μm^2, $p < 0.05$). In summary, the decrease in body weight by TS is accompanied by a loss of fat mass and a reduction in adipocyte size, including visceral compartment. These findings suggest that TS exhibits the potential effect for inducing meaningful body weight loss in addition to treating T2DM.

1001-P

The Novel, Potent and Orally Available GPR119 Agonist AS1790091 Enhances Insulin Secretion and Insulin Promoter Activity, Preserves B-Cell Function, Improves Insulin Resistance, and Reduces Body Weight Gain in Type 2 Diabetic Mice

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GPR119 is a Gs-coupled receptor expressed predominantly in pancreatic β-cells and enteroendocrine cells in the small intestine. Activation of the receptor leads to glucose-stimulated insulin secretion (GSIS) and incretin secretion via an increase in intracellular cAMP. Synthetic GPR119 agonists

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

therefore represent a promising target in treating type 2 diabetes. In this study, we evaluated the therapeutic potential of AS1790091, a novel synthetic GPR119 agonist with an EC_{50} value of 0.5 μM for human GPR119. AS1790091 (0.1-10 μM) dose-dependently enhanced insulin secretion in the mouse pancreatic β-cell line MIN6B1 and transiently activated human insulin promoter transfected in the mouse pancreatic β-cell line NIT-1. The maximum efficacy for human insulin promoter activity occurred at doses of 10-30 μM, which was comparable to that of GLP-1 analog exendin-4 at 3 μM. Multiple once-daily dosing of AS1790091 (0.3-3 mg/kg, po) for 2 weeks in diabetic db/db mice significantly reduced blood glucose and increased plasma insulin levels at 1-3 mg/kg. Similarly, AS1790091 markedly improved pancreatic insulin contents that intend pancreatic preservative effects. In KK/Ay mice, a model of type 2 diabetes with hyperinsulinemia, multiple once-daily dosing of AS1790091 (0.3-3 mg/kg, po) for 1 week improved blood glucose and pancreatic insulin contents at 1-3 mg/kg, findings similar to those observed in db/db mice, particularly with regard to reduced plasma insulin levels. Further, AS1790091 induced a reduction in body weight at 3 mg/kg in both db/db and KK/Ay mice. We found that AS1790091 improved not only GSIS and preservation of pancreatic β-cells but also insulin resistance and body weight. Taken together, these findings suggest that GPR119 agonist will help research move on from the GLP-1 pathway as a new generation agent for type 2 diabetes with obesity.

1002-P

TAK-875, a GPR40 Agonist, in Combination with Metformin Improves Glycemic Control and β-Cell Function in Zucker Diabetic Fatty Rats

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GPR40, a G protein-coupled receptor highly expressed in pancreatic β-cells, mediates free fatty acid-induced insulin secretion. TAK-875 (TAK) is a selective and potent GPR40 agonist that lowers plasma glucose via stimulation of glucose-dependent insulin secretion. Metformin (MET) improves insulin resistance by pleiotropic action. Based on complementary mechanisms of action, the combination of TAK and MET is expected to enhance glycemic control vs either agent alone. In this study, we evaluated acute and chronic effects of TAK plus MET in combination in Zucker Diabetic Fatty (ZDF) rats, which spontaneously develop severe diabetes and progressive β-cell dysfunction. In the oral glucose tolerance test, oral administration of TAK (3 mg/kg) and MET (50 mg/kg) decreased glucose AUC by 21.0% and 15.4%, respectively, and TAK+MET additively decreased glucose AUC by 33.8%. In 19-week old ZDF rats with fasting hyperglycemia (ZDF: 234 mg/dL; lean: 101 mg/dL), combination treatment with TAK (10 mg/kg) and MET (150 mg/kg) additively decreased fasting plasma glucose. In a 6-week multiple dosing study, combination treatment with TAK (10 mg/kg, BID) and MET (50 mg/kg, QD) additively decreased glycosylated hemoglobin (TAK: -1.7; MET: -1.8; TAK+MET: -2.4%) and increased fasting plasma insulin (TAK: +7.4; MET: +8.3; TAK+MET: +13.2 ng/mL). In addition, in TAK+MET-treated ZDF rats, HOMA-β was 9.6-fold higher than in vehicle-treated ZDF rats and pancreatic insulin content was restored to a level comparable to that in lean rats (Vehicle: 26; TAK: 42.3; MET: 58.5; TAK+MET: 67.1; lean: 69.1 ng/mg pancreas). Finally, normal islet architecture was also maintained in TAK+MET-treated rats, as assessed by immunohistochemistry. These results suggest that combination treatment with TAK and MET has the potential to slow the progression of diabetes and β-cell dysfunction in ZDF rats, which may result from improvements in both postprandial and fasting hyperglycemia. Our results also suggest that TAK plus MET combination therapy may be a valuable strategy for glycemic control and β-cell preservation in patients with type 2 diabetes.

1003-P

GPBAR1 Agonism Improves Glucose Metabolism and Decreases Gallbladder Emptying in Mice

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Therapies that increase the circulating concentrations of insulin, like sulfonylureas and related insulin secretagogues, have proven beneficial in the treatment of T2D. DPP-4 inhibitors and peptidyl GLP-1 (glucagon-like peptide-1) mimetics represent new anti-diabetic agents that increase insulin secretion in a glucose-dependent manner, with little or no risk of hypoglycemia. GPBAR1 (G Protein Bile Acid Receptor 1) is a G protein-coupled receptor activated by hydrophobic bile acids and is expressed in enteroendocrine intestinal L cells, which secrete GLP-1. GPBAR1 activation promotes GLP-1 secretion in a murine enteroendocrine cell line. In this study, we examined whether acute administration of compound A, a small molecule GPBAR1 agonist, improves glucose metabolism in mice and if this effect is associated with changes in circulating GLP-1 levels. We also tested the effect of compound A on gallbladder emptying in mice since GPBAR1 activation has been linked to the disruption of gallbladder smooth muscle function.

Oral administration of compound A (mEC50= 25 nM) at 30 and 100 mg/kg led to an acute increase in plasma GLP-1 levels by 4- and 8-fold respectively vs. vehicle-treated mice. In addition, compound A, dosed 30 min before an oral glucose tolerance test (OGTT) led to a dose-dependent decrease in glucose excursion with complete suppression achieved at 30 mg/kg. Finally, compound A (30 mg/kg) and the positive control Devazepide (CCK-1 receptor antagonist) completely blocked both, CCK- and egg-yolk-induced gallbladder emptying.

In conclusion, small molecule GPBAR1 agonists represent a new class of GLP-1 secretagogues with potential for the management of diabetes. The effects of decreased gallbladder emptying by GPBAR1 and the potential to increase the risk of gallstone disease require further evaluation.

1004-P

Single Doses of the Glucagon Receptor Antagonist LY2409021 Reduce Blood Glucose in Healthy Subjects and Patients with Type 2 Diabetes Mellitus (T2DM)

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LY2409021 (LY) is a potent, selective antagonist of the glucagon receptor. In T2DM, glucagon levels are inappropriately elevated and contribute to hyperglycemia. This Phase 1, randomized, double-blind, placebo (PBO)-controlled, crossover study examined the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single escalating doses of LY in healthy subjects (HS; 2.5, 10, 30, 100, 250, and 500 mg LY; N=23 males) and patients with T2DM treated with diet and exercise (T2DM; 75, 200, and 500 mg LY; N=9 [5M and 4F]; fasting blood glucose [FBG] 93.6 to 207.0 mg/dL; HbA1c 5.6 to 8.7%). In each dosing period, serial blood samples were collected for measurement of LY PK and PD and standardized meals were provided. Safety was assessed by medical exams, laboratory tests, vital signs, ECGs, and adverse events (AEs).

PK parameters t_{max}, $t_{1/2}$, and apparent clearance (CL/F) were comparable across dose levels and between HS and T2DM, ranging from 4 to 8 h, 50.8 to 58.6 h, and 0.232 to 0.396 L/h, respectively. Plasma exposure of LY increased in proportion to dose in HS and T2DM.

Least squares (LS) mean changes from baseline in FBG vs. PBO ranged from +2.9 to -11.5 mg/dL in HS and from -21.9 to -33.3 mg/dL in T2DM. Across LY dose groups in HS, the mean predinner (10-h post-dose) glucose value appeared 0.11 to 11.4 mg/dL lower than PBO; in T2DM, mean premeal glucose values at lunch (4-h), dinner (10-h), and breakfast (24-h), respectively, appeared from 3.6 to 42.9 mg/dL, 8.4 to 29.8 mg/dL, and 14.0 to 48.5 mg/dL lower than PBO. There were no consistent dose-related changes in postprandial glucose.

In general, LY reduced fasting serum insulin, with significant LS mean changes vs. PBO ($p \leq .02$) observed at higher dose levels (250 and 500 mg in HS at 24-h, and 200 mg [24-h] and 500 mg [48-h] in T2DM).

Notably, hypoglycemia did not occur in HS or T2DM after LY administration. There were no significant changes in laboratory tests, vital signs, or ECGs, and review of AEs indicated LY was generally well tolerated.

This first-in-man study demonstrated clinically significant glucose-lowering by single doses of LY in T2DM.

1005-P

Ethnicity Modifies the Relationship between FPG and HbA1c in Singaporeans

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There are substantial inter-individual variation in glycated hemoglobin (HbA1c) especially among individuals of different races and ethnic groups. We studied whether HbA1c was significantly different among the Chinese, Malay and Indian population in Singapore. A sample of 3897 individuals, without known diabetes (DM), were selected from a cross-sectional study (Singapore Prospective Study). All subjects underwent a detailed interview, physical examination, including anthropometric and blood sampling for biochemical evaluation. Descriptive analysis, Pearson's correlation, analysis of variance and multiple linear regression analyses were used to examine the influence of ethnicity on HbA1c. Mean unadjusted HbA1c was highest among Indians (6.09%), followed by Malays (5.96%) and Chinese (5.76%)

(p<0.05). After adjustment for fasting plasma glucose (FPG), age, gender, waist circumference, serum cholesterol, serum triglyceride, and HOMA IR, HbA1c was still significantly different between Indian and Chinese ethnicities though the magnitude of difference was small (0.06%, p<0.05).

HbA1c	Chinese (n=2697)	Malay (n=633)	Indian (n=565)
Mean	5.76(0.013)	5.96(0.045)	6.09(0.046)
Adjusted mean	5.83(0.01)	5.85(0.02)	5.89(0.022)

There were significant interaction effects between ethnicity and FPG in the multiple regression model for HbA1c such that for the same increase in FPG, HbA1C showed a greater increase in Indians and Malays (p<0.001).

Variables in model	B	*p*
Age	0.005	‹0.001
Female	0.085	‹0.001
Indian	0.055	0.02
Malay	0.005	0.81
FPG(centred)	0.493	‹0.001
Waist circumference	0.004	‹0.001
S.cholesterol	0.033	‹0.001
Indian*FPG	0.066	‹0.001
Malay*FPG	0.133	‹0.001

Indians and Malays had higher HbA1c compared to Chinese with FPG accounting for most of this difference. There was, however, significant interaction between ethnicity and FPG in determining HbA1c values, with weaker association between HbA1c and FPG in Chinese compared to Indians and Malays. Understanding the biological basis of this interaction could help us understand the inter-individual variation in HbA1c.

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Guided Audio Tour: Pharmacologic Treatment of Diabetes—Novel Therapies III *(Posters 1006-P to 1013-P), see page 15.*

1006-P

Characterization of Novel Selective Inhibitors of 12-Lipoxygenase and Assessment of Their Utility in Preserving Human Islet Function

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The enzyme 12-lipoxygenase (12-LO) and its lipid-derived products, which include 12-HETE, are associated with pancreatic beta cell dysfunction and apoptosis. Significantly, targeted knock-out of 12-LO provided nearly 100% protection from diabetes in NOD mice. Inhibition of 12-LO activity therefore provides an attractive target in developing new therapies for diabetes and its complications.

The 12-LO enzyme is a member of a broader lipoxygenase family. We identified ALOX12 as the major form of 12-LO in human islets. Targeted inhibition of 12-LO requires identification of new selective agents. Using a cell-free screen, novel small molecule weight compounds have been identified with a ≥50 fold selective inhibition of ALOX12. These selective 12-LO-inhibitors (12-LO-Is) show efficacy in whole cell studies. Stimulation of human donor islets with arachidonoc acid or calcium ionophore induced the production of 12-HETE; a measure of 12-LO activity. Production of 12-HETE was reduced (77± 6%, non-diabetic; 73% T2DM) in the presence of 1μM 12-LO-I.

Further, a cocktail of pro-inflammatory cytokines (TNF alpha, INF gamma and IL-1 beta) increased gene expression in human islets that associate with islet dysfunction. The induced gene expression was inhibited by 12-LO-Is. Study of the IL-12-STAT4-IFNγ axis in human islets, revealed the 12-LO-Is reduced pro-inflammatory cytokine stimulated gene induction of IL-12 and IFNγ. Microscopically, cell death induced in human islets by pro-inflammatory cytokines was prevented by the inclusion of 12-LO-Is. These gene changes were not seen with structurally related compounds that were inactive in the cell-free screen. The data represents seven human donors and screening of nineteen separate compounds.

Clear experimental data links a role of 12-LO and the products of its activity in the pathogenesis of beta cell destruction in diabetes. Progression of the identified novel small molecular weight inhibitors 12-LO may significantly aid in strategies to preserve beta cell mass and function.

Supported by: JDRF, NIH DK

1007-P

SRT2104, a Novel Small Molecule SIRT1 Activator Ameliorates Insulin Resistance and Promotes Glucose Utilization Measured under a Hyperinsulinemic-Euglycemic Clamp by Enhancing Both Glycolysis and Carbohydrate Oxidation in Mice Fed a High Fat Diet

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The NAD-dependent protein deacetylase SIRT1 integrates multiple aspects of metabolic regulation. Over-expression of SIRT1 in transgenic mice confers protection from high fat diet induced obesity (DIO), improves insulin sensitivity and reduces hepatic steatosis. Small molecule activators of SIRT1 also produce similar metabolic benefits in DIO mice. We report here that oral administration of the highly selective small molecule SIRT1 activator SRT2104, to DIO mice led to reduced body weight and hepatic steatosis and improved insulin sensitivity. The reduction in body weight was due to increased basal metabolic rate through an increase in both fatty acid and carbohydrate oxidation. To understand the mechanisms underlying improved insulin sensitivity, a hyperinsulinemic-euglycemic clamp was performed. SRT2104 enhanced insulin stimulated glucose infusion rate by 52.7% (p<0.05) and rate of glucose disposal by 15.4% (p<0.05). SRT2104 increased insulin stimulated glucose uptake in several tissues including muscle, heart and brown adipose tissue. In addition, SRT2104 increased insulin mediated suppression of hepatic glucose production (33.4±4.4 vs. 13.1±3.4% in control) (HGP, p<0.05) with no effect on basal HGP. Further dissection of glucose utilization pathways revealed that SRT2104 caused an increase in glycolysis as well as a decrease in glycogen synthesis. Molecular analysis of insulin signaling pathways in muscle showed increased insulin stimulated phosphorylation of insulin receptor, Akt, and GSK-3β in SRT2104 treated animals. Taken together, our data provides direct evidence that pharmacological activation of SIRT1 improves insulin sensitivity and promotes glucose utilization via increasing both glycolysis and carbohydrate oxidation and strongly support SIRT1 activation as a novel therapeutic strategy to improve both metabolic function and glucose homeostasis for the treatment of Type 2 Diabetes.

1008-P

High Affinity Insulin Receptor Antibodies Sensitize the Insulin Receptor to Insulin and Restore Glycemic Control in Murine Models of Diabetes

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Dysregulation of the insulin receptor (INSR) plays a role in the insulin resistance that is associated with both type-2 diabetes mellitus (T2DM) and the metabolic syndrome. As a unique approach to diabetes treatment, we employed our phage display technology to produce a panel of fully human monoclonal antibodies with picomolar affinities that sensitized the INSR to insulin. Biophysical studies demonstrated that these antibodies were allosteric modulators that increased the binding affinity of insulin to the INSR up to 20-fold. Moreover they were active on both forms of the INSR.

These antibodies similarly enhanced insulin stimulation of INSR auto-phosphorylation, tyrosine phosphorylation of IRS-1, serine phosphorylation of AKT, and glucose transport. In contrast, they did not potentiate insulin stimulation of cell growth. Also these antibodies did not influence IGF-1 stimulated autophosphorylation of its receptor, and IGF-1 and IGF-2 dependent activation of mitogenesis. Studies performed in hyperinsulinemic and insulinopenic mouse models of diabetes, demonstrated the capacity of these antibodies to enhance insulin sensitivity *in vivo*, and improve several indices of T2DM. In the diet-induced obesity model of insulin resistance, the antibodies markedly improved fasting blood glucose levels and HOMA, and normalized glucose tolerance. Similar dramatic improvements in fasting blood glucose and glucose tolerance were also observed in the insulinopenic, low dose, streptozotocin-high fat diet mouse. Consistent with restoration of glycemic control, the antibodies improved several markers of dyslipidemia in these mouse models. In neither mouse model did the antibodies cause hypoglycemia. These data indicate therefore that monoclonal antibodies can act as insulin sensitizers both *in vitro* and *in vivo*. They also suggest that these monoclonal antibodies have the potential to be new therapeutic agents for the treatment of human T2DM and other related metabolic disorders.

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

1009-P

Anti-CD20 Antibody Synergizes with Proinsulin Plasmid To Prevent the Onset of T1D in NOD Mice

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B-cells play a role in T1D, likely as antigen presenting cells rather than through antibody-production. Results from a clinical trial in T1D using a B-cell depleting anti-CD20 antibody, published in NEJM recently show that anti-CD20 treatment was efficient at preserving C-peptide production over a time span of 6 months, in some T1D patients. In NOD mice, therapeutic administration of proinsulin plasmid was efficient at reverting the recent onset T1D disease. In order to understand the mechanism and increase the efficacy of anti-CD20 mAb mediated protection, we used a newly developed anti-mouse-CD20 antibody in combination with proinsulin-expressing plasmid to generate antigen specific tolerance and prevent T1D. We found that administration of anti-CD20 by itself delayed the onset of hyperglycemia in NOD mice. While >90% of untreated NOD mice became diabetic by 30 weeks of age, only 60% of mice that received 50 μg of anti-CD20 were diabetic. In the peripheral blood, B-cells were significantly reduced on day 7 after anti-CD20 administration and remained low until day 21. There was a compensatory increase in both CD4 and CD8 T-cell numbers; however, the frequencies of Tregs were not increased. To improve the efficacy of anti-CD20 mediated protection, we combined the administration of anti-CD20 with a plasmid expressing proinsulin. Among those mice that received anti-CD20 and the proinsulin-expressing plasmid, 75% of the mice remained diabetes free at 30 wks of age. Thus, while the administration of anti-CD20 alone delays the onset of hyperglycemia in NOD mice, combining the administration of anti-CD20 with the proinsulin plasmid offers greater protection in reducing the incidence of diabetes.

1010-P

WITHDRAWN

1011-P

Chronic Administration of a New Dual NEP/ECE Inhibitor or Losartan Improves Renal Function in Mice with Diabetic Nephropathy

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Endothelins (ET) are potent vasoconstrictors, growth factors and pro-inflammatory agents and have been implicated in the pathogenesis of diabetic nephropathy. The Abbott compound has a dual action to inhibit both endothelin converting enzymes (ECE) and neutral endopeptidase (NEP), an enzyme which degrades natriuretic peptides, like atrial natriuretic peptide (ANP), which are vasorelaxant, antifibrotic and anti-inflammatory. The dual action reduces ET production, increases ANP, and may have efficacy in the treatment of diabetic nephropathy. We employed a model of low dose streptozotocin (STZ) induced diabetic nephropathy in mice. The angiotensin II receptor antagonist, losartan, was used as a positive control. C57BL/6J mice (n=12) were placed on a high fat diet (60% kcal as fat). After a 3 week period, animals were dosed with STZ (50 mg/kg ip) or vehicle for 5 days. STZ-treatment significantly reduced body weight, and plasma insulin, and significantly increased plasma glucose, blood HbA1c, urine volume, urinary glucose and creatinine as well as albuminuria, compared to vehicle-treated controls (all comparisons $p<0.001$). Drug treatment started 2 weeks after diabetes induction. Once daily treatment (108 days) with the Abbott compound (30, 100 mg/kg po) or losartan (50 mg/kg po reduced to 30 mg/kg po after 57 days of treatment due to marked reductions ($p<0.001$) in blood pressure) reduced albuminuria to non-diabetic control levels ($p<0.05$ from STZ-diabetic controls). In addition, the urinary albumin/creatinine ratio was improved with both drug treatments ($p<0.05$). These effects were evident after 3 months of dosing. However, neither drug treatment significantly improved STZ-induced changes in urine volume, glucose excretion or changes in body weight, plasma insulin or glucose. The effects of both compounds to abolish STZ-induced albuminuria indicate nephroprotection. Unlike losartan, which reduced blood pressure in the study, NEP/ECE inhibition did not lead to changes in blood pressure or heart rate. Thus, the new Abbott compound showed a clear ability to ameliorate diabetes-induced nephropathy independent of blood pressure effects.

1012-P

Chronic Treatment with a Glucokinase Activator Delays the Onset of Hyperglycemia and Preserves β-Cell Mass in the Zucker Diabetic Fatty Rat

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Glucokinase (GK) activators reduce blood glucose levels in animals and in human patients with type 2 diabetes (T2DM) by promoting pancreatic insulin secretion and suppressing hepatic glucose production. We and others have previously demonstrated that GK activators stimulate β-cell proliferation and prevent β-cell death in cell-culture models. A recent clinical trial found, however, that glucose lowering was not durable in patients with T2DM treated chronically with a GK activator. It is thus unclear whether chronic activation of GK has lasting positive effects on β-cell function and

mass. Here, we have examined glycemic control, pancreatic insulin content, and β-cell area in the Zucker Diabetic Fatty (ZDF) rat, an animal model of T2DM. Five-week-old male ZDF rats were treated for 5 weeks with Cpd-C (a potent and highly selective GK activator) or glipizide (a sulfonylurea), both administered as food admixtures. As expected, vehicle-treated controls developed hyperglycemia (postprandial plasma glucose >300 mg/dL) and declining plasma insulin levels at 8–9 weeks of age. Similar development of hyperglycemia and declining insulin was observed in animals treated with 3 or 10 mg/kg-day glipizide. In contrast, animals treated with 3 or 10 mg/kg-day Cpd-C showed a dose-dependent delay in this progressive loss of glycemic control. Treatment with Cpd-C also resulted in significantly lower glucose excursions and greater insulin responses during oral glucose tolerance testing, compared with vehicle- and glipizide-treated animals. Treatment with Cpd-C, but not glipizide, significantly increased pancreatic insulin content and %b-cell area in the pancreas. These findings suggest that chronic activation of GK does not reduce b-cell mass or function in the ZDF rat, a laboratory model in which animals become severely obese and resistant to insulin action.

1013-P

VTP-27999: A Novel Direct Renin Inhibitor with Potential for Superior Renal Protection in Diabetic Nephropathy

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Diabetic nephropathy (DN) is the leading cause of end-stage renal disease. RAAS pathway inhibitors (ACEs and ARBs) slow the progression of DN. Direct renin inhibitors (DRIs) should have greater efficacy in RAAS inhibition since they block the rate-limiting step in the generation of Ang II. VTP-27999 is a novel DRI that has completed Phase I studies. In a single ascending dose study in normal volunteers (NVs), dose proportionate increases in plasma drug levels of VTP-27999 were observed with doses from 40 to 1000 mg. The terminal elimination $t_{1/2}$ was ~ 24 hrs, and estimated oral bioavailability was 20-40% (bioavailability for aliskiren is ~2.5%). The drug was well tolerated with no significant adverse events and no discontinuations. A 10-day multiple ascending dose study was performed in salt restricted NVs at doses of 75-600 mg QD, with 300 mg aliskiren QD as an active comparator. Drug safety, tolerability and pharmacokinetics (PK) were evaluated. In addition, multiple RAAS pathway biomarkers were assayed on day 1 including plasma renin activity (PRA) and plasma renin concentration (PRC). The drug was generally well tolerated without significant adverse events, and the PK was well behaved, consistent with predictions from the single dose study. There was >90% inhibition of PRA at all doses. Renin is made mainly in the kidney, and the level of induction of PRC secondary to inhibition of renin activity is a reflection of the amount of inhibition of renin activity in the kidney. The baseline PRC across all subjects was 26±12 pg/ml, and the maximal PRCs following dosing for each cohort were as follows: 75 mg cohort, 280±114 pg/ml; 150 mg, 556±381 pg/ml; 300 mg, 613±164 pg/ml; 600 mg, 1199±323 pg/ml; 300 mg aliskiren, 333±98 pg/ml; and placebo, 32±12 pg/ml. Historically ACEs and ARBs induce PRC ~5-10 fold (~150-300 pg/ml) versus baseline. Thus, VTP-27999 is a potent renin inhibitor that is more efficacious than aliskiren (and ACEs and ARBs) at inducing renin levels, indicating a more complete inhibition of renin in the kidney and demonstrating the potential to provide greater renal protection for diabetic nephropathy than currently available agents.

1014-P

11-Keto-β-Boswellic Acid (KBA) Suppresses Development of Insulitis-Apoptosis of Pancreatic Islets and Elevation of Proinflammatory Interleukins in Multiple Low Dose Streptozotocin (MLD-STZ)-Induced Diabetes of Mice

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Frankincense has been reported to possess immunomodulatory properties. KBA a pentacyclic triterpene is one of its pharmacological active compounds.

In MLD-STZ diabetic mice -a model for type 1 diabetes- we studied whether or not KBA could suppress insulitis and apoptosis of pancreatic islets, increase of colony stimulating factors (CSF) and proinflammatory interleukins (ILs) as well as blood glucose.

BK+/+ mice were i.p. injected with 40mg/kg STZ for 5 days. A second group in addition was treated i.p. with KBA 7.5 mg/kg over a period of 10 days.

After day 10 lymphocytes infiltration and apoptosis of islets were determined histochemically (CD_3 antibodies and anticaspase3). CSF and proinflammatory ILs were assayed in the blood using Multi-Analyte ELISArray Kit. Samples for measuring blood glucose (Accu-Check) were taken on day 0, 5, 10, 21, 28 and 35.

Cytokines (pg/ml)	Control	STZ	STZ+KBA
G-CSF	28.4±3.4	74.8±12.6**	19.3±3.6***
GM-CSF	0.79±0.036	2.97±0.22**	1.10±0.29**
IL-1A	1.89±0.36	5.18±0.37**	2.04±0.28***
IL-1B	3.13±1.01	10.01±1.06**	3.35±0.56**
IL-2	1.64±0.17	7.55±0.84**	2.38±0.51**
IL-6	5.91±0.63	17.55±2.61**	6.41±1.22**

Data are expressed as Mean±SE, n=3-5
Statistical evaluation: control vs. STZ and STZ vs. STZ+KBA
**P<0.01
***P<0.001

10 days after first STZ-injection lymphocytes and apoptotic cells appeared in pancreatic islets. Moreover, all cytokines tested were significantly increased. There was also a continuous increase of blood glucose over a period of 35 days (control vs. STZ: 120.0±7.36 and 295.5±36.40 mg/dl). Simultaneous administration of KBA reduced the increases of G-CSF, GM-CSF and proinflammatory ILs in the serum (see table) as well as infiltration of lymphocytes and apoptosis in pancreatic islets. Blood glucose levels showed no significant increase (STZ vs. STZ+KBA: 295.5±36.40 and 148.5±13.85 mg/dl).

In conclusion, in MLD-STZ treated mice, KBA suppressed development of insulitis, apoptosis, hyperglycemia and increase of proinflammatory ILs. KBA could be promising in prevention and treatment of autoimmune diabetes.

1015-P

A Glargine (Lantus) Based Insulin Program Is Feasible, Effective and Safe When Used in the Long Term Care Facility (LTCF) Environment

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Diabetic residents within the LTCF present great challenges in optimizing glucose control. The range of medical conditions, patient status and limitation in resources dictate careful and appropriate choices for therapeutic intervention, which minimizes risk for hypoglycemia. Although a number of recommended guidelines for diabetes care exist, there are few validated outcome studies demonstrating benefits of specific programs for diabetes management.

We adapted our successful ward glargine insulin based protocol to residents with diabetes in the associated LTCF at our local VA Medical center. We report the initial outcomes in 50 consecutive patients using our protocol within the LTCF. A training program in utilization of the protocol was conducted for nursing staff and attending geriatricians. Electronic order sets were adapted from the existing protocol in our Electronic Medical Record (EMR).

On admission LTCF residents with diabetes were placed on a basal bolus program using glargine insulin administered in the morning based on BMI. Frequency of capillary blood glucose levels were initially measured three times a day before meals, then reduced depending on intensity of insulin needs. Pre-meal analog insulin was given if glucose levels were above 180 mg%. Glucose control was monitored daily via our VA EMR.

Staff adapted to the protocol with minimal problems and high satisfaction. Achievement of goal blood glucose levels was generally obtained within 48 hours and maintained in over 85% of the patients. All Values are mean ± SD. Age was 64±9 with length on protocol 25±27 with A1C 7.7 ±1.6%. Blood glucose was 151 ± 26 mg%. Significant hypoglycemia (<60mg%) was 0.6 episodes per total patient days.

We conclude that a glargine based diabetes program can be highly successful, safe, and adaptable to the dynamic medical environment in the LTCF and should serve as the standard of care for diabetic residents.

1016-P

A Placebo Controlled Single Ascending Dose Phase 1 for Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics after Subcutaneous Administration of VRS-859 in Patients with Type 2 Diabetes Mellitus

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VRS-859, a GLP-1 analog XTEN fusion protein, is designed to provide monthly dosing in type 2 diabetes mellitus (T2DM) patients. Up to 55 T2DM patients on metformin (met) or met and sulfonylurea (SU) are proposed for the study to evaluate the safety/tolerability, pharmacokinetics (PK)

For author disclosure information, see page 785.

and pharmacodynamics (PD) of VRS-859. T2DM patients on met+SU are withdrawn from SU treatment 2 weeks prior to dosing remaining on met only. Each patient receives a single subcutaneous dose of VRS-859 at 12.5, 25, 50, 100 or 150 mg VRS-859 or placebo on Day 1. In each treatment group, 8 patients receive a single dose level of VRS-859 and 3 patients receive placebo in a randomized blinded manner. PD measurements (fasting glucose (FG) and insulin and oral glucose tolerance test (oGTT)) are performed on Days -1, 4, 8, 11, 15, 18, 22, 25, and 30. Safety assessments including calcitonin, lipase, and amylase levels as well as QTc analyses and immune responses are performed through Day 60.

This clinical study is ongoing and 24 T2DM patients have been treated with VRS-859. 8 patients received 12.5 mg VRS-859; 8 patients received 25 mg VRS-859 and 6 patients received 50 mg VRS-859 with no remarkable AEs. No changes in QTc have been observed and no anti-VRS-859 antibodies have been detected. The PK of VRS-859 closely matched the predicted values with the T_{max} occurring approximately 3 days post-dose and a $T_{1/2}$ of approximately 120 hrs. The mean reduction in FG from baseline at Day 4 and Day 8 for patients receiving 25 mg VRS-859 was 36.7 mg/dL and 25.9 mg/dL, respectively. The mean reduction in glucose AUC after oGTT compared to baseline at Day 4 and Day 8 for patients receiving 25 mg VRS-859 was 56.3 mg.hr/dL and 43.2 mg.hr/dL, respectively. These initial results suggest that 25 mg VRS-859 provided effective glycemic control over a week after dosing without gastrointestinal adverse events, a known side effect of this class of drug. Dose escalation to the predicted monthly dose of 100 mg VRS-859 is planned. In summary, VRS-859 was well tolerated and provided glycemic control in T2DM patients.

1017-P

Achieving the Composite End Point of HbA_{1c} <7%, No Hypos, and No Weight Gain: Comparison between Vildagliptin and Glimepiride after 2 Years of Treatment

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It has previously been shown that, as add-on to metformin vildagliptin has similar efficacy on HbA_{1c} as glimepiride after 2 years of treatment but is associated with markedly reduced hypoglycemia risk and no weight gain. In this study, 3118 patients were randomized (vildagliptin, n = 1562; glimepiride, n = 1556): the overall baseline HbA_{1c} was 7.3%. After two years, a similar proportion of patients reached HbA_{1c} <7% (36.9 and 38.3%, respectively with vildagliptin and glimepiride), but with vildagliptin more patients reached this target without hypoglycemia (36.0% vs. 28.8%; p = 0.004). We thus proceeded to perform a post-hoc analysis, where we investigated whether there were differences in a clinically relevant composite end point of HbA_{1c} <7%, no hypos (symptoms and plasma glucose <3.1 mmol/L), and no significant weight gain (<3%) in relationship to duration of diabetes and/or the age of the patients. In this context, only data from subjects with baseline HbA_{1c} >7% were analyzed (vildagliptin, HbA_{1c} = 7.6±0.52, n = 1036; glimepiride, HbA_{1c} = 7.6±0.55, n = 980).

Success rate (SR) (HbA_{1c} <7% , no hypos, no weight gain)				
	Vildagliptin	Glimepiride	Relative SR	CI 95%
Age (years)	n/tot (%)	n/tot (%)		
<50	44/207 (21.3)	24/197 (12.2)	1.74	1.10 - 2.76
50-60	95/372 (25.5)	60/360 (16.7)	1.53	1.15 - 2.05
60-70	134/372 (36)	86/345 (24.9)	1.45	1.15 - 1.81
70-80	36/85 (42.4)	20/78 (25.6)	1.65	1.05 - 2.60
Duration of Diabetes (years)				
<2	61/200 (30.5)	29/187 (15.5)	1.97	1.33 - 2.92
2-5	100/354 (28.2)	64/311 (20.6)	1.37	1.04 - 1.81
>5	148/482 (30.7)	97/482 (20.1)	1.53	1.22 - 1.91
Overall	309/1036 (29.8)	190/980 (19.4)	1.54	1.31 - 1.80

In patients with type 2 diabetes mellitus and baseline HbA_{1c} in the 7 - 8.5% range, vildagliptin shows a better clinical benefit - as defined by the composite end point of HbA_{1c} <7%, no hypos, and no weight gain, than glimepiride after 2 years of treatment regardless of duration of diabetes or age.

1018-P

Adding Saxagliptin (SAXA) 5 mg Is Superior to Uptitrating Metformin Extended Release (MET XR) in Type 2 Diabetes Mellitus (T2DM) Patients with Inadequate Glycemic Control on a Stable Dose of MET XR 1500 mg

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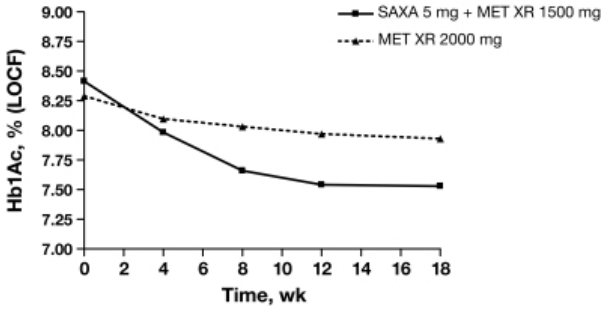
ADA guidelines suggest initiating MET at 500–1000 mg/d, then gradually increasing the dose to improve glycemic control. Dosages >1500 mg/d offer less incremental efficacy and increased risk of gastrointestinal (GI) adverse effects (AEs). Combining 2 oral antihyperglycemic agents with complementary mechanisms of action may improve glycemic control vs uptitrating MET to maximal recommended doses, without compromising safety or tolerability. In this phase 3 multicenter, double-blind study, 282 adults with inadequately controlled T2DM (A1C 7–10.5%) on stable (≥8 wk) MET XR 1500 mg were randomized to receive SAXA 5 mg + MET XR 1500 mg (n=138) or MET XR uptitrated to 2000 mg (n=144) taken once daily with the evening meal. End points included differences in adjusted change from baseline to week 18 in A1C level (primary), 120-min postprandial glucose (PPG) and fasting plasma glucose (FPG; secondary), and the proportion of patients achieving A1C <7% at week 18 (secondary). After 18 weeks, A1C decreased with SAXA+MET (–0.88%) compared with MET 2000 mg (–0.35%) (Figure; difference in adjusted change from baseline –0.52 [95% CI, –0.73 to –0.31; *P*<.001]). For secondary end points of 120-min PPG and FPG, differences in adjusted change from baseline for SAXA+MET vs MET 2000 mg were –23.32 (95% CI, –37.36 to –9.28; *P*<.01) and –13.18 (95% CI, –21.86 to –4.50; *P*<.01) mg/dL, respectively. The proportion of patients achieving A1C <7% at week 18 was 37% with SAXA+MET vs 26% with MET 2000 mg (*P*=.0459). The proportion of patients experiencing any AE or any specific AE was similar between groups, including hypoglycemia and GI disorders. In conclusion, adding SAXA to MET XR provided superior efficacy compared with uptitrating MET XR, without additional safety concerns.

Figure: Mean HbA1c (%) Values Over Time (Last Observation Carried Forward [LOCF])



1019-P

Addition of Sitagliptin, an Oral, Highly-Selective Dipeptidyl Peptidase-4 Inhibitor, Improved Glycemic Control and Was Well Tolerated in Japanese Patients with Type 2 Diabetes on Insulin Monotherapy

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Insulin therapy is widely used in Japan for treatment of patients with type 2 diabetes mellitus (T2DM). Of Japanese patients with T2DM taking antihyperglycemic agents (AHAs), 31% are treated with insulin as monotherapy or combination therapy with oral AHAs. The efficacy and safety of sitagliptin (SITA) or other dipeptidyl peptidase 4 (DPP-4) inhibitors added to insulin monotherapy have not been studied in Japanese patients. This 16-wk, randomized, double-blind, placebo (PBO)-controlled study in Japanese patients with T2DM assessed the efficacy and safety of SITA added to insulin monotherapy. After a 2-wk single-blind PBO run-in period, 266 patients (HbA1c 7.9-10.4%) on both diet/exercise and insulin monotherapy for ≥12 wks were randomized (1:1) to the addition of SITA 50 mg QD (N=129; mean baseline HbA1c=8.9%) or PBO (N=137; mean baseline HbA1c=8.9%). At Wk 16, mean HbA1c, fasting plasma glucose, and 2-hour postmeal glucose significantly decreased from baseline by 0.9% (p<0.001), 11.4 mg/dL (p=0.007), and 39.9 mg/dL (p<0.001), respectively, with SITA

relative to PBO. No significant difference was observed in the incidence of overall clinical adverse experiences (AEs) between the SITA (58.9%) and PBO (51.8%) groups. The incidences of pre-specified gastrointestinal AEs were not meaningfully different between groups (SITA: 1.6%, PBO: 0.7%). Associated with the greater improvement in glycemic control, the incidence of hypoglycemia AEs in the SITA group (20.2%) was higher than in the PBO group (12.4%), but the between-group difference was not statistically significant (p=0.097). In the SITA group, all but one episode of hypoglycemia were generally mild to moderate in intensity and none led to discontinuation of therapy. Small changes from baseline in body weight were observed with SITA (0.6 kg) group and PBO (0.1 kg) at Wk 16. In conclusion, in Japanese patients with T2DM inadequately controlled on insulin monotherapy, the addition of SITA provided significant improvements in glycemic parameters and was generally well tolerated after 16 wks.

1020-P

Age-Specific Barriers Assessment and Intervention Via Phone Improves Glycemic Control and Functionality in Older Adults: A Randomized Controlled Study

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The American Diabetes Association guidelines recommend the assessment of both age-specific barriers and geriatric syndrome to improve diabetes care in older adults. However, the impact of such a strategy on outcomes is unknown. We performed a randomized controlled study to evaluate the effect of assessment and intervention for age-specific barriers, implemented via phone communication between visits, on glycemic control and other parameters in elderly. Adults ³ 69 years with A1C³ 8% were randomized to 3 groups; group 1: attention control(n=31), groups 2 & 3:intervention(n=69). Intervention included assessment of barriers by a geriatric diabetes team and designing strategies to improve patients' ability to follow diabetes management plans prescribed by their providers. The interventions were implemented via phone calls by an office-based diabetes educator in group 2(n=34) and by a care manager in group 3(n=35). The control subjects received equal number of "courtesy" phone calls. All subjects underwent measurement of A1C, functionality (Tinnetti,6-minute walk-6MW) tests, self-care inventory-revised(SCI-r), and diabetes-related distress(PAID). We assessed 100 patients (age 75±5, duration 21±13 years, 67% type-2, 89% on insulin). From baseline to 6-months, the glycemic control improved in the intervention but not in control group. Similarly, functionality and SCI scores improved in intervention groups compared to control. The PAID score decreased in all groups. Conclusion:Phone communication between clinic visits by an educator aware of age-specific barriers improves glycemic control and other outcomes in older adults with diabetes.

Changes from baseline to 6 month (Paired T-test)				
	Group 1	Group2	Group 3	ANOVA between-groups p value
A1C	-0.34 (p=NS)	-0.5 (p<0.01)	-0.43 (p<0.01)	NS
SCI	1.5 (p=NS)	4.6 (p<0.009)	8.5 (p<0.0001)	<0.01
Tinneti	-2.5 (p<0.01)	+1.7 (p<0.03)	+0.5 (p=NS)	<0.003
6MW	-48.7 (p<0.06)	+6.4 (p=NS)	+9.4 (p=NS)	<0.03
PAID	-6.2 (p<0.02)	-5.7 (p<0.01)	-10 (p<0.0009)	NS

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1021-P

Alogliptin Ameliorates Dyslipidemia and LDL-Size in Patients with IGT or Type 2 Diabetes: Comparing Alogliptin and Voglibose

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Alogliptin, a kind of DPP4 inhibitor is a new useful anti-diabetic agent. But it has not been reported whether Alogliptin may ameliorate dyslipidemia or LDL-size. The aim of this study is to clarify whether Alogliptin may ameliorate dyslipidemia and LDL-size in patients with impaired glucose tolerance (IGT) or newly diagnosed type 2 diabetes (DM). Thirty five patients comprised of 24 patients with IGT and 11 patients with DM (IGT+DM group) were recruited. The patients were treated with diet and exercise for at least 3 months before medication. The 35 patients were randomly assigned to the treatment with ether Alogliptin (25 mg daily for 12 weeks) or Voglibose (0.6mg daily for 12 weeks). A 75-g oral glucose tolerance test and laboratory measurements were performed at baseline and after the treatment. Early insulin secretion and insulin resistance were assessed by ΔIRI/ΔPG for 30 minutes and HOMA-IR. LDL size was evaluated by Rm value of the electrophonesis of lipoproteins. After the treatment, the AUC of glucose for 120 min was decreased in groups treated with either Alogliptin (366.4±50.4, 274.3±56.5 P<0.001) or Voglibose (358.9±51.8, 305.5±70.6 P<0.01) as compared with those of the baseline values. However, the treatment with Alogliptin but not Voglibose significantly decreased plasma glucose level at 30 m (179.4±25.2, 152.3±21.3 mg/dl P<0.001) and 60 min (209.4±30.5, 156.4±50.0 mg/dl P<0.001) after the glucose load. ΔIRI/ΔPG (0.68±0.37, 1.34±1.37 P<0.05) significantly increased in Alogliptin group. Furthermore, the treatment with Alogliptin but not Voglibose decreased TG (143.0±53.9, 115.2±41.3 mg/dl P<0.001) and increased HDL-C (49.4±14.8, 52.2±13.3 mg/dl P<0.05) significantly. After the treatment, Rm value showed significantly lower (0.38±0.05, 0.33±0.04 P<0.05) in Alogliptin group as compared with the baseline value. Alogliptin, a kind of DPP4 inhibitor may ameliorate dyslipidemia and LDL-size in patients with IGT or type 2 diabetes.

1022-P

Anti-Human Insulin Antibodies in Type 2 Diabetic Patients Treated with Analog Insulin Preparations

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Recently, analog insulin preparations have been widely used for the treatment of diabetes. However, the detail of the antibody responses to several types of analog insulin preparations is still unknown. Thus, the circulating anti-human insulin antibodies in 30 non-diabetic control subjects and 80 type 2 diabetic patients treated with insulin were measured. The type 2 diabetic patients were treated from the beginning with the human or analog insulin preparation for more than one year. The types of insulin preparations were not changed. The types of insulin preparations and number of patients are described here: human insulin (HI) for 14 patients, insulin aspart (Asp) for 29 patients, insulin lyspro (Lys) for 19 patients, and insulin glargine (Gla) for 18 patients. The doses of human or analog insulin preparation were more than 10 Unit/day. Circulating anti-human insulin antibodies were detected by polyethylene glycol method using ^{125}I-human insulin and were expressed by specific binding (SP) % (Bound % minus bound % in the presence of excess amount of native insulin). SP in non-diabetic control subjects was -0.31±0.69%. The population ratios in type 2 diabetic patients with positive anti-human insulin antibodies (SP > 5%) are 0% for HI, 62.1% for Asp, 31.6% for Lys, and 61.1% for Gla. The patients treated with Asp or Lys were divided into two groups; the patients with positive anti-human insulin antibody (the positive group, N=27) or those without it (the negative group, N=21). The doses of analog insulin preparation were greater in the positive group than in the negative group (0.51±0.18 vs. 0.38±0.13 Unit/kg/day, P=0.006). There was no significant difference of age, A1C level, BMI, or duration of insulin therapy between the groups. In conclusion, the treatments with analog insulin preparations are associated with an increase in the anti-human insulin antibody responses. Lys induces anti-human insulin antibody response less than the other analog insulin preparations. The patients carrying anti-human insulin antibodies needed an approximate 34% increase in the amount of analog insulin preparation to maintain the same A1C as those without the antibodies.

1023-P

ASP1941, a Novel, Selective SGLT2 Inhibitor Improved Both Fasting and Postprandial Glucose Levels in Japanese Type 2 Diabetic Patients

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ASP1941, a novel, selective sodium-dependent glucose co-transporter (SGLT) 2 inhibitor, was investigated in Japanese type 2 diabetes mellitus (T2DM) patients. This was a randomized, placebo-controlled, double-blind study to evaluate daily plasma glucose profiles and urinary glucose excretion (UGE) at ASP1941 doses 50 and 100 mg for 14 days.

Thirty Japanese T2DM patients who were drug-naive or in whom one oral glucose-lowering agent was discontinued, were randomized to ASP1941 50 mg or 100 mg, or placebo. After 14-day once daily administration, fasting plasma glucose decreased from baseline in both ASP1941 groups. The mean plasma glucose $AUC_{0\text{-}3}$ (postprandial) and $AUC_{0\text{-}24}$ (all day) decreased from baseline in both ASP1941 groups compared with placebo. The mean 24 h cumulative UGE notably increased with both ASP1941 doses. Body weight reduction was observed in both ASP1941 groups.

ASP1941 did not cause any clinically significant safety concerns in this study. All treatment emergent adverse events (TEAEs) were mild in severity

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except for a nonfatal myocardial infarction in the ASP1941 50 mg group; no symptomatic hypoglycemia, urinary tract infection, genital infection, or pollakiuria was reported. Serum ketone bodies elevations were observed in ASP1941 groups as a result of fatty acid oxidation.

These results indicate that ASP1941 leads to an increase in UGE and improves both fasting and postprandial glucose levels at doses of 50 and 100 mg in Japanese T2DM patients.

Mean ± standard deviation	Placebo (n=10)	ASP1941 50 mg (n=9#)	ASP1941 100 mg (n=9#)
Baseline fasting plasma glucose (mg/dL)	177.5 ± 33.8	172.9 ± 25.5	165.3 ± 35.1
Change in fasting plasma glucose* (mg/dL)	0.3 ± 20.5	–31.6 ± 24.3	–35.8 ± 29.1
Change in plasma glucose $AUC_{0\text{-}3}$* (h.mg/dL)	2.3 ± 99.5	–171.6 ± 106.6	–174.6 ± 92.0
Change in plasma glucose $AUC_{0\text{-}24}$* (h.mg/dL)	63.8 ± 732.5	–1103.7 ± 639.9	–919.9 ± 636.0
Change in 24 h cumulative UGE* (g/day)	5.3 ± 19.3	80.6 ± 22.2	89.7 ± 12.3
Change in body weight* (kg)	–0.2 ± 0.6	–1.5 ± 0.5	–1.2 ± 0.4

* From baseline to day 14
# Two patients were discontinued treatment because of TEAEs in ASP1941 50 and 100 mg groups.

1024-P

Assessment of Long-Term Safety and Efficacy of Linjeta™ with 18 Months of Continuous Therapy in Patients with Type 1 Diabetes

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Linjeta™ is a rapidly absorbed formulation of recombinant human insulin which has been shown to have a more rapid onset of action than regular human insulin and insulin lispro. This study was performed to characterize the long term safety and efficacy of Linjeta (25 U/ml, pH 4 formulation for reconstitution) in patients with type 1 diabetes. 223 patients who had successfully completed a controlled trial of Linjeta vs. regular human insulin treatment participated in this extension study in which they received Linjeta as prandial insulin for 18 months. A1C, hypoglycemic event rates, weight, insulin doses, injection site toleration and insulin antibody levels were monitored regularly. A1C, hypoglycemic event rates, weight and insulin antibody levels showed only minor variations over the 18 month period of observation (Table 1 shows ITT population results). Similar results were seen for these parameters in patients who completed the study (n=140). Prandial insulin doses were titrated upward while basal doses remained stable over the course of the study. Local injection site adverse events declined with time. Eight subjects withdrew from the study due to injection site reactions. No correlations were identified between insulin antibody levels and measures of glycemic control. In conclusion, treatment with Linjeta over 18 months appears to be associated with stable A1C, hypoglycemic event rates, body weight and insulin antibody levels.

Table 1. Long term safety and efficacy parameters [mean ± SD (n)]

Time Point	A1C (%)	Hypoglycemia (events/ subject-month)	Weight (kg)	Prandial Dose (U/day)	Basal Dose (U/day)	Insulin Antibody Levels (U/ml)
Entry into parent controlled study	8.26 ± 1.36 (222)	8.27 (223)	73.6 ± 21.1 (223)	25.7 ± 15.3 (222)	29.0 ± 14.5 (221)	5.2 ± 6.1 (221)
Entry into extension study	7.77 ± 1.43 (222)	5.49 (223)	74.6 ± 21.1 (223)	26.7 ± 15.2 (221)	30.2 ± 15.4 (221)	4.0 ± 4.6 (221)
Month 15-18	7.83 ± 1.22 (126)	4.70 (142)	75.6 ± 21.8 (127)	30.9 ± 18.4 (142)	30.1 ± 16.2 (142)	3.4 ± 4.0 (126)

1025-P

Assessment of Long-Term Safety and Efficacy of Linjeta™ with 18 Months of Continuous Therapy in Patients with Type 2 Diabetes

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Linjeta™ is a rapidly absorbed formulation of recombinant human insulin which has been shown to have a more rapid onset of action than regular human insulin and insulin lispro. This study was performed to characterize the long term safety and efficacy of Linjeta (25 U/ml, pH 4 formulation for reconstitution) in patients with type 2 diabetes. 284 patients who had successfully completed a controlled trial of Linjeta vs. regular human insulin treatment participated in this extension study in which they received Linjeta as prandial insulin for 18 months. A1C, hypoglycemic event rates, weight, insulin doses, injection site toleration and insulin antibody levels were monitored regularly. A1C, hypoglycemic event rates, weight and insulin antibody levels showed only minor variations over the 18 month period of observation (Table 1 shows ITT population results). Similar results were seen for these parameters in patients who completed the study (n=181). Prandial and basal insulin doses were titrated upward over the course of the study. Local injection site adverse events declined with time. Twelve subjects withdrew from the study due to injection site reactions. No correlations were identified between insulin antibody levels and measures of glycemic control. In conclusion, treatment with Linjeta over 18 months appears to be associated with stable A1C, hypoglycemic event rates, body weight, and insulin antibody levels.

Table 1. Long term safety and efficacy parameters [mean ± SD (n)]

Time Point	A1C (%)	Hypoglycemia (events/ subject-month)	Weight (kg)	Prandial Dose (U/day)	Basal Dose (U/day)	Insulin Antibody Levels (U/ml)
Entry into parent controlled study	8.17 ± 1.31 (284)	2.42 (284)	94.3 ± 22.1 (284)	30.4 ± 22.3 (283)	43.7 ± 27.7 (272)	3.6 ± 7.0 (279)
Entry into extension study	7.44 ± 1.10 (283)	1.55 (284)	95.4 ± 22.4 (284)	32.4 ± 22.0 (281)	48.6 ± 33.0 (281)	2.9 ± 3.7 (279)
Month 15-18	7.62 ± 1.16 (161)	1.59 (183)	93.3 ± 23.2 (162)	37.5 ± 24.7 (183)	53.7 ± 40.6 (183)	2.7 ± 3.9 (159)

1026-P

Associations of Fracture with Lumbar Spine Trabecular Volumetric Bone Mineral Density Measured by QCT in the Senior Diabetic Patients

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The objective of the study was to define whether there is an association of bone mineral density (BMD) with fracture in the senior patients with type 2 diabetes (T2DM).

Ninety-seven patients with long-lasting T2DM were enrolled and followed up for 7 years with yearly recording HbA_1C, fracture events and so on. Their lumbar spine areal BMD (aBMD) were measured by dual-energy X-ray absorptiometry (DEXA) at enrolling time as baseline (0 year) and then the 3rd and 7th year, respectively. In the 7th year, lumbar spine aBMD was also compared with the trabecular volumetric BMD (vBMD), measured by quantitative computed tomography (QCT), for these T2DM patients and 21 age- and body-mass-index-matched healthy people.

Compared to baseline the aBMD in these diabetic patients was significantly decreased in an age-dependent manner ($P<0.05$) although there was no statistical difference between the 3rd and 7th years ($P>0.05$). There were 14 cases of diabetic patients with fracture. Among diabetes with fracture, diabetes without fracture and control group, there was no significant difference for lumbar spine aBMD, measured by DEXA, which was lowest in diabetes with fracture ($P>0.05$); however, there was a significant decrease in lumbar spine vBMD, measured by QCT, in diabetes with fracture compared to that in diabetes without fracture and controls.($P<0.05$). Stepwise multiple regression analysis did not reveal a significant association between lumbar spine aBMD and HbA1c ($P>0.05$). These results suggest that lumbar spine aBMD in elderly patients with T2DM was age-dependent declined, similar to that in normal people, and the decline of the aBMD was not associated with HbA1c levels. The lumbar spine vBMD, but not aBMD, was significantly lower in diabetic patients with fracture than that in diabetic patients without fracture and controls, indicating a better association between fracture and lumbar spine vBMD than lumbar spine aBMD.

1027-P

Associations of Glycemic Control by Intensive Insulin Therapy with Pancreatic β-Cell Function and Insulin Sensitivity in Chinese Patients with Ketosis Prone Diabetes

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This investigation aimed to evaluate insulin therapy on pancreatic β-cell function and periphery insulin sensitivity in ketosis prone diabetes patients before and after insulin therapy. A total of 12 KPD subjects participated in the study.All underwent a 4-h 120mU·m^{-2}·min^{-1} euglycemic-hyperinsulinemic

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clamp to assess insulin sensitivity and a 3-h hyperglycemic clamp to assess insulin secretion at onset and remission.Initial hospitalization included treatment with insulin and fluids. All subjects tolerated the intensive insulin treatment well and excellent glycemic control was successfully achieved. HbA1c, FFAs and β-hydroxybutyrate all declined. The increment of glucose disposal rate (GDR) at steady-state during the euglycemic clamp, an index of insulin sensitivity, were significant increased(5.26±1.76 mg·kg^{-1}·min^{-1} vs 7.86±1.31 mg·kg^{-1}·min^{-1} p<0.01). The acute and second phase insulin response were both marked increaesed during hypergycemic clamp test with the improvement of peripheral insulin sensitivity.Our study demonstrate that prompt insulin therapy can successfully lay a foundation for prolonged good glycemic control and better insulin secretion reservation in KPD patients.

Table 1. Clinical characteristics and lipids profile of KPD patients

	Onset (n=12)	Remission (n=12)	p
Waist circumference(cm)	93.7±4.6	86.5±6.1	<0.05
Body mass index(kg/m²)	29.3±2.8	24.9±3.9	<0.01
waist-to-hipratio(WHR)	1.01±0.03	0.89±0.05	<0.05
Plasma glucose (mmol/L)	23.26±11.56	6.22±1.78	<0.01
HbA1c (%)	10.7±1.2	6.3±0.5	<0.01
Free fat acid(μmol/L)	1273.41±491.84	642.86±242.78	<0.01
β Hydroxybutyrate(mmol/L)	2.37±1.05	0.92±0.39	<0.05
Area under curve (AUC)ins0-10	100.9±27.3	185.3±95.7	<0.05

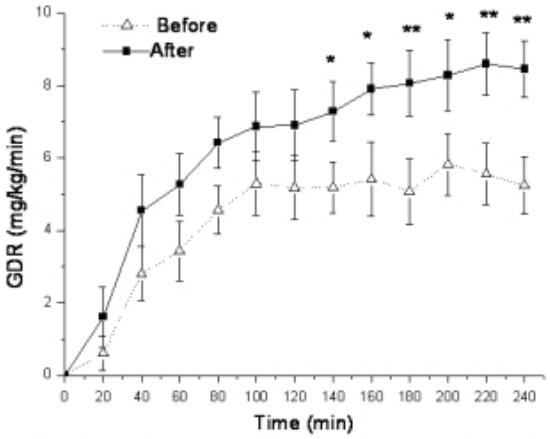

Figure 1. GDR during euglycemic clamp in Patinets with ketosis prone diabetes at onset and near-normoglycemic remission

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1028-P

Beneficial Effects of Pioglitazone/Alogliptin Combination Therapy on Glucose Homeostasis in a Mouse Model of Type 2 Diabetes Mellitus

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Impaired β-cell function on a background of insulin resistance is a hallmark of type 2 diabetes mellitus (T2DM). Among the therapeutic approaches for treating T2DM, the dysregulated secretion and function of GLP-1 have been targeted by using DPP-4 inhibitors known to prolong the action of the incretin. Other approaches have used pioglitazone, a peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist, to counter systemic insulin resistance and/or improve β-cell function. In this study we explored potential synergistic effects of combining a DPP-4 inhibitor (alogliptin) with pioglitazone in the β-cell specific insulin receptor knockout (βIRKO) mouse, a unique model of T2DM that exhibits loss of acute phase insulin secretion and age-dependent decrease in β-cell mass. To this end, we treated βIRKO and control mice with food containing either pioglitazone (PIO only; 0.02% weight/weight) or alogliptin (ALO only; 0.05% w/w) or a combination (PIO+ALO; PIO 0.02% + ALO 0.05% w/w) for 6 weeks. Fasting blood glucose showed a trend to decrease in the PIO only and (PIO+ALO) groups. PIO only and (PIO+ALO) treatments significantly improved glucose tolerance in βIRKO mice (PIO only vs. control: p<0.05, (PIO+ALO) vs. control: p<0.01; n=5-6), whereas treatment with ALO only did not reach statistical significance (ALO only vs. control: p=0.47; n=5-6). (PIO+ALO) group displayed enhanced systemic insulin sensitivity (ITT; (PIO+ALO): 81.2% vs. control: 56.1% decrease in blood glucose at 60 min after insulin injection: p<0.05; n=4-5) and insulin secretion (GSIS; (PIO+ALO): 337.9% vs. control: 100.4% increase in insulin secretion at 2 min: p<0.01; n=4) consistent with improved glucose tolerance. Treatment with either PIO only or ALO only did not alter insulin secretion significantly. In summary, glycemic control was significantly improved together with enhanced β-cell function in the βIRKO mouse model by combining PIO with ALO treatment and this has therapeutic implications for this combinatorial approach to treat T2DM.

1029-P

Change in Alcohol Consumption Following Liraglutide Initiation: A Real Life Experience

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Liraglutide, the once-daily human GLP-1 analogue, is known to change food preference in animal models. Animals treated with liraglutide prefer low calorie diet to high calorie diet. However this effect is not documented in human subjects treated with liraglutide. Alcohol is one of most commonly consumed high calorie diet among patients with type 2 diabetes. It would be interesting to evaluate the effect of liraglutide in alcohol consumption in this setting.

This prompted us to conduct a cross-sectional review of all subjects prescribed liraglutide (1.2 -1.8 mg/day) at our endocrine centre, which is located in an area where alcohol consumption is common. Subjects were asked about alcohol use before and after initiating liraglutide therapy, using the Michigan Alcohol Screening Tool (MAST). Data were collected regarding the quantity and frequency of alcohol consumption.

Of the 63 patients surveyed, 42 admitted to alcohol intake (all males). Of these, six consumed >/=200 ml/ day, and 21 consumed >/=30 ml / day. 27 subjects consumed >/= 30 ml alcohol at least once a week, while the rest (n=15) consumed alcohol less than once a week. The quantity of alcohol consumed per session ranged between 30 and 250 ml. Fourteen subjects scored > 5 on the MAST, which defines alcoholism. The average MAST score was 3.0±3.5. Liver enzymes were within the normal range in all subjects.

After three months of liraglutide use, alcohol intake had decreased markedly in 33 out of 42 patients and nine subjects had completely stopped consuming alcohol. All of them were aware of this change in diet preference. Two subjects continued to take alcohol daily, 17 continued to drink at least once a week, with eight reporting intake less than once a week. Only four patients scored >5 on MAST. The average MAST score fell to 2.0 ± 1.80 (p<0.05). No adverse events were reported by the subjects.

Present data describes apparent change in food preference in type 2 diabetic subjects treated with liraglutide. In a population with significant alcohol consumption this mechanism could be of additional benefit given the established effects of Liraglutide in the treatment of type 2 diabetes.

1030-P

Chromium Picolinate and Chromium Histidinate Protect the Brain Against High-Fat Diet and Streptozotocin-Induced Diabetes by Suppressing the NF-κB Pathway

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Chromium (Cr) has shown both antidiabetic and antidepressdant properties. The present study was conducted to investigate the effects of chromium picolinate (CrPic) and chromium histidinate (CrHis) on nuclear factor-kappa B (NF-κBp65) signaling pathway, IkappaB-alpha (IκBα) protein and NF-E2-related factor-2 (Nrf2) expression in the brain of rats. Male Wistar rats (n=90, 8 wk-old) were divided into six groups. Group I (control) received a standard diet (12% of calories as fat); Group II were fed the standard diet plus CrPic; Group III were fed the standard diet plus CrHis; Group IV (HFD/STZ) received a high fat (40% of calories as fat) diet (HFD) for 2 weeks and then were injected with streptozotocin (STZ, 40 mg/kg i.p.) on day 14; Group V were treated as group IV but supplemented with CrPic; Group VI were treated as group IV but supplemented with CrHis. The induction of diabetes (by HFD/STZ) caused a significant increase in brain expression of NFκBp65. The increased NFκβ p65 in the HFD/STZ-induced brain injury group was inhibited by CrPic and CrHis supplementation (P< 0.05). In STZ-treated rats, a significant decrease in expression of IκBα was found in brain tissue compared to control rats (P< 0.05). A significant increase in the expression of IκBα was observed in CrPic- and CrHis-treated rats compared with STZ-treated rats. Brain Nrf2 expression was significantly decreased in diabetic rats compared with the control rats. Compared to CrPic, supplementation with CrHis increased brain Nrf2 expression and decreased brain NFκBp65 and HNE expression (P< 0.05) in

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diabetic rats. No significant effect of Cr supplementation was detected on all measured parameters in the control group. Our results show that Cr increases Nrf2 expression in parallel with decreases of NFκB in HFD/STZ-induced brain injury, suggesting that Cr may play a role in antioxidant defense system via the Nrf2 pathway by reducing inflammation through NFκBp65 inhibition. The present study also indicates that preventive supplementation with Cr in the form of CrHis was more effective than CrPic in improving the NFκB pathway in HFD/STZ diabetic rats.

1031-P

Chronic Dapagliflozin Treatment Reduces Elevated Hepatic Glucose Production and Enhances Pancreatic Insulin Content in Male ZDF Rats

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Dapagliflozin (Dapa) is a potent (Ki=0.2 nM), selective SGLT2 inhibitor (3000-fold vs SGLT1) which reduces renal glucose reabsorption and may provide an insulin-independent mechanism for type 2 diabetes treatment. We have previously shown that acute Dapa dosing reduced hyperglycemia (0.5 and 1.0 mg/kg), and increased glucose production at 1.0 but not 0.5 mg/kg in the hyperglycemic male ZDF rat. Here we examined whether prevention of hyperglycemia by chronic Dapa treatment in prediabetic male ZDF rats (Obese) improves the impaired hepatic glucose metabolism and peripheral insulin sensitivity observed in this model. Tissue specific outcomes were also evaluated. Pre-diabetic ZDF rats (6 wk of age) were dosed for 5 wk with 0.5 mg/kg Dapa q.d. p.o. or vehicle (Veh). Dapa maintained fed plasma glucose and HbA1C to levels near those observed in age-matched lean ZDFs treated with Veh (Lean). Insulin levels were significantly higher in Dapa vs Veh Obese rats, suggesting that Dapa prevented b-cell destruction. Liver glycogen was unchanged, while pancreatic insulin content was maintained at baseline with Dapa treatment vs the decline in the Obese Veh group. A euglycemic-hyperinsulinemic clamp was performed in all groups 48 hr post-last-dose. Obese Veh rats had increased basal glucose production (9.3±0.8 mg/kg-min) vs Lean (5.1±0.3 mg/kg-min, p<0.001). Dapa decreased basal glucose flux (6.6±0.4 mg/kg-min, p=0.01) vs that seen in the Obese Veh group. During the euglycemic-hyperinsulinemic clamp, the rates of whole body glucose disposal and tissue specific glucose uptake in both epididymal fat and soleus skeletal muscle were similar in the Dapa and Veh Obese groups. Dapa, however, significantly increased glucose infusion rate (8.8±0.7 vs 3.8±0.6 mg/kg-min, Dapa vs Veh respectively, p<0.05), and decreased endogenous glucose production (EGP) on an absolute (3.6±0.5 vs 10.7±2.1 mg/kg-min, p<0.001) and relative basis vs Obese male ZDF Veh (-45±9% vs 20±28%, p<0.05). We conclude that the prevention of progression to hyperglycemia with chronic Dapa treatment in male ZDF rats enhances hepatic insulin action to inhibit EGP and augments b-cell function.

1032-P

Clinical Outcomes in Patients with Type 2 Diabetes (T2D) Who Initiated Exenatide BID or Insulin: 6-Month Data from CHOICE

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CHOICE is an ongoing prospective 24-month observational study of adults with T2D who initiate their first injectable therapy (exenatide BID [Byetta] or insulin) in routine clinical practice in 6 EU countries. Data were collected at initiation and 6 months. As baseline differences between cohorts prevent direct comparison, propensity-adjusted analysis (based on baseline variables) was done and 6-month outcomes were compared on matched patients. Data are means (SD). Exenatide BID cohort: Baseline data (N=1177): age 58y (10); weight 101.1kg (21.6); T2D duration 8y (6); HbA1c 8.4% (1.4). At 6 months (N=1073), HbA1c change was –1.0% (1.4) reaching 7.4% (1.2); 18.4% and 36.1% achieved HbA1c <6.5% and <7.0%, respectively. Weight change was –3.4kg (5.1). Gastrointestinal (GI) symptoms were reported by 20.8% in months 0–3 and 11.0% in months 3–6. Overall 10.3% reported hypoglycemic episodes (minor and/or major). Significant treatment changes were made in 236 patients (22.0%), of which 188 discontinued exenatide BID. Insulin cohort: Baseline data (N=1315): age 64y (11); weight 84.3kg (17.6); T2D duration 10y (7); HbA1c 9.2% (1.9). At 6 months (N=1235), HbA1c change was –1.8% (1.8) to reach 7.3% (1.0); 15.1% and 34.3% achieved <6.5% and <7.0%, respectively. Weight change was +1.2kg (4.7). HbA1c reductions and weight gain observed were highest with basal+prandial insulin and lowest with basal only. Overall 23.4% reported hypoglycemic episodes. Significant treatment changes were made in 278 patients (22.5%), of which 28 discontinued insulins. In propensity-adjusted matched subsets (N=565 exenatide BID, N=565 insulin at 6 months), respective changes from baseline in exenatide BID and insulin patients were: HbA1c –1.2% (1.5) and –1.4% (1.5) (p=.103); weight –2.8kg (4.4) and +0.6kg (5.1) (p<.0001); hypoglycemia rates were 11.9% and 20.4% (p=.0002). Patients initiated on exenatide BID and insulin differ in routine practice. In matched subsets, no significant difference was shown between exenatide and insulin groups in mean HbA1c changes, but weight loss and less hypoglycemia were found in the exenatide group.

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1033-P

Clinical Outcomes in Patients with Type 2 Diabetes Treated with Exenatide Twice Daily or Once Weekly: Retrospective Analysis of Pooled Clinical Data Stratified by Age and Duration of Diabetes

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A variety of factors can influence clinical endpoints of drug therapies, including age and duration of diabetes. The purpose of this post hoc analysis was to examine clinical outcomes, stratified by age and duration of diabetes, of the GLP-1 receptor agonist exenatide administered twice daily (ExBID) or once weekly (ExQW). Subjects with T2DM received exenatide in 1 of 2 separate cohorts of pooled clinical data: (1) a dataset of 12 comparator- or placebo-controlled ExBID studies (10 mcg/injection only; N=1877; age [mean±SD], 57±10 y; A1C, 8.3±1.0%; weight, 93.0±19.3 kg; analysis endpoints at 24-30 weeks) and (2) a dataset of 4 double-blind, comparator-controlled ExQW studies (N=670; age, 55±10 y; A1C, 8.4±1.1%; weight, 94.1±19.8 kg; analysis endpoints at 24-30 weeks). See Table for results. Differences between ExBID and ExQW treatment revealed in the current analysis are consistent with those observed in head-to-head clinical trials (ie, DURATION-1 & -5). Both treatments were generally well tolerated. Although patients treated with ExQW <65 years of age appeared to be more likely to experience nausea than were those ≥65 years of age, conducting statistical comparisons between groups is precluded by limitations of this post hoc analysis. Patients treated with ExQW and ExBID experienced clinically-meaningful improvements in A1C and weight loss from baseline, irrespective of age or duration of diabetes.

		Age		Duration of Diabetes	
		<65 y	≥65 y	<10 years	≥10 years
Selected Endpoints	Treatment	(N=549 [ExQW], 1411 [ExBID])	(N=121 [ExQW], 466 [ExBID])	(N=496 [ExQW], 1250 [ExBID])	(N=174 [ExQW], 627 [ExBID])
A1C, mean (95% CI) Δ, %	ExQW	-1.5 (-1.6, -1.4)	-1.4 (-1.5, -1.2)	-1.4 (-1.5, -1.3)	-1.5 (-1.7, -1.4)
	ExBID	-1.0 (-1.1, -0.9)	-1.1 (-1.2, -1.0)	-0.9 (-1.0, -0.9)	-1.2 (-1.2, -1.1)
Weight, mean (95% CI) Δ, kg	ExQW	-2.8 (-3.1, -2.4)	-2.8 (-3.3, -2.2)	-2.6 (-3.0, -2.3)	-3.2 (-3.9, -2.5)
	ExBID	-2.4 (-2.6, -2.2)	-2.6 (-2.9, -2.3)	-2.5 (-2.7, -2.3)	-2.3 (-2.6, -2.0)
Nausea, No. (%)	ExQW	113 (20.6)	13 (10.7)	89 (17.9)	37 (21.3)
	ExBID	550 (39.0)	185 (39.7)	467 (37.4)	268 (42.7)

1034-P

Clinical Outcomes in Patients with Type 2 Diabetes Treated with Exenatide Twice Daily or Once Weekly: Retrospective Analysis of Pooled Clinical Data Stratified by Body Mass Index

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Although T2DM is often associated with overweight/obesity, it is prevalent across a wide range of BMIs. The purpose of this analysis was to examine clinical outcomes, stratified by baseline BMI, of the GLP-1 receptor agonist exenatide administered twice daily (ExBID) or once weekly (ExQW). Subjects with T2DM received exenatide in 1 of 2 cohorts of pooled clinical data: 1) a dataset of 12 comparator- or placebo-controlled ExBID studies (10mcg/injection only; N=1877; age [mean±SD], 57±10y; A1C, 8.3±1.0%; weight, 93.0±19.3kg; analysis endpoints at 24-30wk) and 2) a dataset of 4 double-blind, comparator-controlled ExQW studies (N=670; age, 55±10y; A1C, 8.4±1.1%; weight, 94.1±19.8kg; analysis endpoints at 24-30wk). Differences between ExBID and ExQW treatment revealed in the current analysis are consistent with those observed in head-to-head trials (ie, DURATION-1&-5). Although rates of hypoglycemia appear different across groups, limitations of this post hoc analysis preclude conducting statistical comparisons between groups. Patients treated with either ExBID or ExQW experienced clinically-meaningful improvements from BL in A1C, body weight, and fasting glucose in all BMI groups.

	ExBID BMI (kg/m²)				ExQW BMI (kg/m²)		
Selected Endpoints	**≥20-<25 (N=83)**	**≥25-<30 (N=575)**	**≥30-<35 (N=666)**	**≥35 (N=550)**	**≥25-<30 (N=209)[a]**	**≥30-<35 (N=222)**	**≥35 (N=224)**
A1C, mean (95% CI) Δ, %	-1.3 (-1.5, -1.0)	-1.1 (-1.1, -1.0)	-1.0 (-1.1, -0.9)	-0.9 (-1.0, -0.8)	-1.5 (-1.6, -1.3)	-1.4 (-1.5, -1.3)	-1.5 (-1.6, -1.3)
Weight, mean (95% CI) Δ, kg	-1.2 (-1.7, -0.6)	-2.1 (-2.4, -1. 9)	-2.4 (-2.7, -2.2)	-2.9 (-3.2, -2.5)	-2.3 (-2.7, -1.9)	-2.3 (-2.9, -1.8)	-3.7 (-4.4, -3.0)
Fasting glucose, mean (95% CI) Δ, mg/dL	-24 (-36, -13)	-20 (-24, -15)	-22 (-26, -18)	-17 (-22, -13)	-38 (-44, -31)	-33 (-39, -27)	-34 (-42, -26)
Nausea, No. (%)	28 (33.7)	237 (41.2)	270 (40.5)	198 (36.0)	35 (16.7)	42 (18.9)	47 (21.0)
Hypoglycemia (major or minor), No. (%)[b]	23 (27.7)	87 (15.1)	115 (17.3)	48 (8.8)	17 (8.1)	8 (3.6)	9 (4.0)

[a]Only 15 patients had a BMI <25 and were excluded.
[b]Major hypoglycemia occurred in 5 ExBID patients and 1 ExQW patient.

1035-P

Combination of the Dipeptidyl Peptidase-4 Inhibitor Linagliptin with Other Anti-Diabetic Agents in Rodent Models

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Linagliptin is a novel dipeptidyl peptidase (DPP)-4 inhibitor in late-stage clinical development for the treatment of type 2 diabetes (T2DM). The efficacy of linagliptin was investigated in diabetic rodents in combination with metformin and pioglitazone, and with the novel, selective sodium-glucose-transporter (SGLT)-2 inhibitor BI 10773, which is also in clinical development.

In a study in db/db mice, linagliptin (1 mg/kg) plus metformin (200 mg/kg) significantly improved glucose tolerance after 1 week of treatment, with fasting glucose lowered by 4 mM after 2 weeks' treatment. Changes with linagliptin or metformin monotherapy, however, were not statistically significant (–1.5 mM and –2.1 mM, respectively).

In a study in fully diabetic ZDF rats, linagliptin alone substantially increased glucagon-like peptide (GLP)-1 levels, but did not significantly affect HbA_{1c} after 4 weeks' treatment. However, linagliptin (3 mg/kg) combined with pioglitazone (10 mg/kg for 2 weeks; and then 3 mg/kg) resulted in a –0.4% change in HbA_{1c}; this combination also improved glucose tolerance (area under curve [AUC] reduction –34%). Thus, although worsening insulin resistance may prevent long-term glycemic control by a DPP-4 inhibitor in the ZDF model, linagliptin was effective in combination with an insulin sensitizer.

BI 10773 acts by increasing urinary glucose excretion via an insulin-independent mechanism. In an acute oral glucose tolerance test in young ZDF rats, the combination of linagliptin and BI 10773 (both at 1 mg/kg) additively decreased glucose excursion compared with either monotherapy (AUC reduction: linagliptin –40%, BI 10773 –25%, combination –68%). Similar results were obtained in non-diabetic C57Bl/6 mice.

In conclusion, in these rodent model studies, all the combination therapies evaluated were well tolerated. The levels of glycemic control achieved with linagliptin combination therapies were at least additive compared with the respective monotherapies, offering the possibility of a substantially expanded range of therapies available for T2DM.

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1036-P

Combination of Vildagliptin and Rosiglitazone Ameliorates Non-Alcoholic Fatty Liver Disease in C57BL/6 Mice

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Results: Insulin resistance plays a fundamental role in development of non-alcoholic fatty liver disease (NAFLD). For effective treatment of NAFLD, combination of anti-diabetic agents which are acting through different mechanisms may be a logical approach. The present investigation was aimed to assess efficacy of anti-diabetic agents metformin (Biguanide) and rosiglitazone (PPAR-gamma agonist) alone and in combinations with vildagliptin (DPP IV inhibitor) on hepatic steatosis in diet induced NAFLD in C57BL/6 mice.

Male C57BL/6 mice fed with high fat diet (60 Kcal %) and fructose (40%) in drinking water for 60 days to induce NAFLD. After the induction period, animals were divided into different groups and treated with vehicle, vildagliptin (10 mg/kg), metformin (350 mg/kg), rosiglitazone (10 mg/kg), vildagliptin (10 mg/kg) + metformin (350 mg/kg), and vildagliptin (10 mg/kg) + rosiglitazone (10 mg/kg) for 28 days. Body weight was recorded throughout the experimental period. The animals were bled at 24 h post administration of last dose. Biochemical parameters were determined by colorimetric assay. At the end of the experiment animals were sacrificed, liver samples collected and subjected to histopathological examination and triglyceride estimation.

The animals treated with anti-diabetic agents in combination showed better efficacy than any given alone. Vildagliptin and rosiglitazone combination group showed significant reduction in fasting plasma glucose ($P<0.05$), hepatic steatosis ($P<0.05$) and liver triglycerides ($P<0.01$). Though the Vildagliptin and metformin combination showed significant reduction in body weight gain ($P<0.01$) from12th day of treatment, but did not show reduction in hepatic steatosis and triglycerides.

In conclusion, animals treated with vildagliptin and rosiglitazone in combination showed significant reduction in hepatic steatosis and triglycerides. Our data suggests that combination therapy of a DPP IV inhibitor with a PPAR-gamma agonist may be a new therapeutic strategy for the treatment of NAFLD.

1037-P

Comparison of Glucose Variability Assessed by a Continuous Glucose Monitoring System in Patients with Type 2 Diabetes Switched from NPH Insulin to Insulin Glargine: The COBIN2 Study

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The COBIN2 study aimed to compare blood glucose (BG) variability with insulin glargine versus NPH insulin in patients with type 2 diabetes mellitus (T2DM) using a continuous glucose monitoring system (CGMS). This was a multicenter, prospective, open-label, single-arm study in patients treated for ≥ 2 months with NPH and metformin combined with sulfonylurea or glinide. Primary end point was BG variability during a 4-week NPH treatment phase and a subsequent 12-week glargine treatment phase (with active titration to attain fasting BG < 5.5 mmol/L) using CGMS. Oral drugs were continued throughout. Based on 72-h CGMS, BG variability was assessed by area under the curve (AUC [h · mmol/L]). Differences (glargine–NPH) in AUC within 24 h in the BG ranges of ≥ 15, ≥ 10, ≥ 7.5, ≤ 3.9, and ≤ 3.3 mmol/L were evaluated. Hypoglycemia included symptomatic (BG ≤ 3.3 mmol/L), uncomfirmed, and asymptomatic events.

A total of 116 patients switched from NPH to glargine (mean age, 62; mean BMI, 31.7 kg/m^2; mean A1C, 6.5% [IFCC]). 101 patients had evaluable 24-h CGMS measurements. BG AUCs for the lowest BG ranges (≤ 3.3, ≤ 3.9 mmol/L) did not change significantly after treatment with glargine (Table). Those in the higher ranges (≥ 7.5 mmol/L) were significantly lower, while BG AUC in the normal range (3.9-7.5 mmol/L) was significantly higher at the end of glargine treatment. Circadian fluctuation of BG assessed by M-value showed a significant decrease after glargine treatment ($P < 0.003$). No significant differences in hypoglycemia were found between treatment phases.

As monitored by CGMS, switching from NPH to glargine with active titration shifted BG from abnormally high to normal levels with reduced fluctuation and without increased risk of hypoglycemia.

BG Range [mmol/L]	**Δ AUC Mean (SD) [h*mmol/L]**	***P* Value***
≤ 3.3	1.26 (7.70)	0.232
≤ 3.9	1.62 (10.14)	0.232
3.9-7.5	15.48 (41.21)	< 0.001
≥ 7.5	-43.88 (89.27)	< 0.001
≥ 10	-39.14 (89.51)	< 0.001
≥ 15	-15.43 (51.08)	< 0.001
Total 24-h measurements	-26.79 (55.74)	0.057

*Wilcoxon signed rank test *P* value (with stepdown Bonferroni correction).

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For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

1038-P

Comparison of Safety with Continuous (Exenatide Once Weekly) or Intermittent (Exenatide Twice Daily) GLP-1 Receptor Agonism in Patients with Type 2 Diabetes

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The GLP-1 receptor agonist exenatide improves glycemic control and promotes weight loss in patients with type 2 diabetes. Continuous or intermittent GLP-1 receptor agonism is achieved with exenatide once weekly (ExQW) or exenatide twice daily (ExBID), respectively. The objective of this posthoc pooled analysis was to examine safety and tolerability profiles of ExQW (2 mg) vs ExBID (5 mcg [4 wks] then 10 mcg) in 2 randomized, open-label studies (DURATION-1 and DURATION-5) of 30- or 24-weeks duration. The studies were conducted in 545 patients with type 2 diabetes treated with diet/exercise or up to 2 oral antidiabetic medications. The safety profiles of ExQW and ExBID were generally comparable. Serious adverse events (AEs; 4% in each group) and AEs leading to withdrawal (5% in each group) were infrequent. The most common AEs were nausea (ExQW, 21% vs ExBID, 35%), diarrhea (12% vs 9%), injection-site pruritus (12% vs 1%), and vomiting (8% vs 14%). These events were mostly mild/moderate in intensity. More ExBID (4%) than ExQW (1%) patients withdrew due to gastrointestinal (GI) AEs. Mild nausea occurred most frequently upon initiation of ExQW (days 1-14) and at initiation (days 1-14) and dose escalation (weeks 4-6) of ExBID. Nausea incidence decreased with ongoing therapy; in the final 2 weeks of each study, events of nausea occurred in <1% ExQW and <2% ExBID patients. Vomiting similarly decreased in incidence over time. Mild to moderate injection-site related (ISR) AEs were more common with ExQW and generally occurred early (no new events after week 14). Two ExQW patients withdrew due to ISR AEs. No major hypoglycemia occurred; minor hypoglycemia occurred primarily in patients using a sulfonylurea and was infrequent, with no difference between groups and no temporal association with initiation/dose escalation. Overall, continuous vs intermittent exenatide exposure did not impact the general safety profile of exenatide and there was no evidence of prolonged AE duration with ExQW vs ExBID. Improved GI tolerability was observed with ExQW. ISR AEs were more frequent with ExQW, but rarely led to withdrawal (<1%).

1039-P

C-Peptide Improves Erectile Function in Type 1 Diabetes

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Erectile dysfunction is reported to be present in 40-60% of men with type 1 diabetes and PDE5 inhibitors have shown limited usefulness. Proinsulin C-peptide augments the expression of eNOS in human cavernosal cells *in vitro* and is known to improve autonomic nerve function in patients with type 1 diabetes. It was hypothesized that C-peptide administration may be beneficial for ereile function in type 1 diabetes. Sexual performance and erectile function were analysed in 50 type 1 diabetes patients who received C-peptide (n=39) or placebo (n=11) by subcutaneous injection for 6 months. This study was part of a larger trial of C-peptide effects in diabetic neuropathy for which the neurological results have been published. All patients (age 45±7yrs, diabetes duration 28±10 yrs, A1C 7.6 ±0.1%) had manifest peripheral neuropathy. A validated questionnaire (International Index of Erectile Function) was used. It included 10 questions, four focusing on evaluation of erectile function. Each question had five alternative answers each coded 1 - 5, where 1 indicated severe and 5 no dysfunction. The individual results for the ten questions were summed to form a variable reflecting the overall sexual performance. The data were dichotomized so that a positive change was coded 1 and a worsening or no change coded 0. The sum of the dichotomized improvements for each subject was also calculated. The average change in score points after 6 months were positive for C-peptide, indicating improvement, and negative for placebo treated patients both with regard to the erectile function questions (C-peptide vs placebo: P<0.02) and all questions (C-peptide vs placebo P<0.06). On average patients reported improvements in response to 9 of the 10 questions in the C-peptide group compared to 1 of 10 in placebo treated patients. Erectile function was improved in 46% of the patients on C-peptide therapy compared to 9% in placebo patients (P<0.035). No adverse effects related to C-peptide were reported. It is concluded the C-peptide administration may be beneficial in the treatment of erectile dysfunction in men with type 1 diabetes.

1040-P

CVX-343, a Long-Acting FGF21 CovX-Body, Demonstrates Prolonged Anti-Diabetic Efficacy in Diabetic Mouse Models

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FGF21, a member of the FGF19 subfamily, plays an important role in regulating glucose and lipid homeostasis in animal models. Administration of FGF21 improves insulin sensitivity, reduces body weight, and reverses hepatic steatosis in diabetic rodents and monkeys. Due to its short half-life, daily injection of the protein is required for *in vivo* bioactivity. Here we describe a novel long acting bivalent FGF21 CovX-Body, CVX-343, created by covalently linking two FGF21 proteins to the Fab of CVX-2000 IgG1 mAb via a linker. Similar to the FGF21 protein, CVX-343 increased Glut1 mRNA expression in 3T3-L1 adipocytes with an EC_{50} of 3.4 nM. In *ob/ob* mice, a single SC administration of CVX-343 significantly reduced body weight gain, improved glucose tolerance, and lowered liver triglyceride levels in a dose-related manner compared with the vehicle control up to 6 days post dose, demonstrating the prolonged pharmacodynamics of this molecule *in vivo*. A 2.5-fold increase of *Ucp1* expression was also observed in white adipose tissue by CVX-343 treatment. In diet-induced obese mice, once weekly administration of 10 mg/kg CVX-343 for 2 weeks caused 7% weight loss without affecting food intake, significantly decreased glucose AUC by 17% in an oral glucose tolerance test, and lowered serum triglycerides and NEFA levels by 48% and 69%, respectively, in comparison with vehicle controls. In *db/db* mice, once weekly administration of CVX-343 (10 mg/kg) improved glucose tolerance and increased pancreatic β-cell mass by 2.4 fold in the absence of a body weight effect. In summary, the FGF21 CovX-Body CVX-343 shows comparable potency as the wild type FGF21 and prolonged efficacy across multiple preclinical models. This long-acting FGF21 molecule has an attractive therapeutic profile for type 2 diabetes.

1041-P

Dapagliflozin Selectivity for Glucose Transporters GLUT1, 2 and 4

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Dapagliflozin is a potent (Ki, 0.2nM) and selective sodium-glucose cotransporter 2 (SGLT2) inhibitor (3000-fold vs SGLT1) that reduces hyperglycemia in type 2 diabetes by reducing renal glucose reabsorption, causing excretion of glucose and associated calories. We have evaluated the selectivity of dapagliflozin by examining effects on the GLUT transporters using human erythrocytes (GLUT1), Hep G2 cells (GLUT2), and human differentiated adipocytes (GLUT4). Protein expression of the relevant GLUT was confirmed in each tissue used by Western blot and by mRNA expression relative to the housekeeping gene cyclophilin A. GLUT1 activity was measured as the amount of D-[6-^{3}H] glucose transported into the erythrocyte over 1 minute at room temperature. GLUT2 activity was assessed using 2-deoxy-D-[1-^{3}H] glucose over 15 minutes at 37°C. GLUT4 activity was measured using insulin-stimulated 2-deoxy-[U-^{14}C]-glucose over 1hour at 37°C.

In all tissues, dapagliflozin, over the concentration range 20–100 μM, was pre-incubated for an hour prior to the administration of the relevant glucose analogue. At GLUT 1, dapagliflozin had minimal inhibition even at 100 μM (3.6 ± 3.6% inhibition, n=4). At GLUT 2, 100 μM dapagliflozin resulted in 11.6 ± 3.2% inhibition (n=4). At GLUT4, dapagliflozin did not alter the insulin EC_{50}, but the maximum response was reduced by 100 μM dapagliflozin (by 23 ± 4%, n=4), whilst 20 μM had minimal effect on the maximum response (8 ± 2% reduction). Positive response to cytochalasin B and/or phloretin was observed for all systems studied. Given the 0.2 nM potency of dapagliflozin for SGLT2, these data show that the compound has at least 100,000-fold selectivity over GLUT1, 2 and 4. Therefore, at the concentrations achieved following administration of therapeutic doses of dapagliflozin, we do not expect there to be inhibition of GLUT1, 2 or 4 protein or adverse effects upon insulin-stimulated glucose disposal.

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1042-P

Dapagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, Has a Low Propensity To Cause Hypoglycemia in Patients with Type 2 Diabetes

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Hypoglycemia (hypo) is associated with recurrent morbidity in subjects with type 2 diabetes mellitus (T2DM) and is often a barrier to achieving glycemic targets. Dapagliflozin (DAPA), a selective inhibitor of renal sodium-glucose cotransporter 2 (SGLT2), reduces hyperglycemia in T2DM patients by increasing urinary glucose excretion. This is dependent on plasma glucose levels and renal filtration rate, and independent of insulin, suggesting a low hypo risk.

Hypo episodes were reviewed from 5 phase 3 studies of DAPA (4 placebo, 1 active controlled) either alone or in combination with other antidiabetic agents (table).

Placebo controlled studies				Patients with ≥1 hypo episode in each treatment group, x/n (%)			
ID	**Design**	**Duration (weeks)**	**Para-meters**	**Placebo**	**DAPA 2.5mg**	**DAPA 5mg**	**DAPA 10mg**
NCT00528372 MB102-013	Mono-therapy	24	Total*† AM dosing PM dosing	2/75 (2.7)	1/65(1.5) 1/67 (1.5)	0/64 0/68	2/70 (2.9) 1/76 (1.3)
NCT00528879 MB102-014	Add-on to metformin	102	Total*†	8/137 (5.8)	5/137 (3.6)	7/137 (5.1)	7/135 (5.2)
NCT00680745 D1690C00005	Add-on to glimepiride	48	Total† major	10/146 (6.8) 0	15/154 (9.7) 1/154 (0.6)	15/145 (10.3) 0	17/151 (11.3) 0
NCT00673231 D1690C00006	Add-on to insulin	48	Total† major	102/197 (51.8) 2/197 (1.0)	122/202 (60.4) 3/202 (1.5)	118/212 (55.7) 2/212 (0.9)	105/196 (53.6) 3/196 (1.5)
Active comparison study (forced titration)				**Glipizide 20mg‡**	**DAPA 10mg‡**		
NCT00660907 D1690C00004	Add-on to metformin	52	Total major discontinuation	162/408 (39.7) 3/408 (0.7) 6/408 (1.5)	14/406 (3.4) 0 0		

Total = total episodes (eps); major = eps requiring external assistance; *no major eps; †no discontinuations due to hypo; ‡mean titrated dose 16.4mg for glipizide, 9.2mg for DAPA

Proportions of patients with hypo were low with DAPA alone or added to metformin. Proportions were higher compared with placebo when DAPA was added to glimepiride or insulin, a typical effect when agents with low hypo propensity are added to a sulfonylurea or insulin. In the active comparison study, hypos were more than tenfold less frequent for DAPA vs glipizide. These data suggest that DAPA has a low intrinsic propensity to cause hypo in T2DM.

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1043-P

Dapagliflozin, an SGLT2 Inhibitor, Reduces Plasma Levels of Uric Acid in Patients with Type 2 Diabetes

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Diabetes is considered a cardiovascular (CV) risk-equivalent. Dapagliflozin (DAPA), a selective inhibitor of the renal sodium-glucose cotransporter 2 (SGLT2), improves hyperglycemia in patients with type 2 diabetes by increasing urinary glucose excretion in an insulin-independent manner.

Plasma uric acid (UA) is an emerging marker for CV and renal disease. The effect of DAPA on changes in UA from data collected in 5 phase 3 studies is reported.

Study ID	Design	Dose of DAPA or comparator (mg)	N	Time from baseline (weeks)	Mean baseline plasma uric acid (mg/dL)	Mean change from baseline (mg/dL)	(95%CI) [SE]
NCT00528372 MB102-013	Monotherapy*	QAM	65	24	5.92	-0.66†	(-0.86, -0.46)
		2.5	64		5.55	-0.85†	(-1.05, -0.65)
		5	70		5.67	-0.87†	(-1.06, -0.68)
		10					(-1.19, -0.80)
		QPM	67		5.38	-1.00†	(-0.92, -0.53)
		2.5	68		5.10	-0.73†	(-1.02, -0.64)
		5	76		5.49	-0.83†	(-0.38, -0.01)
		10	75		5.10	-0.20†	
		Placebo					
NCT00528879 MB102-014	Add-on to metformin*	2.5	137	102	5.41	-0.94	(-1.23, -0.65)
		5	137		5.31	-0.78	(-1.10, -0.47)
		10	135		5.41	-0.89	(-1.18, -0.61)
		Placebo	137		5.22	-0.03	(-0.39, 0.32)
NCT00660907 D1690C00004	DAPA versus glipizide add-on to metformin (forced titration)‡	DAPA 10mg**	406	52	5.65	-0.76	[0.057]
		Glipizide 20mg**	408		5.44	0.27	[0.056]
NCT00680745 D1690C00005	Add-on to glimepiride‡	2.5	154	48	5.07	-0.29	[0.091]
		5	145		5.11	-0.30	[0.092]
		10	151		5.06	-0.44	[0.078]
		Placebo	146		5.30	0.34	[0.093]
NCT00673231 D1690C00006	Add-on to insulin‡	2.5	202	48	5.48	-0.19	[0.079]
		5	212		5.44	-0.21	[0.079]
		10	196		5.46	-0.24	[0.083]
		Placebo	197		5.61	0.07	[0.080]

*Exploratory efficacy variable; ‡Data from safety analysis sets
N= number of patients randomized and treated
†Adjusted (LOCF)
**mean titrated dose 16.4mg for glipizide and 9.2mg for DAPA

DAPA consistently lowered plasma uric acid levels across 5 Phase 3 studies. Mean UA reductions ranged from 0.19 to 1.00 mg/dL from baseline and were sustained over 102 weeks. The mechanism for this effect is unknown, but may be due to an inhibitory effect of glucosuria on renal uric acid reabsorption. Further research is needed to establish the clinical significance of modest UA reductions in diabetic subjects with normal baseline UA levels.

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1044-P

DB959-101: A Phase 1 Randomized, Placebo-Controlled, Double-Blind, Escalating Single-Dose Study To Evaluate the Safety, Tolerability, Pharmacokinetics, and Food Effect of DB959Na in Healthy Male and Female Volunteers

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DB959, a non-TZD dual PPAR-delta/gamma agonist in development for the treatment of T2D, has shown efficacy in animal models of diabetes and dyslipidemia. This First-In-Human study enrolled 64 normal healthy volunteers in 8 dose-escalating cohorts (6 active and 2 placebo per cohort). Doses ranged from 2 to 200 mg. Safety was assessed by hematology, blood chemistry, urinalysis, physical examination (PE), vital signs (VS), ECGs, and adverse events (AEs). Pharmacokinetic (PK) parameters were calculated using non-compartmental analysis of concentrations measured from samples taken 0.5 to 72 hrs post dose. Six additional subjects received DB959 under fed and fasted conditions in a crossover cohort to assess the effect of food.

All subjects completed the study with no serious AEs. In the dose-escalation cohorts, 6% of DB959 subjects (3 of 48) and 13% of placebo subjects (2 of 16) had AEs considered to be drug related. In the food effect cohort, 2 fasted subjects (33%) and 1 fed subject (17%) had AEs considered to be drug-related. All AEs were mild, and AE frequency did not increase with increasing dose. No clinically-significant PE, VS, or ECG changes were observed.

Cmax was slightly less than dose proportional; AUCinf increased linearly with dose; mean Tmax ranged from 2 - 6 hrs; mean t½ ranged from 14.8 - 19.9 hrs (excluding 2 mg dose); CL/F was independent of dose (mean CL/F values ranged from 5.54 L/h to 8.51 L/h); there was a slight trend for Vz/F to increase with dose (mean Vz/F values ranged from 78.0 to 179 L). Intersubject

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variability for PK parameters was moderately high in some cohorts. Based on urinary excretion data, DB959 is not excreted unchanged in the urine. Fed/fasted results indicated that a high fat meal slightly delays absorption of DB959 and causes small decreases in Cmax and AUCinf.

The administration of single, oral, 2 to 200mg doses of DB959Na was safe and well tolerated, and the half-life of DB959 indicates that once daily dosing is feasible. These results provide compelling reasons for continued clinical development of DB959Na.

1045-P

Delay in Beginning or Optimizing Insulin Therapy Despite Poor Glycemic Control: Data from the A_1chieve Study

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A_1chieve is a 24-week, open-label, multinational, observational study evaluating the safety and clinical effectiveness of insulin detemir, insulin aspart and biphasic insulin aspart (premix) in people with type 2 diabetes in routine clinical practice. A total of 66 726 patients from 28 countries across Asia, Africa, Europe and Latin America were enrolled. Here we report on baseline glycemic control by category of prestudy therapy: medication naïve, oral glucose-lowering drug (OGLD) users or insulin users. Mean A1C between regions was 9.4 to 10.0% across treatment groups. In spite of this poor glycemic control, 11% of participants had been on no medication for an average duration of 4.6 years of diabetes, this varying markedly by region, from 2.2 years in south Asia to more than 8 years in Middle East/Gulf and Latin America (Table). Duration of diabetes when beginning insulin in patients using OGLD only also varied markedly between regions, from 6.2 to 13.8 years, and more than 77% of OGLD-only users were taking two or more OGLDs. Glycemic control was also poor (A1C 9.4 %) in people transferring from other insulin therapy, whose mean daily dose was only 0.26 U/kg, suggesting a lack of treatment optimization. In conclusion, baseline glycemic control in people starting insulin analogs was poor across all regions, with factors suggesting high variability of practice but always reflecting a delay in beginning or optimizing insulin therapy.

Table. Glycemic control and diabetes duration at baseline for treatment-naïve, insulin-naïve and insulin-experienced people by region

	China	South Asia	East Asia	North Africa	Middle East/Gulf	Latin America	Russia	Total
Drug naïve (n)	3372	1456	925	114	1463	44	66	7524
A1C (%)	10.4 (2.5)	9.3 (1.3)	10.6 (2.6)	10.8 (2.3)	9.7 (1.8)	10.6 (2.5)	10.6 (2.1)	10.0 (2.2)
Diabetes duration (yr)	3.3 (5.6)	2.2 (4.7)	8.0 (8.5)	5.8 (7.2)	8.1 (5.5)	8.5 (9.2)	4.1 (6.9)	4.6 (6.4)
OGLD users (n)	4772	16 574	5626	1836	5616	570	1813	36 810
A1C (%)	9.5 (2.2)	9.3 (1.3)	9.8 (1.9)	9.8 (1.8)	9.8 (1.7)	10.1 (2.2)	9.6 (1.6)	9.5 (1.7)
Diabetes duration (yr)	8.9 (7.1)	6.2 (4.5)	12.0 (7.7)	9.8 (6.3)	9.5 (5.9)	13.8 (8.6)	8.9 (6.1)	8.3 (6.3)
Insulin users (n)	2785	4343	3411	2030	7137	482	1163	21 351
A1C (%)	9.1 (2.3)	9.2 (1.4)	9.6 (2.0)	9.3 (1.7)	9.6 (1.8)	9.3 (2.1)	9.5 (1.6)	9.4 (1.8)
Diabetes duration (yr)	11.9 (8.6)	10.2 (6.1)	14.6 (9.3)	13.1 (7.4)	11.2 (6.7)	18.2 (10.5)	11.1 (6.6)	12.0 (7.7)

Mean (SD) or number; OGLD, oral glucose-lowering drug

1046-P

Detemir Is Associated with a Higher Insulin Dose Compared to Insulin Glargine across a Wide BMI-Range

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Insulin detemir is formulated at a 4-fold molar dose per IU compared to other insulins (2400nmol/l vs. 600 nmol/l). Despite this higher molar formulation, detemir is still associated with higher unit-dose requirements compared to insulin glargine, particularly when initiating basal insulin in type 2 diabetes. It has been suggested that the higher dose requirements are attributable to a subset of obese people requiring more insulin.

The L2T3 study was a 24-week 'treat-to-target' basal insulin initiation trial in 973 patients with type 2 diabetes comparing detemir bid to glargine od. In this study metabolic control was similar but daily insulin requirements for detemir (76.5 IU) were significantly higher than for glargine (43.5 IU).

In this post-hoc analysis of the L2T3 completers population we determined which factors influenced final insulin dose, with a specific focus on the relation between BMI and insulin dose.

Firstly we looked at the univariate Pearson correlations between baseline factors and final insulin dose. Subsequently we performed two stepwise regression analyses, one using all univariately associated baseline characteristics, and one using clinical characteristics (univariately associated) only.

BMI clearly correlated with final insulin dose (Pearson correlation 0.42 [0.37;0.48], p <0.001), with similar correlations but steeper slopes for detemir (n=436; b = 4.56; adjusted r^2 = 0.19) compared to glargine (n=456; b = 2.85; adjusted r^2 = 0.20).

Important significant determinants in the first regression model (adjusted r^2 = 0.49) were allocated treatment, (continued) use of insulin secretagogues, high cholesterol, high HDL and high LDL, with weight taking precedence over BMI in this model. Major determinants in the clinical model (adjusted r^2 = 0.40) were allocated treatment, (continued) use of insulin secretagogues, gender and BMI.

In conclusion, our data show an independent contribution of BMI to final insulin dose. However, this effect is outweighed by the strength of treatment allocation, with a >1.5-fold higher insulin dose when using detemir compared to glargine across a wide BMI-range.

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1047-P

Deterioration of Post-Operative Glucose Control in Diabetes after Intra-Operative Dexamethasone for Anti-Emesis

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High dose glucocorticoids are a common reason for the acute deterioration of blood glucose (BG) control in hospitalized patients with diabetes. Intra-operative (IP) dexamethasone (Dx) is increasingly being used to prevent post-operative (PO) nausea and vomiting. We retrospectively studied PO BG control and insulin therapy in 100 patients with type 2 diabetes who received a single dose of IP Dx compared with 100 age/sex matched patients with type 2 diabetes who did not receive IP Dx. Mean age was 64 years, 61% were female. 64% were receiving metformin, 40% sulfonylurea, and 28% insulin prior to surgery. 75% underwent orthopedic and 25% other surgical procedures. Mean admission HBA1C was 7.3%. 55% of Dx treated patients received 4-6 mg, and 45% received 8-12 mg. 100% of patients were NPO on PO day 0, but 80% were tolerating a solid diet by the end of PO day 1. Mean pre-op BG was similar: 154±47 mg/dl. PO day 0 mean BG at 1800h was higher after Dx 213±45 mg/dl vs. 174±51 mg/dl after no Dx (p<. 01). PO day 0 mean BG at 2300h was also higher after Dx 208±66 mg/dl vs. 180±50 mg/dl after no Dx (p<. 01). PO mean BG levels were similar between the Dx and non-Dx groups thereafter: 168 mg/dl on PO day 1, 155 mg/dl on PO day 2, and 150 mg/dl on PO day 3. All patients were treated with basal and prandial insulin. 85% of Dx treated patients received insulin on PO day 0, mean total dose 30±20 units, while only 64% of non-Dx treated patients received insulin on PO day 0, mean total dose 19±20 units (p<. 01). No Dx treated patients experienced a BG<70 mg/dl, while 4 non-Dx patients each had 1 BG reading of <70 mg/dl. Mean length of hospital stay was similar between groups: 3.6 days Dx vs. 3.8 days non-Dx. 5 patients from each group were readmitted within 60 days for a PO infection.

IP Dx causes PO hyperglycemia lasting ~ 24 hours. It was necessary to give more insulin on PO day 0 to Dx treated patients in order to try to blunt the hyperglycemic affect of IP Dx. However, prior to PO day 1, Dx induced hyperglycemia was difficult to prevent. It may be preferable to avoid using Dx as an IP anti-emetic agent in patients with type 2 diabetes.

1048-P

Development of a Chemiluminescent Assay for Insulin Glargine

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Insulin glargine (Lantus) is a long-acting insulin analogue, differing from human insulin by the substitution of asparagine for glycine at the C-terminal end of the A chain and the addition of two arginine molecules to the C-terminus of the B chain. These small changes in structure mean that in most assays for human insulin, insulin glargine is either not measured specifically or is measured with variable cross-reactivity, making it difficult to interpret results. We have developed an immunochemiluminometric assay (ICMA) using a solid phase antibody to insulin (14B) and a newly developed, acridinium ester labelled monoclonal antibody to insulin glargine (RR32.1). Monoclonal antibodies were raised to a 13 amino acid peptide sequence, representing the C-terminus of the insulin glargine B chain, coupled to bovine thyroglobulin carrier protein. Insulin glargine standards within the intended assay range of 0 – 250mU/L, were prepared by diluting medicinal insulin glargine. Optimum assay conditions, as demonstrated by the greatest relative light units (RLU) at the highest dose with low background RLUs, were

found to be 24 hours incubation at 4ºC using a 50µl sample. A reproducible standard curve was obtained, with good differentiation between zero and 5mU/L.

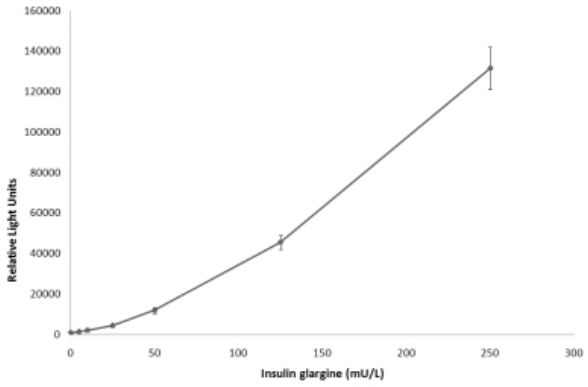

Fig: Standard curve for immunochemiluminometric assay for insulin glargine At a concentration of 250mU/L, cross reactivity was found to be <0.1% for the insulin analogues lispro (Humalog), glulisine (Apidra) and detemir (Levemir), <2% for insulin aspart (Novorapid) and approximately 9% for human insulin (Actrapid). Low dose clinical samples were recognised in the assay in the appropriate range. This specific assay for insulin glargine may prove useful in clinical applications and pharmaceutical development.

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1049-P

Development of a Long-Acting C-Peptide

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C-peptide is co-secreted in equimolar amounts with insulin in response to consumption of carbohydrates. In the past two decades, substantial data have been accumulated suggesting that C-peptide, contrary to previous views, is an endogenous peptide hormone in its own right. In this regard, the C-peptide/insulin dual hormone story mirrors that of GLP-1/GLP-2/glucagon. It has been proposed that the absence of C-peptide in type 1 diabetes patients is an important contributing factor in the onset and progression of long-term complications of the disease. To test this hypothesis, several preclinical studies in animal models of type 1 diabetes as well as clinical trials with C-peptide replacement therapy have been completed. These studies demonstrated beneficial effects after C-peptide administration in diabetic peripheral neuropathy as reflected by improvement in nerve conduction velocity and global neuropathy score. Additionally, a reduction in microalbuminuria and improvement of glomerular structural abnormalities were observed in diabetic nephropathy. Efforts to develop an attractive therapeutic to replace circulating levels of C-peptide have been stymied by its short half-life (>1 hour). Cebix has successfully developed a long-acting product with subcutaneous delivery through the PEGylation of the peptide's N-terminus, distal from the biologically active C-terminus. This resulted in an extension of the half-life to 70 hours in monkeys. PEGylated C-peptide (CBX129801) was demonstrated to be a homogeneous, monomeric product by SDS-PAGE, sedimentation velocity, and RP-HPLC. The preservation of the native conformation was confirmed by circular dichroism. The retention of in vitro biological activity of the PEGylated C-peptide was confirmed by its ability to elicit ERK 1/2 phosphorylation in human kidney cells. In vivo potency was demonstrated following subcutaneous administration in a streptozotocin-induced rat model of type 1 diabetes by a 4 m/sec reversal of sensory nerve conduction velocity impairment. It is concluded that PEGylated C-peptide is potentially an attractive therapeutic agent due to the product's substantial extension of half-life and biological activity comparable to that of the native peptide.

1050-P

Differential Contribution of Basal and Prandial Components to Total Hyperglycemia in Younger vs Older Patients with Type 2 Diabetes

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This study aimed to determine the relative contribution of basal hyperglycemia (BHG) vs postprandial hyperglycemia (PPHG) to hyperglycemic exposure (HE) in younger (<65 y) and older (≥65 y) adults with T2DM. Participant-level data were pooled from 6 controlled clinical trials in which, over 24 to 28 weeks, insulin glargine or other therapies (NPH, premixed, or prandial insulin, or increasing oral agents) were added to oral therapy and insulin was titrated to glucose targets according to predefined algorithms. From 7-point, self-measured blood glucose profiles, HE (>100 mg/dl) due to BHG and PPHG were calculated and compared between younger and older patients. Of 1699 patients, 1190 (70%) were younger than age 65 (mean 55 y, duration of diabetes 8 y, A1C 8.72%), and 509 (30%) were ≥65 y (mean 70 y, duration of diabetes 11 y, A1C 8.63%). At baseline, the relative contribution of BHG vs PPHG to HE was 79% in the younger and 75% in the older group (P<0.01). After 24 to 28 weeks of treatment with insulin glargine or a comparator, A1C decreased to 7.05% in the younger group and 7.02% in the older group. The contribution of BHG in relation to PPHG also decreased, contributing 45% to total HE in the younger group vs 38% in the older group (P<0.01). Relative contribution of BHG was positively correlated with A1C both at baseline and after treatment in the younger (r^2=0.08, P<0.01, r^2 =0.062, P=0.03) but not in the older cohort. Over 24 to 48 weeks of treatment, incidence of glucose-confirmed (<50 mg/dL) hypoglycemia was 34% and 31% for the younger and older age groups, respectively (P=NS). In conclusion, although BHG and PPHG were directionally similar between groups, the postprandial contribution to overall hyperglycemia may be greater in older compared with younger adults. These findings suggest that different approaches aimed at lowering basal and postprandial hyperglycemia may be needed in treating younger vs older patients with T2DM.

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1051-P

Effect of Basal Insulin Plus Oral Antidiabetes Drug Therapy on beta-Cell Function and Glycaemic Control in Patients with Newly Diagnosed Type 2 Diabetes

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Early basal insulin plus antidiabetes drug therapy in patients with newly diagnosed type 2 diabetes might improve beta-cell function and result in extended glycaemic control. We did a randomized trial to compare the effect of basal insulin plus antidiabetes drug (insulin+OAD) therapy with only antidiabetes drug (OAD) therapy on beta-cell function.

129 patients, aged 35-50 years, were enrolled between June, 2005 and June, 2009. The patients, with fasting plasma glucose≥9.0mmol/L and HbA1c≥9.0%, were randomly assigned to therapy with insulin+OAD or only OAD only for initial correction of hyperglycaemia. Treatment was stopped three months later. Patients were then followed-up on diet and exercise. If diet and exercise were not enough, OAD but not insulin would be given again to maintain target glycaemic. Blood glucose, HbA1c and insulin were measured before and after therapy withdrawal and at one-year follow-up.

More patients achieved target glycaemic control in the insulin+OAD group [98.3% (58 of 59)] in less time [(10.4±2.5) days] than those in only OAD group [95.7% (67 of 70) and (12.4±3.4) days]. At one-year follow-up, more patients maintained target glycaemic without OAD in the insulin+OAD group [37.9% (22 of 58)] than those in only OAD group [28.4% (19 of 67)], beta-cell function in the insulin+OAD group [lg(HOMA-beta) : 2.17±0.14] was better than that in only OAD group [lg(HOMA-beta) : 2.11±0.13] ,and insulin resistance in insulin+OAD group [lg(HOMA-IR): 0.50±0.09] was similar with that in only OAD group [lg(HOMA-IR): 0.48±0.09].

The present study suggested that insulin+OAD therapy in patients with newly diagnosed type 2 diabetes had better maintenance of glycaemic control and preservation of beta-cell function than only OAD treatment.

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1052-P

Effect of BLX 1002 on Key Features of Non-Alcoholic Fatty Liver Disease (NAFLD) in Animal Models

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Results: Non alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome. It is closely associated with visceral obesity and insulin resistance. In present investigation effect of BLX 1002 a novel small molecule was evaluated on hepatic steatosis, obesity and insulin resistance using three different animal models.

In mice (C57BL/6) models of diet induced NAFLD (High fat 60 Kcal % and 40% fructose fed for 2 months), Obesity (High fat 60 Kcal % for 3 months), Obesity with severe insulin resistance (High fat 60 Kcal % for 4 months),

For author disclosure information, see page 785.

we investigated the effect of therapy with BLX 1002. The NAFLD animals were treated once daily for 28 days with BLX 1002 at 10, 30 and 100 mg/kg. Diet induced obese (DIO) mice and DIO mice with severe insulin resistance animals were treated with BLX 1002 at 100 and 30 mg/kg once daily for 28 days respectively. During the course of treatment body weight was recorded. Plasma glucose and ALT levels were determined by colorimetric assay. Insulin was estimated by ELISA. At the end of the experiment, animals were sacrificed, liver obtained and weighed. Hepatic steatosis in NAFLD animals were assessed by histopathology.

The NAFLD animals were treated with BLX 1002 at 10, 30 and 100 mg/kg showed reduction in body weight gain (72.57 %, 32.35 %, and 71.26 % respectively), and ALT (37.21 %, 30.61 %, and 46.29 % respectively), which were significant at 10 and 100 mg/kg treated group. Histopathological examination of liver revealed substantial improvement in hepatic steatosis compared to disease control. The DIO animals treated with BLX 1002 at 100 mg/kg showed 12.67% reduction in body weight as compared to disease control which was significant from 24th day of treatment. DIO animals with severe insulin resistance treated with BLX 1002 at 30 mg/kg showed significant improvement (46.27 %) in insulin resistance which was assessed by HOMA-IR.

In conclusion, these data demonstrate a remarkable effect of BLX 1002 on hepatic steatosis, body weight, ALT and insulin resistance in different animal models and suggest that BLX 1002 may be a therapeutic option for the treatment of NAFLD.

1053-P

Effect of Combination L-Methylfolate, Pyridoxal-5´-Phosphate, and Methylcobalamin on Neuropathy Symptoms and Inflammatory Biomarkers in Patients with Diabetic Peripheral Neuropathy (DPN)

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DPN affects at least 1 in 5 persons with diabetes yet has a limited array of treatment options. The effects of the medical food L-methylfolate calcium 3 mg, pyridoxal-5´-phosphate 35 mg, and methylcobalamin 2 mg (LMF-MC-PP; Metanx®) on signs, symptoms, and biomarkers associated with DPN were assessed in a 24-week, multicenter, randomized, double-blind, placebo-controlled trial involving 214 patients with DPN (baseline vibration perception threshold [VPT]: 25-45 volts) but without peripheral vascular disease. Patients who had had previous surgery with residual neurologic deficit, or A1C >9% were excluded. Concomitant opiate use was not permitted, but other DPN medications could be used as long as doses were kept constant during the study. The mean patient age was 62.6 ± 8.9 years, and there were no differences between the LMF-MC-PP and placebo groups at baseline in age, race, ethnicity, duration of diabetes or neuropathy, or baseline outcome measures. At 24 weeks, change in VPT, the primary outcome, did not differ between the LMF-MC-PP and placebo groups (Table 1). In terms of secondary outcomes, a significant difference in mean neuropathy total symptom score–6 (NTSS-6) was observed with LMF-MC-PP vs placebo, and the mental component scale (MCS) of the short form 36 (SF-36, a validated quality of life survey) improved significantly. Table 1 shows the change in homocysteine, an inflammatory factor associated with diabetic complications including DPN. Adverse events were infrequent, occurring in <2% of all subjects; none were considered serious. These findings suggest that LMF-MC-PP may be a safe and effective symptomatic therapy for patients with DPN, leading to improvement in components of quality of life and inflammatory biomarkers, despite a lack of change in vibration sensation.

	LMF-MC-PP	Placebo	P Value
VPT (Left), volts	-1.97±15.22	-4.77±11.60	0.927
VPT (Right), volts	-1.94±13.66	-1.77±13.45	0.464
NTSS-6	-0.96±1.54	-0.53±1.69	0.033
MCS	1.99±8.57	-0.29±8.48	0.031
Homocysteine, µmol/L	-2.7±3.0	0.5±2.4	0.0001

Supported by: Pamlab, LLC.

1054-P

Effect of Different Antidiabetic Drugs on Diabetic Wound Healing Via Regulation of Connexins and Oxidative Stress Markers

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Cellular communication through gap junction is very important during wound healing but its role in diabetic conditions is not well explored. This study was aimed to analyze the effects of different groups of antidiabetic drugs on the expression of gap junction protein i.e. connexins (Cx), NO production, antioxidant enzyme status viz. SOD and LPO in wound tissues of streptozotacin induced diabetic mice. The equilibrated concentrations of metformine (60mg/kg), insulin (1.25U/kg), glibenclamide (8.3mg/kg) and pioglitazone (20mg/kg) were given daily post wounding till the closure of wounds. A decrease in the levels of serum glucose and LPO was observed on day 7 and 13 after treatment with all the drugs but the results were more significant ($p<0.001$) in pioglitazone treated mice (Fig.1A,B). The reduced levels of SOD and NO were improved on day 7 and 13 more significantly with pioglitazone treated mice as compared to other drugs (Fig.1C,D). The expression levels of Cx 26, 30.3, 31, 31.1 and 43 declined on day 7 following treatment, and again pioglitazone was more effective ($p<0.001$) than other drugs (Fig.1E,F).

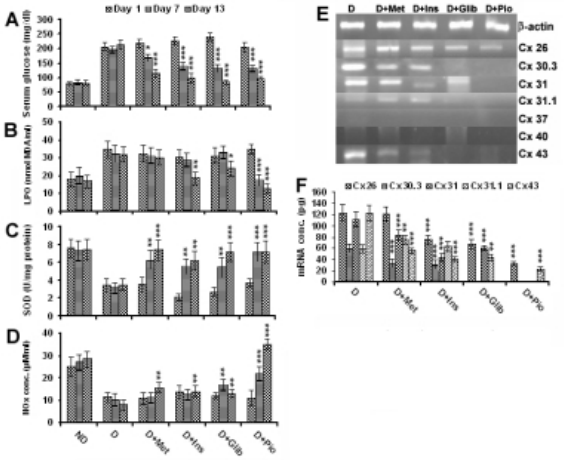

Figure 1. A. Levels of serum glucose; B. Lipid peroxidation (malonaldehyde formed); C. Superoxide dismutase; D. total nitric oxide; E. Connexin expression by RTPCR; F. semiquantitative estimation of concentration of connexin mRNA by densitometric analysis. (ND= non diabetic control mice, D= diabetic control, D+Met= diabetics with metformin treatment, D+Ins= diabetics with insulin treatment, D+Glib= diabetics with glibenclamide treatment, D+Pio= diabetics with pioglitazone treatment.) [*p<0.05, **p<0.01, ***p<0.001 using one way ANOVA followed by Student-Newman Keuls test]

This study suggests that increased glucose level and augmented oxidative stress at wound site may be responsible for increased Cx expression in diabetes. The antidiabetics improve antioxidant status at wound site that eventually results in down regulation of Cx gene expression to enhanced rate of wound repair in diabetics. However, the results suggests that pioglitazone has advantage over other antidiabetic drugs in diabetic wound closure, probably via down regulating Cx gene expression and improving glycemic and oxidative stress control.

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1055-P

Effect of Liraglutide, Exenatide, and Sitagliptin on the Composite Outcome of Glycemic Control and Weight Loss

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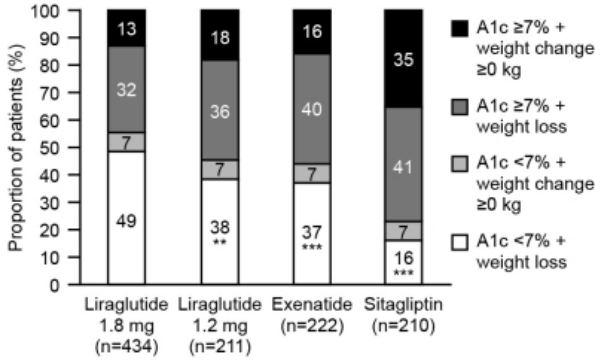
Achieving durable glycemic control in type 2 diabetes with existing antidiabetic agents is commonly accompanied by weight gain, which frustrates patients and potentially increases the risk of cardiovascular disease. Incretin-based therapies, however, offer enhanced glycemic control with weight neutrality (dipeptidyl peptidase-4 inhibitors) or weight loss (glucagon-like peptide-1 receptor agonists). We compared the number of patients reaching the composite endpoint of glycated hemoglobin (A1c) levels <7% and weight loss after 26 weeks' treatment with liraglutide 1.8 mg or 1.2 mg once daily, exenatide 10 µg twice daily, and sitagliptin 100 mg once daily (with metformin +/- sulfonylurea background therapy) using patient-level data from 2 large randomized trials. A logistic regression analysis was performed on intent-to-treat populations (last observation carried forward) with treatment and country as fixed effects and baseline A1c and baseline

body weight as covariates. A1c and weight changes for each treatment group are shown in the table. Significantly more patients reached the composite endpoint with liraglutide 1.8 mg than with liraglutide 1.2 mg (odds ratio [95% CI]: 1.66 [1.14, 2.41]; $p<0.01$), exenatide (2.10 [1.41, 3.14]; $p<0.001$), or sitagliptin (5.70 [3.63, 8.94]; $p<0.001$; Figure). In summary, patients are more likely to achieve glycemic control with weight loss on liraglutide 1.8 mg than exenatide or sitagliptin.

	Liraglutide 1.8 mg (pooled) (n=434)	Liraglutide 1.2 mg (n=211)	Exenatide 10 µg (n=222)	Sitagliptin 100 mg (n=210)
A1c at baseline (%)	8.3 (0.9)	8.4 (0.8)	8.1 (1.0)	8.5 (0.8)
A1c change (%)	-1.3 (0.1)	-1.1 (0.1)	-0.9 (0.1)	-0.9 (0.1)
Body weight at baseline (kg)	93.8 (19.2)	93.7 (18.5)	93.0 (19.5)	93.1 (18.9)
Body weight change (kg)	-3.0 (0.2)	-2.7 (0.3)	-2.3 (0.2)	-0.8 (0.2)

Baseline data are mean (SD); change data are mean (SE)



p-values are from logistic regression analysis;
**$p<0.01$ and ***$p<0.001$ vs liraglutide 1.8 mg

1056-P

Effect of Sitagliptin in Type 1 or Advanced Type 2 Diabetic Patients with Absolute Insulin Deficiency

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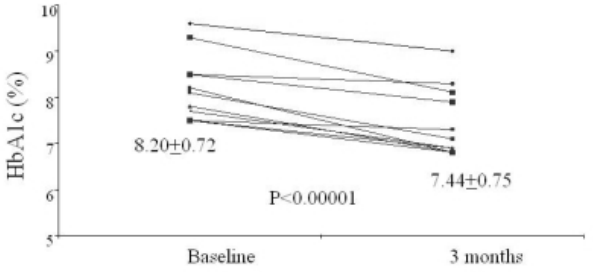
It is generally believed that incretin-based therapies are effective in subjects with certain levels of remaining beta-cell function. The aim of this study was to evaluate the effect of sitagliptin in T1DM (n=5) and T2DM (n=4) patients with absolute insulin deficiency. Mean age and duration of diabetes were 56.4 and 13.9 years, respectively. Mean body weight was 55.4 kg. None of these subjects had detectable postprandial C-peptide levels (below 0.1 ng/ml). Although they were receiving intensive insulin therapy (mean dose: 44.1 U/day) together with oral hypoglycemic agents, their glycemic control remained poor. Sitagliptin was added to the ongoing regimen. Other therapies were unchanged. At 12 weeks, effective reductions of HbA1c levels were observed without any clinically significant adverse events (from 8.20 % to 7.44 %, p<0.00001).



However, most subjects reported mild hypoglycemic episodes. No gastrointestinal complaints (e.g. delayed gastric emptying) or body weight changes were noted. However, one subject was a non-responder whose HbA1c levels slightly increased. Surprisingly postprandial C-peptide levels remained undetectable after sitagliptin treatment with all the subjects. This study demonstrates that sitagliptin may be still effective as add-on to insulin in patients with T1DM or advanced T2DM lacking residual beta-cell function. The improvement in glycemic control could not be due to enhanced endogenous insulin secretion, but could be a result of other factors, such as suppression of glucagon levels. However, it is known that the glucagon-suppressive effects of sitagliptin are rather small and short-lived. Based on these data, a novel hypothesis that the glycemic effects of sitagliptin may be through mechanisms that are independent of the GLP-1 axis (beyond inhibition of DPP-4) will be presented.

1057-P

Initial Therapy with the Fixed-Dose Combination (FDC) of Sitagliptin and Metformin (JANUMET™) in Patients with Type 2 Diabetes Mellitus (T2DM) Provided Superior Glycemic Control vs. Metformin Alone, Based on the AACE/ACE Diabetes Algorithm

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The AACE/ACE diabetes treatment algorithm recommends a stratified approach to initial therapy to achieve an A1C goal of ≤6.5% in pts with T2DM who have inadequate glycemic control on diet and exercise alone: monotherapy for A1C ≤7.5%; dual therapy for A1C >7.5-9.0%; and dual or triple therapy (if asymptomatic) or insulin (if symptomatic) for A1C >9.0%. We conducted a *post hoc* analysis of a large, randomized, double-blind study comparing initial dual therapy with sitagliptin and metformin (SITA/MET; administered as an FDC tablet) to initial monotherapy with metformin (MET) in drug-naïve pts with T2DM (A1C ≥7.5%) to examine A1C goal attainment based on these stratified A1C categories. 1250 pts (mean baseline A1C=9.9%) were randomized 1:1 to twice-daily (BID) SITA/MET or MET for 18 wks. SITA/MET and MET were up-titrated over 4 wks to 50/1000 mg BID and 1000 mg BID, respectively. At Wk 18, a higher percentage of pts in the SITA/MET group had A1C levels of ≤6.5% and <7% than those in the MET group within each baseline A1C subgroup (table). Of pts who initiated SITA/MET with a baseline A1C of >7.5-9.0%, 48.6% achieved an A1C of ≤6.5% at Wk 18 compared with 23.1% of pts who initiated MET monotherapy (p<0.001). In pts with a baseline A1C of >9.0%, 24.0% on SITA/MET achieved an A1C of ≤6.5% compared with 12.8% on MET (p<0.001). In summary, in pts with a baseline A1C of >7.5-9.0%, substantially more pts achieved the AACE/ACE A1C goal of ≤6.5% with initial treatment with dual therapy (SITA/MET) than with initial monotherapy (MET), in agreement with the AACE/ACE treatment algorithm.

	Baseline A1C ≤7.5%		Baseline A1C>7.5-9.0%		Baseline >9.0%	
	Wk 18	Wk 18	Wk 18	Wk 18	Wk 18	Wk 18
	[N] A1C≤6.5%	A1C<7%	[N] A1C≤6.5%	A1C<7%	[N] A1C≤6.5%	A1C<7%
Treatment	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
MET	[37] 15 (40.5)	29 (78.4)	[182] 42 (23.1)	85 (46.7)	[345] 44 (12.8)	9 (22.9)
SITA/MET	[35] 24 (68.6)*	30 (85.7)	[183] 89 (48.6)**	127 (69.4)**	[341] 82 (24.0)**	118 (34.6)**

*p<0.01 vs MET; **p<0.001 vs MET

1058-P

Effects of Aleglitazar, a Balanced Dual Peroxisome Proliferator-Activated Receptor-α/γ Agonist, on Diabetic Complications in Zucker Diabetic Fatty (ZDF) Rats

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Complications of type 2 diabetes (T2D) affect organs including the pancreas (loss of islet integrity and β-cells) and kidneys (glomerulosclerosis, proteinuria). This study evaluated the effects of aleglitazar on organ integrity and function in relation to metabolic parameters during development of T2D.

Six-week-old, male (ZDF) rats received aleglitazar (0.3 mg/kg/day) as food admix vs vehicle for 12 wks (n=10 per group). Age-matched male Zucker Lean (ZL) rats served as non-diabetic controls. Metabolic parameters in plasma and urine were measured at several time points; histomorphometry of pancreas, kidney and eye was performed at study end.

In vehicle-treated ZDF rats, plasma insulin levels initially increased from baseline (4.8±0.5 ng/mL), peaking at wk 4 (8.3±1.1 ng/mL), then rapidly declined to wk 12 (2.6±0.5 ng/mL), while glucose levels increased throughout the study. Aleglitazar treatment prevented early hyperinsulinemia, preserving near-normal insulin levels in ZDF rats (5.0±0.7 at baseline; 1.9±0.2 ng/mL at wk 12). Aleglitazar treatment of ZDF rats completely prevented hyperglycemia (+0.3 [ZDF + aleglitazar] vs +18.2 mmol/L [ZDF]) and hypertriglyceridemia (−0.4 [ZDF + aleglitazar] vs +6.7 mmol/L [ZDF]) compared to pre-treatment values. Urine analysis detected a progressive increase in excreted glucose and protein (81±0.4 mmol/L and 4.4±1.2 mg/mL at wk 12) in vehicle-treated ZDF rats that was prevented by aleglitazar (0.5±0.1 mmol/L and 0.3±0.1 mg/mL). Consistent with its effects on metabolic parameters, aleglitazar protected islet integrity as demonstrated by 1) preventing β-cell loss (aleglitazar vs vehicle [ZDF] −75% vs controls [ZL] +6%); 2) reducing the

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

number of abnormal islets; and 3) preserving α-cell localization. Consistent with its effects to prevent abnormal urine glucose and protein excretion, aleglitazar prevented renal glomerular hypertrophy, podocyte degeneration, and glomerulosclerosis.

In summary, these data demonstrate that, in addition to prevention of diabetes progression in ZDF rats, aleglitazar protects against T2D-associated organ damage and dysfunction.

1059-P

Effects of Basal Bolus vs Basal Plus Insulin Regimens on Weight in Patients with Type 2 Diabetes

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Patients (pts) with type 2 diabetes (T2D) may require prandial insulin injections in addition to basal insulin, but optimal regimens for individual pts are difficult to determine. This subanalysis of a randomized controlled study compared the 1-year efficacy and safety of insulin glargine (GLAR) plus 1, 2, or 3 daily injections of insulin glulisine (GLU) in pts with or without weight gain. Pts were grouped according to those who received 1 (n=114), 2 (n=128), or 3 (n=209) GLU injections in addition to GLAR and oral medications; results within each injection category were stratified by pts who gained weight vs those with no weight gain (or weight loss). Baseline demographics and clinical characteristics were similar among the 3 groups, except for a higher percentage of males and lower mean A1C in the 1 GLU group vs groups 2 or 3. At week 52, 33.0% and 31.6% of pts in 1 GLU and 3 GLU groups, respectively, lost a mean (SD) of 2.0 (2.2) kg and 1.9 (1.9) kg; 26.3% and 25.8% of these pts achieved A1C goal of ≤7.0% (Table). Overall, at week 52, 3 GLU pts were more likely to reach A1C goal vs 1 GLU pts, (ΔA1C = -0.7 vs -0.1, *P*<0.01) but they were not more likely to gain weight (1.9 kg vs 1.3 kg, *P*=NS). Pts receiving 1 GLU who lost weight had 3X greater odds of achieving A1C goal <7.0% vs pts who gained weight (*P*=0.04). Overall, the difference in weight change from baseline at week 52 between the 1 GLU and 3 GLU was similar (*P*=NS). The incidence and event rates of hypoglycemia were similar among the 3 injection groups (Table). The results of this analysis suggest that pts with a basal plus insulin regimen can achieve glycemic goals while also maintaining or losing weight. Increasing the number of daily GLU injections from 1 to 3 does not significantly increase weight gain or risk of hypoglycemia.

Table. Analysis of results from a randomized controlled trial of patients with type 2 diabetes treated with oral antidiabetic drugs, basal insulin glargine, and 1 to 3 daily injections of insulin glulisine, by number of glulisine injections and change in body weight (Δ wgt : weight maintenance/loss versus weight gain)

	Glulisine x1		Glulisine x2		Glulisine x3	
	Δ wgt ≤ 0 kg n = 38	Δ wgt > 0 n=76	Δ wgt ≤ 0 n=37	Δ wgt >0 n= 91	Δ wgt ≤ 0 n= 66	Δ wgt > 0 n= 143
Baseline A1C, % Mean (SD)	8.1 (0.9)	8.3 (1.1)	8.1 (0.8)	8.7 (1.3) *P*<0.01*	8.5 (1.1)	8.5 (1.1)
52 week A1C, % Mean (SD)	7.8 (1.1)	8.3 (1.3) *P*=0.04*	7.5 (1.2)	8.0 (1.1) *P*=0.03*	7.9 (1. 5)	7.8 (1.2)
Change from baseline to 52 week A1C, % Mean (SD)	-0.25	0.01	-0.59	-0.69	-0.59	-0.74
% of patients achieving A1C <7% at week 52	26.3	10.5 *P*=0.04*†	40.5	13.2 *P*=0.01*†	21.2	22.4
% of patients achieving A1C ≤7% at week 52	26.3	11.8	40.5	15.4 *P*<0.04*†	25.8	25.9
Baseline weight, kg Mean (SD)	85.9 (18.2)	80.8 (17.1)	82.6 (16.9)	81.9 (16.0)	86.7 (15.1)	81.0 (15.0) *P*=0.01*
52 week weight, kg Mean (SD)	83.9 (17.7)	83.7 (17.7)	81.0 (16.3)	83.0 (16.7)	84.8 (14.8)	84.6 (15.4)
Weight change from baseline to 52 week, kg, mean (SD)	-2.0 (2.2)	2.9 (2.0) *P*<0.01*	-1.7 (2.1)	3.1 (2.2) *P*<0.01*	-1.9 (1.9)	3.6 (2.4) *P*<0.01*
Total Hypoglycemia incidence, %	50	42.1	54.1	59.3 *P*<0.04**	43.9	45.5
Total Severe, %	0	1.3	0	0	0	1.4
Total < 50 mg/dL, %	13.2	26.3	13.5	26.4	9.1	18.2
Total <70 mg/dL, %	47.4	40.8	51.4	53.9 *P*<0.04**	40.9	39.9
Total Nocturnal, %	21.1	29.0	21.6	28.6	22.7	18.2

**P*-value vs Δ wgt ≤ 0; †Logistic regression including weight gain category and baseline A1C as covariates
***P*-value is for 2 vs 3 GLU injections, weight change >0

Supported by: sanofi-aventis US

1060-P

Effects of Fenofibrate on Inflammatory Markers in Hispanics with Hypertriglyceridemia

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Fenofibrate (Feno), a fibric acid derivative, is a triglyceride-lowering agent. Fibrates activate nuclear peroxisome proliferator-activated receptors a (PPARa). In trials such as FIELD and ACCORD, Feno decreased TG level significantly. Reports concerning Feno's ability to improve insulin resistance (IR), HDL-C and inflammatory status have been inconsistent. Furthermore, there is no Feno study reported in the Hispanic population. Thus we initiated this study to explore the effect of Feno on IR, lipids and inflammation in a Los Angeles (LA) Hispanic population. Specifically, self-reported Hispanics (n=278) in LA with TG level >140 mg/dl were recruited, excluding subjects with existing or newly diagnosed diabetes mellitus (DM). Subjects were given 8 weeks of treatment preceded by 4 weeks of wash out (when necessary). Liver enzymes (ALT, AST, GGT), lipids (TG, FFA, Chol, and HDL-C and cytokines (MCP-1, TNFR1 and TNFR2) were determined at baseline and after treatment. TG and FFA decreased by 34% and 14% respectively (both p<,0001); HDL-C increased by 12% while Chol decreased by 10% (both p<.0001). Insulin also decreased by 14% (p<.03) without a change in glucose, suggesting improvement in insulin sensitivity. A small (10%) elevation of liver enzymes (ALT and AST) (p<.02) and inflammatory markers (TNF R1 and R2) (p<.0001) was found. There was no change seen in GGT, adiponectin and MCP-1.

We further divided the subjects into three groups: fast responders, slow responders, and non-responders. In general, those with TG >300 responded in two weeks and TG levels reduced to ~120. Those with TG between 150-300 responded modestly with longer treatment time to maximum effect. Finally, TG less than 150 responded poorly. Whether genetic background determines the response remains to be seen.

In summary, Feno treatment resulted in improvement of lipids and insulin sensitivity. Although liver enzymes and inflammatory markers were mildly increased, there was no clinical significance concerning these changes. We conclude fenofibrate should continue to be considered as an effective lipid lowering drug. We also propose that pharmacogenetic studies using this cohort are warranted.

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1061-P

Effects of Long Acting Insulin Versus Rapid Acting Insulin on Oxidative Stress in Patients with Type 2 Diabetes

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Many evidences show that postprandial hyperglycemia is associated with systemic oxidative stress in patients with type 2 diabetes. However, recent report also suggests that insulin itself has antioxidative property independently of its glucose lowing effect (Monnier L et al. Diabetologia 2010). We investigated which of rapid acting insulin injection three times (before each meal) a day (n =16) or long acting insulin injection a day (n =19) or provides more strong antioxidative effects. Patients with type 2 diabetes, who have poor glycemic control and hospitalized because of initiation of insulin treatment, were randomly assigned into long acting insulin (Levemir®) group or rapid insulin (Novorapid®) group. Sulfonylureas were discontinued when insulin therapy was initiated. Mean observation periods after initiation of insulin therapy were 10 days in each group. Patients' ages and body weights were 59.1±10.2, 64.2±11.3 year, and 62.7±16.2, 58.2±10.0 kg in patients with rapid acting insulin or long acting insulin. In rapid acting insulin group, fasting and postprandial plasma glucose respectively changed from 183.4±68.7 to 138.2±34.0 mg/dl, and from 309.8±65.0 to 197.7±43.8 mg/dl (P <0.05, respectively). On the other hand, In long acting insulin groups, these parameters were respectively changed from 181.3±69.4 to 130.5±47.5 mg/dl, and from 307.4±64.9 to 254.9±67.5 mg/dl (P <0.05, respectively). Body weights did not significantly change in each group before and after insulin therapy. Urinary 8 iso-prostaglandin F2-alfa, which reflects systemic antioxidative stress, changed from 170 (135.25, 240.25) to 218(135, 272) pg/g.Cr (no significance) in rapid acting insulin group, and changed from 217 (176, 279) to 192(161, 238) pg/g.Cr (P <0.05) in long acting insulin group. There was significant difference in urinary 8 iso-prostaglandin F2-alfa values in baseline between both groups. Results in this study suggests that long acting insulin a day more effectively decreases oxidative stress than rapid acting insulin three times a day in patients with type 2 diabetes.

1062-P

Effects of Nateglinide Versus Acarbose on Postprandial Plasma Glucose Excursion and Postprandial Lipid Profiles in Patients with Type 2 Diabetes

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Both nateglinide and acarbose are oral anti-diabetic agents that can decrease rapid fluctuation of postprandial plasma glucose through different mechanism. There are lack comprehensive data on effects of nateglinide versus acarbose on plasma glucose level, lipid profiles and inflammatory

response of postprandial status in drug naive Chinese patients with T2D. A 4-week, multi-center, open-label, randomized, active-control, parallel-group designed study were conducted to compare effects of nateglinide and acarbose on postprandial glucose excursion (PPGE), glycosylated serum albumin (GSA), postprandial lipid profiles and high sensitivity C-reactive protein (hsCRP). A total of 160 anti-diabetic drug naive T2D patients (HbA1c 7.5±0.65%) were randomized to receive either nateglinide 120 mg TID, a.c. or acarbose 50 mg TID, a.c. for 4 weeks. The evaluation variables were assessed by standardized meal test. The trial showed that, compared with baseline, both nateglinide and acarbose could reduce PPGE 2h significantly ($p<0.01$) and had comparable effects on reducing GSA (-1.2+1.57%, -1.2+2.13%, $p<0.01$). Nateglinide can slightly increase HDL-C and markedly decrease FFA at postprandial 30 minute, 60 minute, 90 minute ($p<0.05$), however, acarbose significantly reduced fasting HDL-C ($p<0.01$) and has no effect on FFA. The differences between the two groups were significant at fasting HDL-C and postprandial 60 minute FFA ($p<0.05$). There were no significant effects on LDL-C and hsCRP in the two groups. The number of people experiencing adverse events was similar in the two groups (Nateglinide 13.8%, Acarbose 18.8%) and frequency of symptomatic hypoglycemia was low (nateglinide 5%, Acarbose 1.3%). No confirmed or serious hypoglycemia was observed. This study indicated that nateglinide and acarbose were similar in controlling the postprandial glucose in Chinese drug naive patients with T2D. In addition, better performance on improving lipid metabolism under postprandial status induced by nateglinide may be associated with the restoration of early-phase insulin secretion and may impart a cardiovascular advantage in comparison with acarbose.

1063-P

Effects of Pramlintide in Patients with T2DM Using Larger Doses of Insulin—A Tertile Analysis Based on Daily Insulin Dose

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Increased insulin use in patients with T2DM is due to decreased beta cell function and increased insulin resistance. This posthoc analysis examined the effects of 6 mo of pramlintide (PRAM, 120mcg with major meals) in patients with T2DM stratified by their daily insulin dose in 3 clinical trials.

The first data set was a pooled analysis of 2 placebo (PBO)-controlled trials. BL data were well matched across the 3 tertiles (TERT) and treatments (PRAM vs PBO). For both PRAM and PBO arms, insulin use in TERT3 was ~3 times higher than in TERT1 and correlated with BMI.

PRAM led to similar decreases in A1C and body weight across the 3 TERTs. Insulin use, which was per protocol to remain stable, decreased by 3.6% in TERT3.

Nausea was the most frequently observed AE in the PRAM arm (32%, 35%, and 17% in TERT 1,2,&3), compared to 12%, 12%, and 10% for PBO. The event rate/patient y of severe hypoglycemia for the PRAM arm was 0.55%, 0.32%, and 0.13% for TERT 1,2,&3, compared to 0.14%, 0.16%, and 0.32% for PBO.

Similar results were seen in an open-label clinical practice trial, where BL insulin units ranged from 43.2U/d in TERT1 to 196.2U/d in TERT3. Reduction in A1C was slightly less for TERT3 compared to TERT1. Weight loss and reduction in insulin use were similar, as was the AE profile, with nausea being the most frequent (32%, 32%, & 36% for TERT 1,2,&3).

In summary, PRAM elicited similar reductions in A1C as an adjunctive therapy to insulin in patients with T2DM regardless of their baseline insulin dose (~100-200U/day). PRAM also offered weight loss and decreased insulin use.

	Pivotal Trials				Clinical Practice Trial	
	TERT1 PRAM	TERT3 PRAM	TERT1 PBO	TERT3 PBO	TERT1 PRAM	TERT3 PRAM
N	100	100	92	95	57	56
Total Daily Insulin (U)	33.3±10.4	97.2±34.1	30.4±8.7	106.3±31.4	43.2±15.4	196.2±114.9
Baseline Weight (kg)	81.8±15.0	103.4±23.4	81.4±17.2	102.6±22.0	102.0±19.9	121.1±25.7
Baseline A1C (%)	9.2±1.1	9.1±1.0	9.5±1.5	9.4±1.4	8.1±1.4	8.4±1.5
Δ A1C (%)	-0.66±0.10	-0.54±0.10	-0.18±0.11	-0.30±0.14	-0.59±0.31	-0.26±0.25
Δ Weight (kg)	-1.5±0.4	-1.9±0.3	-0.3±0.3	+0.7±0.3	-3.0±0.7	-2.8±0.7
Δ Total Insulin (%)	+0.1±1.5	-3.6±1.7	+7.0±1.8	+0.5±1.5	-5.1±4.7	-5.7±4.2

1064-P

Efficacy and Safety of a New Basal Insulin with a Bolus Boost (IDegAsp) Used Once Daily in Combination with Insulin Aspart (IAsp) in People with Type 1 Diabetes

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Insulin degludec (IDeg; formerly named SIBA) is a new basal insulin that forms soluble multi-hexamers upon sc injection, resulting in an ultra-long action profile. Insulin degludec/insulin aspart (IDegAsp) is a soluble insulin preparation comprising IDeg (70%) and IAsp (30%). This phase 3, 26-week, open-label, treat-to-target trial investigated the efficacy and safety of IDegAsp in people with type 1 diabetes inadequately controlled on any insulin. In total, 548 subjects (mean: age 41 yr, A1C 8.3%, FPG 189 mg/dl) were randomized 2:1 to IDegAsp or insulin detemir (IDet). IDegAsp was dosed once daily at any meal with IAsp at the remaining meals; IDet was dosed according to label, with IAsp at all meals. A similar proportion of subjects completed the trial with IDegAsp (87%) and IDet (86%). IDegAsp and IDet improved overall glycemic control (A1C) by 0.73% and 0.68%, respectively (treatment difference (TD) IDegAsp-IDet: -0.05% [95% CI: -0.18; 0.08]). FPG decreased to a similar level in both groups (TD: IDegAsp-IDet: 4.1 mg/dl [-8.3; 16.4] p=0.52). Mean total daily insulin dose was 69 U (0.86 U/kg) for IDegAsp and 79 U (1.00 U/kg) for IDet. Rates of severe hypoglycemia were low: 0.33 and 0.42 episodes/patient yr for IDegAsp and IDet, respectively. Confirmed hypoglycemia (PG <56 mg/dl or severe) was reported for ~94% of subjects in both groups; rates were similar (39 vs. 44 episodes/patient yr; rate ratio (RR) IDegAsp/IDet: 0.91 [95% CI: 0.76; 1.09] p=0.27). The rate of nocturnal confirmed hypoglycemia was 37% lower with IDegAsp (3.7 vs. 5.7 episodes/patient yr; RR: 0.63 [95% CI: 0.49; 0.81] p=0.0003). Weight increased more with IDegAsp (TD: IDegAsp-IDet: 1.04 kg [0.38; 1.69] p=0.0021). Overall rates of adverse events were similar between groups with no treatment-specific pattern or clustering. In conclusion, IDegAsp given once-daily at any meal with IAsp at the remaining meals provided similar glycemic control to IDet with mealtime IAsp. The IDegAsp regimen was associated with significantly less nocturnal hypoglycemia, and has the added convenience of fewer daily injections than conventional basal-bolus therapy.

1065-P

Efficacy and Safety of Adjunctive Subcutaneous Injections of Pramlintide in Patients with Type 1 Diabetes Using Insulin Pumps

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The number of patients with T1DM delivering insulin via a pump has significantly increased over the past decade and simplified management of diabetes for many patients. Pramlintide (PRAM) as a subcutaneous injection was approved by the FDA in 2005 as an adjunct to mealtime insulin to improve glycemic control. This analysis evaluated the efficacy and safety of PRAM in a subset of patients with T1DM from 2 different clinical trials, who used an insulin pump. In both trials, PRAM was uptitrated as tolerated in 15 mcg increments to a final dose of 30 or 60 mcg with major meals.

Trial 1: In a blinded placebo (PBO)-controlled non-inferiority trial, patients were randomized to PRAM (N=82) or PBO (N=73) for 29 weeks. Baseline characteristics were well matched: age: 42±14 vs 41±12y, weight 79.0±16.3 vs 79.6±17.0kg, BMI 27.0±4.0 vs 27.9±4.8kg/m^2, A1C 8.1±0.7 vs 8.0±0.8%, diabetes duration 20±12 vs 24±12y (mean ±SD).

At 29 weeks, A1C decreased by -0.4±0.1% and -0.3±0.1% (mean ±SE) in the PRAM and PBO arm, respectively. Weight decreased by -2.2 ±0.5kg in the PRAM arm, but increased by +1.4 ±0.3kg in the PBO arm. Changes in total daily, short acting and long acting insulin were -9.0±3.0%, -23.8±5.2% and +6.9±3.7% for the PRAM arm and +6.8±5.0%, -3.2±4.1% and +23.4±9.6% for the PBO arm, respectively. As reported before, the most frequently reported adverse event (AE) was nausea (67.1 vs 37.0%). The event rate/patient year of severe hypoglycemia was 0.56 vs 0.34.

Trial 2: In an open label clinical practice trial, N=150 patients received PRAM for 6 months. Baseline characteristics were: age: 42±10y, weight 80.1±15.6kg, BMI 28.4±4.3kg/m^2, A1C 8.0±1.1%, diabetes duration 22±9y (mean±SD).

After 6 months, A1C and body weight had decreased by 0.26±0.10% and 3.30±0.40kg. The changes in total daily, short acting and long acting insulin were -13.7±1.8%, -27.5±2.9% and +0.4±2.3% (mean±SE).

Nausea was the most frequently reported AE (42%). The event rate of severe hypoglycemia was 0.12/patient year.

In these studies, PRAM reduced glycemic parameters and weight with a safety profile consistent with that seen in previous clinical trials.

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

1066-P

Efficacy and Safety of Exenatide Once Weekly across Background Therapies: A Pooled Analysis of DURATION Studies

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Treatment with the GLP-1 receptor agonist exenatide once weekly (QW) in patients with type 2 diabetes on a broad range of background therapies, ranging from diet and exercise to combination oral therapy, resulted in A1C reduction and weight loss (the DURATION clinical trials). It is of clinical interest to understand the safety and efficacy of exenatide QW across these background treatments. Thus, a novel pooled analysis by background therapy was performed on ITT patients who initiated exenatide QW in the 24-30 week controlled periods of all four completed DURATION trials included in an ongoing integrated database (DURATION-1, -2, -3, and -5). A1C and FPG were significantly reduced with exenatide QW across all background therapies (Table). Weight loss was observed in all cohorts, but did not reach statistical significance in the small cohort of patients on MET+TZD background. Nausea, the most frequent adverse event, occurred in 9% of patients who received exenatide QW monotherapy (diet/exercise) vs. 20%, 14%, and 35% for MET, MET+SFU, and MET+TZD background therapies, respectively. Nausea led to withdrawal in only 4 patients. Overall hypoglycemia incidence was 33% in patients with MET+SFU background vs. 7%, 8%, and 12% for diet/exercise, MET, and MET+TZD background therapies, respectively. One case of major hypoglycemia was observed, and did not require medical intervention. Thus, patients treated with exenatide QW exhibited similar improvements in glycemic control and body weight irrespective of background therapy.

	Diet/Exercise	MET	MET+TZD	MET+SFU
DURATION trial	1, 5	1, 2, 3, 5	1, 5	1, 3, 5
N	43	427	26	150
A1C Baseline (%)	8.4±1.1	8.4±1.1	8.1±1.0	8.5±1.1
Δ A1C (%)	-1.6 (-2.0, -1.2)	-1.4 (-1.6, -1.3)	-1.5 (-1.8, -1.2)	-1.5 (-1.6, -1.3)
A1C <7% at endpoint	72%	63%	65%	53%
FPG Baseline (mg/dL)	165±44	169±46	158±50	182±55
Δ FPG (mg/dL)	-34 (-48, -20)	-35 (-40, -30)	-37 (-55, -18)	-35 (-45, -26)
Baseline weight (kg)	97.0±20.6	92.7±19.4	103.1±21.9	94.4±19.7
Δ Weight (kg)	-2.3 (-3.5, -1.1)	-3.0 (-3.3, -2.6)	-2.3 (-4.6, 0.1)	-2.6 (-3.3, -1.9)

ITT per-patient analysis. Baseline = mean±SD. Δ = mean (95%CI).

1067-P

Efficacy and Safety of Linagliptin in Patients with Type 2 Diabetes and Poor Glycemic Control

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A large analysis of pooled Phase 3 data was performed to determine the safety and efficacy of the novel dipeptidyl peptidase (DPP)-4 inhibitor linagliptin in type 2 diabetes mellitus (T2DM) patients with poor glycemic control. Three randomized, placebo-controlled, clinical trials were analyzed. 2258 subjects treated with linagliptin or placebo in monotherapy or as add-on to metformin (MET) or MET plus sulphonylurea (SU) were eligible for this analysis.

In total, 396 patients had baseline HbA_{1c} ≥9%. At enrolment, 59% were treated with ≥2 oral anti-diabetic (OAD) drugs, and 58% had diabetes duration of >5 years. After 24 weeks' treatment with linagliptin, HbA_{1c} showed highly significant changes from baseline of –1.2% ± standard error [SE] 0.2; n=287) vs –0.4% ± 0.2; n=101) for placebo (p<0.0001 for mean difference). The placebo-corrected effect of linagliptin monotherapy on HbA_{1c} was –1.0% ± 0.3 (n=79) and –0.7% ± 0.2 (n=184) when added to MET ± SU. Multivariate analyses of the pooled data showed that treatment and wash-out of previous OADs prior to randomization were the only independent predictors of treatment response. In patients without previous wash-out, the change in HbA_{1c} from baseline was –1.4% ± 0.3 for linagliptin (n=231) and –0.6% ± 0.3 for placebo (n=80). Linagliptin was well tolerated, with an adverse event (AE) rate comparable to placebo (61.9% vs 62.7%, respectively). Most of these events were mild, with no specific type of serious AE being predominant. Hypoglycemia with linagliptin in these poorly controlled patients was rare, both as monotherapy and as add-on therapy to MET (≤1%). Hypoglycemic event rates were increased only when linagliptin was administered in combination with SU (linagliptin 17.9% vs placebo 8.3%), with 96% of reported events arising from the study in which this combination was used. In conclusion, linagliptin provides clinically meaningful efficacy in patients with poor glycemic control, when used alone or in combination with SU or MET. This pooled analysis shows that linagliptin is likely to provide an effective and well-tolerated treatment option for patients with T2DM and uncontrolled hyperglycemia.

Supported by: Boehringer Ingelheim Pharmaceuticals, Inc.

1068-P

Efficacy and Safety of Linagliptin in Patients with Type 2 Diabetes with or without Renal Impairment: Results from a Global Phase 3 Program

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Renal impairment (RI) is a frequent comorbidity associated with type 2 diabetes mellitus (T2DM). Decline in renal function is a major factor in limiting the choice of glucose-lowering agents. Linagliptin is a novel dipeptidyl peptidase (DPP)-4 inhibitor with a primarily non-renal route of excretion, and thus may provide a new treatment alternative for T2DM. This pooled analysis of 3 randomized, placebo-controlled, Phase 3 clinical trials evaluated the effect of renal function on the efficacy and safety of linagliptin.

Data were available for 2141 patients with T2DM who were grouped by renal function as normal (glomerular filtration rate [GFR] ≥80 mL/min, n=1684), mild RI (GFR, 50 to <80 mL/min, n=418), or moderate RI (GFR, 30 to <50 mL/min, n=39). Compared with individuals with normal renal function, patients with RI were older, had lower BMI, were less insulin-resistant, had a longer disease duration, and had an increased prevalence of common diabetes-related comorbidities, including macro- and microvascular disease, and hypertension. The primary endpoint in all trials was change from baseline HbA_{1c} after 24 weeks. Linagliptin showed consistent placebo-corrected adjusted mean HbA_{1c} changes across all 3 groups: normal renal function (–0.63%; p<0.0001), mild RI (–0.69%; p<0.0001), and moderate RI (–0.69%; p=0.0174), with no significant inter-group difference (p=0.865). Linagliptin was generally well tolerated. The incidence rates of serious adverse events with linagliptin in the normal/mild/moderate groups were 2.5%, 5.4%, and 3.7%, respectively, and similar to placebo (3.4%, 3.8%, and 8.3%, respectively). Notably, renal function, as assessed by GFR, and albuminuria, expressed as the urinary albumin/creatinine ratio, were unaffected in all 3 groups after 24 weeks of linagliptin treatment.

This large Phase 3 analysis demonstrates a favorable renal safety profile for linagliptin. In addition, linagliptin provides reliable efficacy in patients with normal renal function, and also in T2DM subjects with relatively advanced renal complications.

Supported by: Boehringer Ingelheim Pharmaceuticals, Inc.

1069-P

Evaluation of Efficacy and Tolerability Using Exposure-Response Modeling for BI 10773, a Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitor, in Patients with Type 2 Diabetes (T2DM)

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Data from 3 Phase I (*A,B,C*) and 2 Phase II (*D,E*) randomized, placebo-controlled, multiple oral dose studies of BI 10773, a SGLT-2 inhibitor, were used to develop exposure-response models for efficacy (HbA_{1c}, FPG) and tolerability endpoints in T2DM patients. *A* (N=48) was an 8-day study (qd doses from 2.5 to 100mg). *B* (N=78) and *C* (N=100) were 4-week studies (qd doses from 1 to 100mg). *D* (N=353) and *E* (N=395; included background metformin) were 12-week studies (qd doses from 1 to 50mg). Nonlinear mixed effects models were developed to describe the relationship between drug exposure, FPG and HbA_{1c}. General additive models were used to evaluate exposure-tolerability response. Maximal FPG decrease occurred within 3-4 weeks from initiation of BI 10773 treatment and was dose and exposure (area under concentration time curve, AUC) dependent. Maximal HbA_{1c} decrease, also dose and exposure-dependent, was approached 8-12 weeks after treatment initiation. The model linked the BI 10773 FPG-exposure response to HbA_{1c} response and estimated a 16% maximal FPG decrease. Half maximal FPG reduction corresponded to an approximate 3mg BI 10773 qd dose (5mg for Study *E*, estimated separately). BI 10773 10 and 25mg qd doses were expected to target 80-90% of the maximal FPG and HbA_{1c} response. A 0.47% HbA_{1c} change from baseline was expected for every 1mM FPG change; *e.g.*, 0.7% HbA_{1c} reduction for a FPG decrease from 9.4 to 7.9mM. Monte Carlo simulations indicated that 26% of placebo patients would achieve a 0.7%

HbA_{1c} decrease (from baseline FPG=9.4mM; HbA_{1c}=8%). Achievement of this same target for 10 and 25mg BI 10773 doses was expected for 57 and 63% of patients, respectively. There was no evidence from Studies *D* and *E* of exposure-response for hypoglycemia (N=4), urinary tract infection (N=17), and genital/vulvovaginal-related (N=16) events, although low prevalence rates may have precluded a more accurate evaluation. In summary, exposure-response analyses showed that BI 10773 qd doses of 10 and 25mg achieved near maximal (>80%) glucose-lowering efficacy.

Supported by: Boehringer Ingelheim Pharmaceuticals, Inc.

1070-P

Exenatide Once Weekly Did Not Affect Corrected QT Interval in Patients with Type 2 Diabetes

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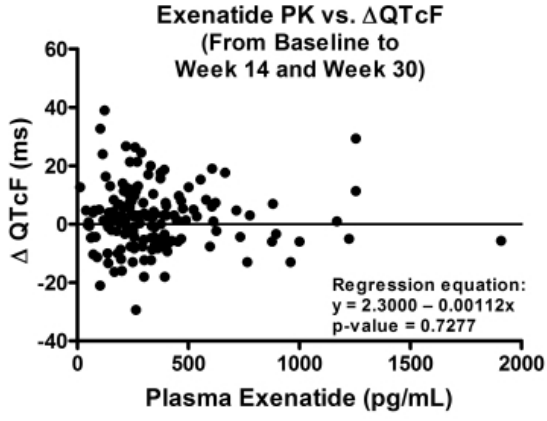
Exenatide once weekly (QW) is a glucagon-like peptide-1 (GLP-1) receptor agonist under development for treatment of type 2 diabetes. The objective of this analysis was to evaluate the safety of exenatide QW in patients with type 2 diabetes with respect to cardiac repolarization by analyzing the Fridericia's corrected QT (QTcF) interval and the relationship between QTcF and plasma exenatide concentration (conc.). Patients enrolled in the DURATION-1 Phase 3, randomized, open-label, comparator-controlled trial were treated with exenatide QW (2 mg). Electrocardiograms (ECGs) were recorded in triplicate (averaged for each time point), and at approximately the same time, blood samples were collected for exenatide conc. at baseline (prior to study treatment) and after 14 weeks (steady-state achieved) and 30 weeks of treatment or early termination. The relationship between exenatide conc. and QTcF was analyzed using a mixed-model repeated measure method. The analysis included 148 patients with mean diabetes duration of 7 years. Mean A1C change from baseline to Week 30 was -1.9% [SE 0.1%]). A small increase in heart rate (mean change, 2-sided 90% CI) was observed at 14 (3.6 bpm, 2.3- 4.8; n=135) and 30 weeks (3.5 bpm, 1.9-5.0; n=82). QTcF changes from baseline (ΔQTcF, 2-sided 90% CI) were small and clinically insignificant at 14 (1.7 ms, 0.3-3.1) and 30 weeks (3.0 ms, 0.9-5.1). No patient had a QTcF interval during treatment that exceeded 450 ms or a ΔQTcF >60 ms; 3 patients had a ΔQTcF >30 ms (30.2, 32.7, and 39 ms). There was no accentuated change in QTcF in patients with the highest exenatide conc. and a slight, non-significant negative correlation between exenatide conc. and ΔQTcF was observed (Figure). These results demonstrated that exenatide QW treatment did not affect cardiac repolarization, measured by the QTcF interval, in patients with type 2 diabetes.



1071-P

Exenatide or Glimepiride on Insulin Resistance in Type 2 Diabetic Patients

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The aim of this study was to evaluate the effect of exenatide (Ex) compared to glimepiride (Gl) on insulin resistance in type 2 diabetic patients. We enrolled 111 patients with uncontrolled type 2 diabetes mellitus and intolerant to metformin at maximum dosage (3000 mg/day). Patients were randomised to receive Ex 5 μg twice a day or Gl 1 mg three times a day and titrated after 1 month to Ex 10 μg twice a day or Gl 2 mg three times a day for 12 months. We evaluated these parameters: body weight, body mass index (BMI), HbA_{1c}, glycemic control, fasting plasma insulin (FPI), homeostasis model assessment insulin resistance index (HOMA-IR) index, adiponectin (ADN), tumor necrosis factor-α (TNF-α), and high sensitivity C-reactive protein (Hs-CRP). After 12 months BMI was significantly reduced by Ex, but not by Gl (from 28.0±1.2 to 26.6±0.9 Kg/m^2, p< 0.001 vs baseline, and from 28.6±1.5 to 28.2±1.3 Kg/m^2, ns vs baseline, p< 0.05 vs Ex, respectively). HbA_{1c} was decreased from 8.1±0.6 to 7.5±0.3% (p< 0.01 vs baseline) with Ex, and from 8.4 ± 0.7 to 7.4 ± 0.2% (p< 0.01 vs baseline) with Gl; FPG was reduced by 20±6 mg/dl (p< 0.01) with Ex, and by 21±7 mg/dl (p< 0.01) with Gl; PPG was decreased by 34±8 mg/dl (p< 0.01), and by 37±9 mg/dl (p< 0.01), in Ex and Gl group, respectively. FPI was decreased by 3.8±0.6 μU/ml (p< 0.05 vs baseline) in Ex group, and was increased by 0.6±0.09 μU/ml in Gl group (ns vs baseline, p< 0.05 vs Ex). HOMA-IR was reduced by 1.9±0.8 (p< 0.05 vs baseline), and by 0.8±0.1 (ns vs baseline, p< 0.05 vs Ex), in Ex and Gl group, respectively. ADN was increased by 1.3±0.4 μg/ml (p< 0.05 vs baseline), and by 0.6±0.03 μg/ml (ns vs baseline, p< 0.05 vs Ex), in Ex and Gl group, respectively; TNF-α was reduced by 0.5±0.04 ng/ml (p< 0.05 vs baseline), and by 0.2±0.01 ng/ml (ns vs baseline, p< 0.05 vs Ex), in Ex and Gl group, respectively. Hs-CRP was decreased by 0.8±0.5 (p > 0.01 vs baseline) with Ex, and by 0.4 with Gl (ns vs baseline, p< 0.05 vs Ex). There was a significant correlation between BMI value decrease and ADN increase, and TNF-α decrease. Ex and Gl improved diabetes control when added to metformin, but only Ex improved insulin resistance related-parameters.

1072-P

Exposure-Response Modeling of Canagliflozin Effects on the Renal Glucose Threshold in Subjects with Type 2 Diabetes (T2DM)

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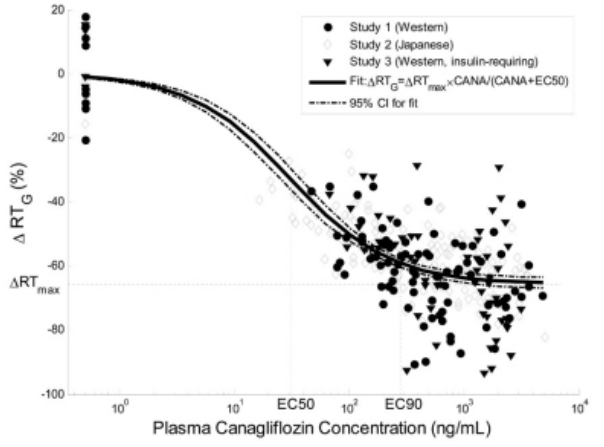
Canagliflozin (CANA), an inhibitor of sodium glucose co-transporter 2 (SGLT2), is in development for treatment of type 2 diabetes mellitus (T2DM). By inhibiting SGLT2, CANA reduces the renal threshold for glucose excretion (RT_G), thereby increasing urinary glucose excretion (UGE) and potentially decreasing plasma glucose (PG). The exposure-response relationship for the effects of CANA on RT_G was characterized using data from 3 randomized phase 1 studies in patients with T2DM. In study 1, 36 Western subjects (50% male, mean BMI=31 kg/m^2, A1c=8.1%) received either CANA 50, 100, or 300 mg QD or placebo (PBO) for 7 days. In study 2, 61 Japanese subjects (82% male, BMI=26 kg/m^2, A1c=8.3% [JDS]) received CANA 25, 100, 200, or 400 mg QD or PBO for 16 days (dosed on days 1 and 3-16). In study 3, 29 insulin-requiring Western subjects (52% male, BMI=34 kg/m^2, A1c=8.4%) received CANA 100 mg QD, 300 mg BID, or PBO for 27 days. In each study, 24-hour PG profiles, UGE, and estimated glomerular filtration rates were used to determine RT_G on day -1 and the last treatment day. CANA was well tolerated, consistent with previous reports, and decreased RT_G in a concentration-dependent manner (Figure); the data were well-described by a sigmoid relationship: $\Delta RT_G=\Delta RT_{max}\times[CANA]/([CANA]+EC50)$, where ΔRT_G is the percent change from baseline RT_G, ΔRT_{max} is the maximal suppression achieved, and EC50 is the half-maximal effective concentration. There were no significant differences in either ΔRT_{max} or EC50 between any of the studies; the best-fit values for a pooled analysis of all 3 studies are ΔRT_{max}=-65.7% (95% CI=-67.5, -63.9%) and EC50=31 ng/mL (24-38 ng/mL) with R^2=0.73. In summary, CANA reduces RT_G in a concentration-dependent manner and lowers RT_G by ~66% at maximally effective concentrations, with similar effects in Western and Japanese subjects.



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1073-P

First Basal Insulin Evaluation in Asia (FINE Asia) Study: Baseline Characteristics of the Study Population

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First Basal Insulin Evaluation in Asia (FINE Asia), a multinational, 6-month, prospective observational study, assessed the use of basal insulin in insulin-naïve Asian patients (aged ≥ 20 years) with type 2 diabetes mellitus, uncontrolled (A1C ≥ 8%) on oral antihyperglycemic drugs (OADs). Basal insulin was initiated with or without concomitant OADs; all treatment choices were at the physician's discretion. A total of 2921 patients from 11 Asian countries were enrolled at baseline; 2679 patients with both baseline and 6-month A1C values were included in the analysis. Demographic characteristics and insulin regimen at baseline are shown in the table. Most patients initiated insulin therapy with insulin glargine. Across the countries/region, mean duration of diabetes ranged from 6.3 to 11.5 years and mean baseline A1C ranged from 9.4% to 10.5%. The prevalence of microvascular disease ranged from 14% to 39%, coronary artery disease from 9% to 21%, and dyslipidemia from 49% to 84%. The results indicate that treatment intensification and the initiation of insulin are delayed in patients in these countries, irrespective of international, regional, and local treatment guidelines, and that management of other metabolic risk factors is delayed as well.

	China n = 491	India n = 681	Korea n = 291	Pakistan n = 139	SE Asia[a] n = 212	Taiwan n = 417	Thailand n = 448
Age, y	56.0	54.9	57.6	50.8	56.6	60.1	56.3
Weight, kg	69.7	71.9	65.0	76.6	61.3	65.5	65.8
BMI, kg/m^2	25.5	27.6	25.0	27.9	24.2	25.4	26.4
Duration of diabetes,y	6.3	9.8	10.7	8.6	9.5	11.5	9.1
Duration of OAD use, y	5.8	9.2	9.2	7.8	8.4	11.5	9.0
A1C, %	9.4	9.4	9.7	10.1	10.5	10.2	10.2
FPG, mg/dl	185	211	205	205	230	226	216
Insulin regimen, %							
Glargine	61.9	94.3	90.7	100	53.3	73.6	55.1
NPH	37.5	5.0	9.3	-	42.9	12.5	44.9
Detemir	-	0.7	-	-	-	13.4	-
Other	0.6	-	-	-	3.8	0.4	-

[a]Bangladesh, Hong Kong, Indonesia, Singapore, Vietnam

Supported by: sanofi-aventis

1074-P

Gliquidone Features Different from Glibenclamide in Closing the K_{ATP} Channels in Cardiomyocyte and Vascular Smooth Muscle Cell

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The effect of glibenclamide(Glb) and gliclazide(Glc) on sulphonylurea receptor(SUR) in β cell, heart muscle and vascular smooth muscle cell(VSMC) have been reported. If gliquidone(Glq) has similar or different effect with Glb and Glc in heart cell and VSMC was not determinated. The aim of this study is to determine the effect of Glq on SUR1 in β cell(βc),SUR2A in cardiomyocyte(CMC) and SUR2B in VSMC. The action of the Glq with different concentrations(conc.)(0.001,0.01,0.1,1,10,100,500μM) was studied by whole cell patch clamp current recording of ATP sensitive potassium(K_{ATP}) channels in single HIT-T15 cell, SD rat CMC and VSMC.A parallel study with different conc.(0.001,0.01,0.1,1,10μM and 0.01,0.1,1,10,50,100,500μM, respectively) of Glb and Glc as controls. The conc. of Glq closes the 50% K_{ATP} channels of βc is more higher than Glb but lower than Glc, When the current of the K_{ATP} reach 50%, the conc. of Glq was 5 times as the Glc and only 1/4 of the Glb. The IC50 of these drugs for βc was 0.301μM of Glq, 0.067μM of Glb and 1.266μM of Glc respectively. for CMC was 12.088μM of Glq, 0.0526M of Glb, 14.631μM of Glc respectively. The inhibition ratio of the therapeutic conc. of Glq on the K_{ATP} in rat CMC was lower than 15%. The IC50 of Glq was 21 times as the therapeutic conc. The IC50 of Glc on K_{ATP} in rat CMC was 1.9 times as the therapeutic conc. The IC50 of Glb was lower than the therapeutic conc. and possibly the half. the IC50 of three drugs for VSMC was 52.70μM of Glq, 0.026μM of Glb and 50.84 μM of Glc respectively. The inhibition ratio of the therapeutic conc. of Glq on the K_{ATP} in rat VSMC was lower than 5%. The IC50 of Glq was 92 times as the therapeutic conc. The IC50 of Glc on the K_{ATP} in rat VSMC was 6 times as the therapeutic conc., The IC50 of Glb was lower than the therapeutic conc. and possibly the quarter. Our results indicate that Glq is a highly selective SU with high affinity for βc and very week effect on SUR subunits of heart muscle cell and VSMC compared with Glb. Glc has a similar effect to Glq.

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1075-P

Glucagon-Like Peptide 1 (GLP-1) Analogue Combined with Insulin Reduces HbA1c and Weight with a Low Risk of Hypoglycemia and High Treatment Satisfaction

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Information concerning the efficacy and safety of combining liraglutide and insulin is absent, and sparse for exanatide. Since these combinations are used in clinical practice it is of importance to evaluate effects on HbA1c, weight and risk of hypoglycemia.

Patients with type 2 diabetes and insulin therapy receiving a GLP-1 analogue in 4 Swedish centra were included. Hypoglycemia was evaluated using glucometers and diabetes diaries. The Diabetes Treatment Satisfaction Questionnaire (DTSQ), was used to evaluate treatment satisfaction, hypo- and hyperglycemia.

Four patients discontinued the therapy, none owing to hypoglycemia, and none had a suspected severe adverse event. In 61 patients continuing the therapy over a mean of 7.0 months, 68% had liraglutide and 32% exanatide.

HbA1c decreased by a mean of 1.0% (95% CI 0.7-1.4) from 8.8% to 7.8% (p<0.001). Weight decreased by 8.7 kg (95% CI 6.6-10.9) from 111.0 kg to 102.3 kg (p<0.001). Five patients discontinued insulin treatment during follow up. Insulin doses in the total cohort decreased by 40.7 units (95% CI 30.8-50.6, p<0.001) from 92 to 51 units. Patients were in 50% of cases treated with basal insulin only, 25% basal + prandial insulin, 10% prandial insulin only and 5% mix insulin.

One patient had a severe hypoglycemia. The mean number of asymptomatic hypoglycemia per patient and month, reported for the last month, was low (0.085 below 70 mg/dl, 0 below 52 mg/dl) and documented symptomatic hypoglycemia (0.24 below 70 mg/dl and 0.068 below 52 mg/dl). The DTSQs showed a low rating of current hypoglycemia, 0.53 (scale 0-6) and the DTSQc that patients experienced less hypoglycemia than with previous regimen, -0.96 (scale -3 to +3, p<0.001). Current treatment satisfaction was high of 31.3 points (max 36) in the DTSQs and in the DTSQc higher than with the previous regimen of 11.9 (scale -18 to +18 points, p<0.001).

In conclusion, the addition in clinical practice of GLP-1-analogues to different types of insulin regimens in patients with type 2 diabetes reduces HbA1c, weight and insulin doses, with a low risk of hypoglycemia and high treatment satisfaction.

1076-P

Glucose Lowering Efficacy of Glucagon-Like Peptide-1 Receptor Agonists: A Meta-Analysis

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The glucose lowering efficacy of glucagon-like peptide-1 receptor (GLP-1R) agonists has been investigated in several randomized controlled trials (RCTs). We aimed to systematically review RCTs comparing the glucose lowering efficacy of GLP-1R agonists with placebo, insulin or oral anti-diabetic drugs (for ≥20 weeks) in patients with type 2 diabetes.

Eligible RCTs were systematically identified and additional data obtained through correspondence with trialists. Sensitivity, subgroup, regression and trial sequential analyses were performed on included trials (liraglutide (8 trials), exenatide (9 trials), exenatide long acting release (3 trials)).

In total, 5,683 patients treated with a GLP-1R agonist and 2,526 patients treated with placebo, insulin or oral anti-diabetic drugs were followed for 20 to 52 weeks. All trials were categorized as having low risk of bias. For all comparisons GLP-1R agonists reduced HbA_{1c} by 0.64% (weighted mean difference (WMD); CI: 0.63 to 0.65%). No evidence of small study effects (e.g. publication bias) were identified (Egger's test P=0.90). The effect of GLP-1R agonists remained significant after adjusting for multiple comparisons in trial sequential analysis. The highest doses of GLP-1R agonists exhibited more pronounced HbA_{1c} reductions compared with placebo (WMD: 0.88%; CI: 0.86 to 0.89%) and active interventions (WMD: 0.28%; CI: 0.27 to 0.29%). Compared with active control interventions, GLP-1R agonists more efficiently reduced fasting plasma glucose (WMD: -0.63 mmol/L; CI: -0.66 to -0.61 mmol/L) and increased the proportion of patients who achieved target HbA_{1c} (HbA_{1c} <7%) (Relative risk (RR): 1.92; CI: 1.62 to 2.26). The mean proportion of patients with mild to moderate hypoglycemia did not differ between patients randomized to GLP-1R agonists or active control interventions (RR: 0.97; CI: 0.67 to 1.40).

In conclusion, our meta-analysis of high-quality RCTs provides evidence that GLP-1R agonists improve glycemic indices in patients with type 2 diabetes.

1077-P

Glycemic and Weight Lowering Effects of Exenatide Once Weekly Are Associated with Blood Pressure Changes in Patients with Type 2 Diabetes

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Treatment of type 2 diabetes (T2DM) patients (pts) with the GLP-1 receptor agonist exenatide has demonstrated improvements in glycemic control (A1C) coupled with weight (Wt) loss and lowered blood pressure (BP). We examined the interplay of improved glycemic control and weight loss and the relationship with blood pressure (BP) reduction in pts with T2DM treated with exenatide once weekly (ExQW).

Combining data from 3 controlled trials (DURATION 1, 2 and 3), 540 (54% male) pts (baseline mean [SD]: age 50 [10] y, Wt 94 [20] kg, SBP/DBP 130/80 [16/9] mm Hg, A1C 8.4 [1.1]% with 6 y of diabetes duration) treated with ExQW were observed on 10 occasions over 30 wks. Using the weighted means (WM) of the 10 longitudinal measures of A1C (7.3%) and Wt (92 kg), all pts were subdivided into 4 groups by glycemic and weight responses--those with A1C and Wt measures above WM became the reference group (R). The remaining 3 groups corresponded to A1C responders (A), Wt responders (W) and both A1C and Wt responders (AW). The WM were calculated using means of 10 longitudinal measures, weighted by inverse of corresponding variances. Mixed-effects linear and logistic regression models with autoregressive correlation under GEE setup were used for analyses.

Adjusting for age and diabetes duration, and comparing to R, pts in AW, A and W had significantly improved SBP by 7, 5 and 3 mm Hg respectively. Compared to hypertensive pts (SBP ≥130 mm Hg), pts in AW had 75% higher likelihood of improving SBP <130 mm Hg (OR: 1.75, 95% CI: 1.34, 2.28) than R. Compared to R, those in A had 29% higher likelihood of reducing SBP (OR: 1.60, 95% CI: 1.21, 2.11) than those in group W (OR: 1.31, 95% CI: 1.07, 1.61). A similar but less robust pattern of responses was noted with changes in DBP.

Although the mechanism of the BP lowering effect of GLP-1 is not fully understood, the observed BP reduction in this pt cohort appears to be closely related to concomitant effects on glycemia and body wt, with the BP effect more closely associated with glycemic lowering than with wt loss. These data offer mechanistic insight into the cardiometabolic effects of GLP-1 receptor agonism.

1078-P

Glycemic Control outside the Cardiac Intensive Care

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Postsurgical hyperglycemia is associated with deleterious outcomes. There is no consistent practice for transition from intravenous insulin infusion (IVII) to subcutanous insulin (SQI) regimen. Our objective is to report the effectiveness of blood glucose management in the 24 hours after IVII following cardiac surgery.

We reviewed hospital charts of 197 adult patients who underwent cardiac surgery and received IVII for atleast 8 consecutive hours at St Joseph's hospital, MN between July 2009 and Sept 2010. Data abstracted included dose and duration of IVII, dose of SQI used for transition, blood glucose values and dose of SQI used during the 24 hours after discontinuation of IVII. Calculation of daily SQI requirement was extrapolated from the stable hourly IVII rate prior to its discontinuation. Hyperglycemia, normoglycemia and hypoglycemia were defined as blood glucose value over 180 mg/dl, between 110-180 mg/dl and below 70 mg/dl respectively.

The mean age of the 197 patients included in the study was 68 years (range 39-89 years). Males comprised 68% of the study population. The mean BMI was 30.9 (range 19.7 to 62.2). The average length of hospital stay was 9.3 days (range 4-27 days).

The mean dose and duration of IVII was 76 units (range 3-658) and 22 hours (range 8-155) respectively. A long acting insulin was administered subcutaneously in 59 patients (30%) within 24 hours of discontinuing IVII. In 19 patients, the long acting insulin was given subcutaneously, prior to discontinuing the IVII. The median dose of SQI administered within 24 hours of discontinuing IVII was 26.7 % of the daily calculated SQI requirement. Blood glucose details at 4-8 hours and at 20-24 hours after discontinuing IVII was available in 156 and 153 patients respectively. Hyperglycemia and normoglycemia was noted in 36% and 60% respectively at 4-8 hrs and in 25% and 71% respectively at 20-24 hrs. Hypoglycemia did not occur during this period.

To conclude, ineffective transition strategy from IVII to SQI therapy is a major contributor to poor glycemic control in the immediate post intensive care phase of cardiac surgical patients. Aggressive transition strategies should be used in these patients.

1079-P

High Correlation between Estimated Glomerular Filtration Rate and Estimated Creatinine Clearance for Sitagliptin Dose Selection in Patients with Renal Insufficiency

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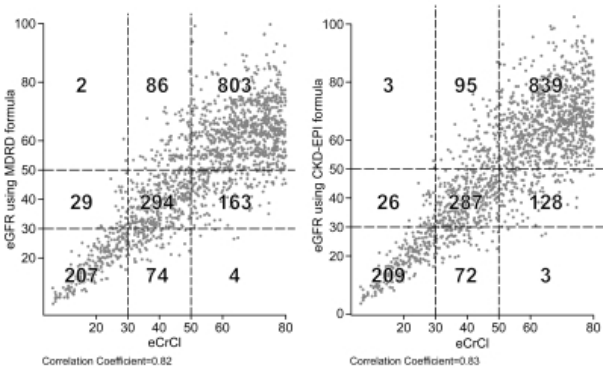
Sitagliptin may be used in patients with type 2 diabetes (T2D), regardless of their renal function. For patients with moderate (estimated creatinine clearance [eCrCl] ≥30 to <50 mL/min) or severe (eCrCl <30 mL/min) renal insufficiency (RI), the dose of sitagliptin is selected based on serum creatinine level or eCrCl (Cockcroft-Gault) to provide similar drug exposure to that in patients with normal (eCrCl ≥80 mL/min) or mildly impaired (eCrCl ≥50 to <80 mL/min) renal function. The glomerular filtration rate (GFR) is considered the best index of renal function. In clinical practice, GFR is estimated (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula or the Chronic Kidney Disease Epidemiology Collaboration (CKD) formula. In the present analysis, we assessed the agreement between eGFR and eCrCl for dose selection of sitagliptin. Screening data from 4 double-blind, randomized clinical trials of sitagliptin in patients with T2D and mild to severe RI were pooled (n=1662), excluding patients with eCrCl >80 mL/min and patients on dialysis. Renal function for each patient was estimated using eCrCl and eGFR. The correlations between eCrCl and eGFR were assessed and the recommended dose assignment based on the 2 methods was determined. The recommended dose of sitagliptin would have been the same using eCrCl and eGFR by MDRD (CKD) for 78.5% (80.3%) of patients, lower for 14.5% (12.2%) of patients, and higher for 7.0% (7.5%) of patients. Among patients classified differently by the two methods, 67.3% (62.1%) would have received a lower dose (i.e., either 50 or 25 mg/day versus 100 or 50 mg/day) based on eGFR. Disagreement by >1 dose category occurred in <0.4% (<0.4%) of patients. These data show a high correlation between eCrCl and eGFR for dose-selection of sitagliptin.

Figure
Counts of Patient Renal Function Category
Assessed via eGFR (MDRD and CKD) versus eCrCl (Cockcroft-Gault)



1080-P

Implementation of a Simple Subcutaneous Insulin Algorithm for Management of the NPO Hyperglycemic Patient in the ICU

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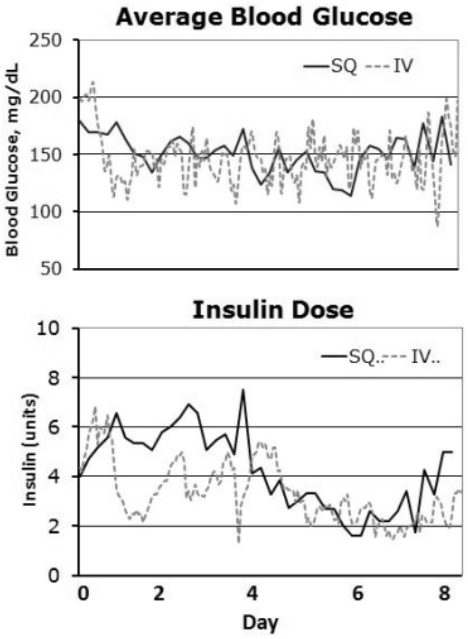
Diabetes patients who are in the ICU and either NPO, on enteral feedings, or TPN, are often treated with either sliding scale insulin (despite an absence of evidence showing benefit) or with intravenous (IV) insulin infusion, a nursing intensive procedure. As part of a quality improvement project, we developed a simple subcutaneous (SQ) insulin algorithm that titrates insulin needs to the requirements of the individual patient. In this study, 12 consecutive hyperglycemic patients (7 with diabetes) admitted to ICU-A were placed on the following protocol. Patients in an identical med-surg ICU-B were treated with the usual IV insulin protocol.

SQ Insulin Protocol: Check blood glucose (BG) q4hr and adjust insulin dose as follows:

BG <80 mg/dl Do not administer insulin and call house officer
BG 80-120 give same amount of insulin as 4 hours earlier less 2 units
BG 121-180 give same amount of insulin as 4 hours earlier
BG 181-240 give same amount of insulin as 4 hours earlier + 2 units
BG >240 give same amount of insulin as 4 hours earlier + 2 units + give additional 4 units X 1 (Do not include this extra 4 units in determination of next insulin dose).

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research



The glucoses and insulin doses from the patients in ICUs A and B are shown in figure 1. The average duration on the SQ protocol was 5.8 ±1.2 days yielding a total of 432 glucose checks in ICU-A. For the SQ group there were 7 (1.6%) episodes of hypoglycemia (BG <70) none which resulted in a serious adverse event. In conclusion, a simple SQ insulin algorithm allows insulin doses to be adjusted to the patient's needs and may work well enough to meet current ICU standards for glycemic control. Its adoption may allow for elimination of sliding scale insulin and makes possible a SQ insulin protocol to be used every 4 hours instead of hourly as is needed for IV insulin.

1081-P

Initial Insulin Doses Should Be Decreased in Hospitalized Patients with Renal Insufficiency and Type 2 Diabetes

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Hospitalized patients with diabetes (DM) commonly have renal insufficiency (RI). RI may increase the risk for hypoglycemia in patients treated with basal-bolus insulin, however there are no guidelines for dose modification in RI. We conducted a multicenter, prospective, randomized trial to compare the efficacy and safety of two weight-based insulin regimens begun at hospital admission for patients with DM and RI. We randomized 99 patients, 57% female, mean age 64±12 yrs, mean weight 92±27 kg, to begin daily insulin glargine (G) 0.125 units/kg (55 patients) or 0.25 units/kg (44 patients). Inclusion criteria were type 2 DM for >1 year with an initial blood glucose (BG) >180 mg/dl, and GFR < 45 ml/min but not requiring dialysis. If they were eating, they also received glulisine at 1/3rd of the daily G dose with each meal. Doses were adjusted based on four-time daily BGs. No oral antidiabetic agents (OAD) were continued. Prior to admission 35 % received an OAD and 77 % insulin, equally NPH or G. Mean HBA1C was 8±2 %; mean GFR was 29±9 ml/min. There were no significant differences between groups in the percent of BGs within the target range of 100-180 mg/dl on any of the 6 study days. On the first day, this BG target was achieved in 67.3% of the .125 group's BGs and 63.6% of the .25 group's BGs (p=0.71). On days 2-6, the BG target was achieved by 74% of the BGs in both groups. Mean BG on the first day was 195±55 mg/dl in the .125 group and 198±74 mg/dl in the .25 group (p=0.82). On days 2-6 mean BG was 171±44 mg/dl in the .125 group and 175±55 mg/dl in the .25 group (p=.7). There were no significant differences between groups for the mean BG at any of the four time points. In the .125 group, 15% of patients had hypoglycemia, BG<70 mg/dl, compared with 30% of the .25 group. (p=0.07). In conclusion, BG control in hospitalized patients with DM and RI was equivalent with either .125 or .25 units/kg/day insulin glargine. However the .125 group experienced only 50% as much hypoglycemia as the .25 group. A reduced insulin dosing algorithm is safe and effective for hospitalized patients with DM and RI.

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1082-P

Insulin Analogs Versus Human Insulins in the Management of Medical Patients with Type 2 Diabetes: A Randomized Controlled Trial in Paraguay

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Few studies have focused on the optimal management of hyperglycemia in non-ICU patients with type 2 diabetes mellitus (T2DM) in Latin America. Accordingly, we conducted a prospective, randomized open-label trial to compare the safety and efficacy of a basal bolus regimen with insulin analogs (glargine/glulisine) to human (NPH/regular) insulin in T2DM patients admitted to general medicine wards in a University Hospital in Asuncion, Paraguay. A total of 134 patients (M49/F45; age: 59.6±11 yr, duration DM: 8.6±7 yr, BMI: 26.5±6 kg/m2) with a BG between 140-400 mg/dL (mean BG: 260±70 mg/dL, A1C: 10.1±2.7%) were treated with glargine/glulisine (Gla+Glu, n=66) or NPH/regular insulin (NPH/REG, n=68). Both groups were started at a total daily dose (TDD) of 0.4 U/kg for BG between 140-200 mg/dL or 0.5 U/kg for BG between 201-400 mg/dL. Half of TDD was given as glargine once daily or NPH twice daily and half divided in three equal doses of glulisine or regular before meals. Doses were adjusted daily based on pre-meal and bedtime BGs. There were no differences in daily BG after the 1st day of insulin treatment (157±37 mg/dL vs 158±44 mg/dL) between groups. A BG target <140 mg/dl before meals was achieved in 76% in the GLA/GLU group and in 74% of NPH/REG, p= N.S. The mean TDD insulin in the GLA/GLU group was 0.76±0.3 U/kg (GLA 22±9 U/d, GLU 31±12 U/d) and was not significantly different from the NPH/REG group (0.75±0.3 U/kg [NPH 28±12 U/d, REG 23±9 U/d]). Treatment with NPH/REG resulted in higher frequency of hypoglycemia <70 mg/dl (38% vs 35%, p=0.68), severe hypoglycemia <40 mg/dL (53% vs 46%, p=0.04), and recurrent hypoglycemia (61% vs 43%, p=0.2) than GLA/GLU regimen. There were no differences in length of hospital stay or mortality between treatment groups.

Conclusions: Basal bolus regimen with insulin analogs glargine and glulisine resulted in equivalent glycemic control but in lower frequency of severe hypoglycemic events than treatment with human insulin with NPH and regular insulin in hospitalized patients with T2DM.

1083-P

Liraglutide Induced Anorexia Is Not Mediated Via Brainstem GLP-1 Neurons

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The Glucagon-Like Peptide-1 (GLP-1) analog liraglutide effectively lowers blood glucose as a treatment for type 2 diabetes. Liraglutide also reduces food intake and body weight in diabetes patients as well as in numerous animal models. However, the mechanism for this effect is not fully understood and may have both peripheral and central components. Since GLP-1 is produced in the brainstem solitary tract nucleus it is of special interest to explore if those neurons are involved in mediating the effect of peripherally administered liraglutide. We have used the immediate early gene c-Fos to identify key appetite regulatory brain areas activated following liraglutide administration. To be able to fully discriminate between effects of drug (liraglutide, 100µg/kg) and effects of feeding, rats were dosed before lights out in the presence (fed) or absence (unfed) of food. The study was terminated by perfusion fixation 4h later, brains were removed, cut into frozen sections and immunoreacted for c-Fos. Irrespective of feeding condition liraglutide increased c-Fos in the area postrema, the nucleus of the solitary tract, the lateral parabrachial nucleus and the central nucleus of amygdala, whereas liraglutide decreased the number of c-Fos positive nuclei in the hypothalamic arcuate nucleus. Given the role of brainstem GLP-1 neurons in appetite regulation we speculated that liraglutide induced anorexia could be mediated by activation of these neurons. Interestingly, double immunofluorescence revealed that liraglutide reduced activation of brainstem GLP-1 neurons when food was present (veh fed 54±3; lira fed 32±2; P<0.05). In the absence of food none of the GLP-1 neurons expressed c-Fos indicating that brainstem GLP-1 neurons are activated by feeding only. Liraglutide administration reduces food intake and hence leads to fewer activated GLP-1 neurons. A similar effect was observed in the arcuate pool of CART/POMC neurons with increased c-Fos in fed un-treated animals which was reduced by liraglutide. In summary, the data demonstrate that acute administration of liraglutide affects key food regulatory areas in the brainstem but does not lower food intake via the endogenous brain GLP-1 system.

1084-P

Liraglutide Provides Effective Glycemic Control, with Weight Loss and a Low Incidence of Hypoglycemia, in Patients with Type 2 Diabetes in Clinical Practice: First Available Audit Data

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Phase 3 trials with the once-daily human GLP-1 analog liraglutide demonstrated that it provides effective glycemic control with minimal hypoglycemia, weight loss and reduced systolic blood pressure (SBP) in patients with type 2 diabetes. Insulin-naïve patients prescribed liraglutide at a center in Northern Ireland were audited to assess outcomes in clinical practice. Patients attending Ulster Hospital who were prescribed liraglutide (June 2009–September 2010) were assessed at baseline and first post-initiation visit. Patients providing data at both visits were included in the analysis. The primary endpoint was change in A1c from baseline. Changes in weight and blood pressure were also assessed, as was frequency of hypoglycemic events. Data from 143 patients are reported (baseline A1c 8.9%, mean age 55.8 years, diabetes duration 7.7 years, BMI 39.4kg/m^2, 67.8% male). Average time to first visit after initiation was 14 weeks, at which point 15 patients (10.5%) were still prescribed 0.6 mg liraglutide, and 128 (89.5%) were prescribed 1.2 mg liraglutide. From initiation to first visit, mean change in A1c was -0.9% and mean body weight change was -2.2 kg. Changes in blood pressure were SBP -2.2 mmHg, diastolic blood pressure +0.2 mmHg. Gastrointestinal side effects were experienced by 12.6% of patients and were mainly transient. The number of patients experiencing minor hypoglycemic events was low (7.0%), and no major events were reported. In conclusion, data from clinical studies translate into clinical practice: liraglutide provided improved glycemic control after 14 weeks' treatment, accompanied by weight loss and low incidence of hypoglycemia.

1085-P

Long-Term Effects of Pitavastatin on Renal Function in Patients with Type 2 Diabetes Mellitus and Combined Dyslipidemia and in Non-Diabetic Patients with Primary Hyperlipidemia or Mixed Dyslipidemia and ≥2 Risk Factors for CHD

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Recent studies showed that statins might differ in their effects on renal function, especially in patients with diabetes mellitus. This *post hoc* analysis examined long-term effects of pitavastatin (PTA) on renal function [estimated glomerular filtration rate (eGFR)] in patients with type 2 diabetes mellitus (T2DM) and combined dyslipidemia (CD), as well as in non-diabetic patients with primary hyperlipidemia (PH) or mixed dyslipidemia (MD) and ≥2 risk factors for CHD. We evaluated effects on eGFR over 56 weeks for PTA 4 mg (n=143) vs atorvastatin (ATR) 20 mg (n=64) in patients with T2DM and CD from baseline of a 12-week multinational Phase 3 trial (NK-104-305) through completion of its subsequent 44-week extension (NK-104-310). Similarly, we assessed PTA 4 mg (n=121) vs simvastatin (SIM) 40 mg (n=52) in patients with PH or MD and ≥2 risk factors for CHD from baseline of a 12-week multinational Phase 3 trial (NK-104-304) through completion of its subsequent 44-week extension (NK-104-309). We used the abbreviated 4-variable MDRD equation to calculate eGFR. Within-group changes for eGFR were assessed using Student's paired t-test. Changes in the proportion of patients with chronic kidney disease (CKD), defined as eGFR<60 mL/min/1.73m^2, were evaluated using McNemar's test. At 56 weeks, no decline in eGFR (mean±SD, mL/min/1.73 m^2) was noted in patients with T2DM and CD treated with PTA (1.8±14.0, p=0.13) or ATR (1.5±9.0, p=0.18). Percent of patients with CKD numerically decreased from 19.3% to 15.0% for PTA (p=0.18) and was unchanged at 12.5% for ATR (p=1.000). In patients with PH or MD and ≥2 risk factors for CHD, increases in eGFR were observed after 56 weeks for PTA (4.8±10.5, p<0.001) and SIM (4.0±9.6, p=0.006). Excluding T2DM patients in this group, results were similar [PTA (n=115, 4.8±10.3, p<0.001) vs. SIM (n=49, 4.4±9.6, p=0.003)]. Long-term therapy with PTA 4 mg preserved renal function in patients with T2DM and CD as well as in non-diabetic patients with PH or MD and ≥2 risk factors for CHD.

Supported by: KPA, Inc. & Lilly USA, Inc.

1086-P

Long-Term Safety and Efficacy of Saxagliptin after 4-Year Follow-Up of Patients with Type 2 Diabetes

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Studies of DPP-4 inhibitors are limited to 2-years of follow-up. We evaluated data from 4-year extensions of 2 randomized, placebo (PBO)-controlled, double-blind trials of the selective DPP-4 inhibitor saxagliptin (SAXA) 2.5, 5, or 10 mg in drug-naïve patients (pts) with T2D (Study 11 [S11]) or as add-on to metformin (MET; Study14 [S14]). Efficacy was assessed at wk 24, followed by a 42-mo extension. Pts not meeting predetermined HbA_{1c} goals (wk 30, 37, 50: ≤8.0%; wk 63, 76: ≤7.5%; wk 89–193: ≤7.0%) were rescued with open-label MET (S11) or pioglitazone (S14) added to blinded study medications. Mean baseline characteristics in S11 and S14 were: age 53 and 55 y, duration of T2D 2.6 and 6.5 y, HbA_{1c} 7.9 and 8.0%, and BMI 32 and 31 kg/m^2, respectively. Mean durations of exposure to study drugs were longer overall in the SAXA groups vs PBO (95-109 vs 98 wk in S11 and 124-130 vs 95 wk in S14). Proportions of pts with adverse events (AEs, not adjusted for differences in exposure) were 87-88% in SAXA groups vs 79-81% in PBO. AEs reported in >10% of pts and with an incidence 1% greater for SAXA vs PBO were influenza (11% vs 6% in S11, 15% vs 15% in S14), diarrhea (11% vs 8% in S11, 12% vs 13% in S14), upper respiratory (14% vs 16% in S11, 12% vs 10% in S14) and urinary tract infections (11%, vs 8% in S11, 12% vs 8% in S14), and arthralgia (10% vs 7% in S11, 12% vs 7% in S14); most AEs were mild or moderate. Serious AEs were infrequent and balanced across groups. Two deaths in SAXA-treated pts were judged unrelated to study drug (stroke, pulmonary embolism). Confirmed hypoglycemic episodes (blood glucose ≤50 mg/dL) were infrequent in all groups (0-1.4%). There were no clinically meaningful changes in body weight. Efficacy analyses used data before rescue, limiting interpretation of results as most pts were rescued by 4 years due to the stringent rescue criteria. Numerically greater reductions in HbA_{1c} for SAXA 5 mg vs PBO were observed in the extension phase of S14. In S11, all pts on PBO received MET after wk 24 and no efficacy comparisons were made. In conclusion, SAXA as monotherapy or add-on to MET was well tolerated for up to 4 years in pts with T2D.

1087-P

Long-Term Tolerability of Saxagliptin as Add-On Therapy in Type 2 Diabetes (T2D): Pooled Analysis

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This pooled analysis evaluated the long-term tolerability of saxagliptin (SAXA) 5 mg (n=630), a selective DPP-4 inhibitor, compared with placebo (n=630) in 3 randomized, double-blind, placebo (PBO)-controlled studies with SAXA as add-on therapy to either metformin (MET), a thiazolidinedione (TZD), or glyburide for 76–206 weeks in T2D patients inadequately controlled on prior monotherapy. In this analysis, total time at risk (in years) for adverse events (AEs) was summed for all patients who received SAXA 5 mg from day of first dose to day of event or day of last dose. Weighted incidence rates (IRs, per 100 person-years±SE), IR ratios (IRRs) and 95% CI for the IRRs comparing SAXA vs PBO were calculated using the Mantel Haenszel method. IRs were generally similar among SAXA- and PBO-treated patients for all AEs, serious AEs (SAEs), treatment-related SAEs, AEs causing study discontinuation (D/C), and serious AEs causing study D/C; deaths were rare (2 vs 6 patients SAXA vs PBO).

IR per 100 person-years±SE	Saxagliptin 5 mg (n=630)	Placebo (n=630)	IRR (95% CI) Saxagliptin vs Placebo
AE	233.2±10.2	266.5±11.7	0.88 (0.78–0.99)
SAE	6.3±0.8	7.2±0.9	0.88 (0.61–1.27)
Related SAE	0.5±0.2	0.4±0.2	1.43 (0.34–6.08)
AE causing D/C	5.3±0.8	3.6±0.7	1.50 (0.95–2.36)
SAE causing D/C	1.3±0.4	0.8±0.3	1.57 (0.60–4.10)
Death	0.2±0.2	0.7±0.3	0.31 (0.07–1.51)

Likewise, IRs were similar for confirmed and all reported hypoglycemia, infection, lymphopenia, and skin- and acute cardiovascular (CV)-related AEs. Hypersensitivity was the only AE category where SAXA had a higher IR than PBO, with most hypersensitivity-related events classified as mild or moderate in intensity.

For author disclosure information, see page 785.

IR per 100 person-years±SE	Saxagliptin 5 mg (n=630)	Placebo (n=630)	IRR (95% CI) Saxagliptin vs Placebo
CV	1.0±0.3	1.5±0.4	0.63 (0.27–1.47)
Infection	66.8±3.7	73.8±4.1	0.91 (0.78–1.05)
Lymphopenia	1.2±0.4	0.9±0.3	1.26 (0.50–3.17)
Hypersensitivity	1.6±0.4	0.5±0.2	3.36 (1.11–10.2)
Skin	8.7±1.0	8.5±1.1	1.02 (0.74–1.43)
Hypoglycemia			
Confirmed	1.1±0.3	1.3±0.4	0.87 (0.37–2.05)
All Reported	10.6±1.1	11.1±1.2	0.95 (0.71–1.28)

In summary, overall tolerability of SAXA as add-on to ongoing MET, TZD, or sulfonylurea treatment was similar to PBO.

1088-P

Long-Term Use of Colestimide Is Effective Against Hyperglycemia and Overweight in Patients with Type 2 Diabetes

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Although short-term use of colestimide, anion-exchange resin, is known to improve not only hypercholesterolemia but also hyperglycemia in patients with type 2 diabetes, little is known whether or not its long-term use would ameliorate glucose metabolism in them. In this study, we investigated the effects of colestimide in 16 diabetic patients [6 male and 10 female, age 64±9 years (mean ±SD)], who had already been treated with anti-diabetic drugs but with poor glycemic control (HbA1c > 7.0%). Patients were treated with colestimide (3g/day) for 12 months, and body weight (BW), fasting plasma glucose (FPG), HbA1c, total cholesterol (T-C), HDL-C, triglyceride (TG), and apolipoprotein B-100 (Apo B) were measured before and after 3, 6, and 12 months of the administration. After 3 months, marked improvement of hyperglycemia and hypercholesterolemia was observed with significant decrease in FPG (154 ± 34 to 137 ± 33 mg/dl, p=0.008) and HbA1c (8.3 ± 1.0 to 7.4 ± 0.8, p<0.001), as well as significant decrease in T-C (204 ± 26 to 192 ± 36 mg/dl, p=0.004), LDL-C (124 ± 21 to 101 ± 26 mg/dl, p<0.001), Apo B (98 ± 20 to 88 ± 17 mg/dl, p=0.016) and significant increase in HDL-C (58 ± 12 to 63 ± 15, p=0.019). Body mass index was also significantly decreased after 3 months (26.1 ± 2.9 to 25.6 ± 2.9, p=0.019). Ten patients (62%) had kept these good status until 12 months without addition of another drugs. These findings suggest that long-term use of colestimide may also be effective against hyperglycemia and overweight as well as hypercholesterolemia in patients with type 2 diabetes. Its administration could be beneficial for diabetic patients complicated with obesity and high cholesterol level.

1089-P

LY2189265, a Long-Acting GLP-1 Analog, Does Not Prolong QTc Interval in Healthy Subjects at Supratherapeutic Doses

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We investigated the effect of a single supratherapeutic dose of LY2189265 (LY), a long-acting GLP-1 analog, on cardiac repolarization as assessed by QTc interval in a randomized, placebo-controlled, double-blind, 3-period crossover study. Healthy subjects (N=147) with normal baseline ECG (QTc <450 ms) received 4 or 7 mg single doses of LY, 400 mg moxifloxacin, and matching placebo. LY doses were selected to achieve ≥5 times the steady-state LY concentrations of the therapeutic dose (1.5 mg) in patients with type 2 diabetes. Sixty-four women and 83 men (mean age 42 years; mean BMI 26.4 kg/m^2) received LY, placebo, and moxifloxacin on 3 occasions separated by approximately 21 days of washout. Twelve-lead ECGs in triplicate and time-matched blood samples for LY concentration profile were collected predose and 24, 48, 72, and 168 h postdose. Change from predose QT intervals was corrected for heart rate using Fridericia's and other methods. LY concentration–QTc relationships were also evaluated using a circadian rhythm model.

LY did not prolong QT compared with placebo, as the upper bound of the 2-sided 90% CI for the time-matched mean difference from placebo was <10 ms for all correction methods used. Statistically significant decreases in QTc compared to placebo were observed at times of maximum LY concentrations (range -6.0 to -11.2 msec) for both LY doses. The circadian rhythm model also described a concentration-dependent decrease in QTc for LY. No subject had QTc >480 ms or QTc change from baseline >30 ms after LY dosing. Moxifloxacin increased QTc (range 5.9 to 7.9 msec) compared to placebo. LY doses of 4 and 7 mg were not well tolerated (high incidence of nausea and vomiting). Four subjects were diagnosed with pancreatitis after showing notable elevations in amylase/lipase; none reported typical acute pancreatitis–type abdominal pain, and there was no evidence of pancreatitis on CT scan. The cases were adjudicated by an independent external review committee; 2 were considered to be acute pancreatitis. All subjects made a full recovery.

This study demonstrates that LY2189265 did not prolong the QTc interval in healthy subjects at supratherapeutic doses.

1090-P

Mechanism of Action: Canagliflozin, an SGLT2 Inhibitor, Increases Urinary Glucose Excretion (UGE) in ZDF Rats by Lowering the Renal Glucose Threshold (RT_G)

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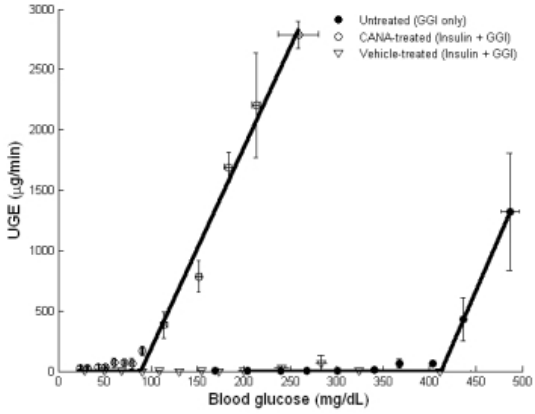
Canagliflozin (CANA) is a potent sodium glucose co-transporter 2 (SGLT2) inhibitor in development for the treatment of patients with type 2 diabetes. The manner in which SGLT2 inhibitors increase urinary glucose excretion (UGE) has not been established; whether they increase fractional excretion of filtered glucose at all blood glucose (BG) concentrations or lower renal glucose threshold (RT_G) while maintaining a threshold relationship between BG and UGE has not been shown. To address this, 2 graded glucose infusion (GGI) experiments were performed to determine the relationship between BG and UGE in untreated and CANA-treated diabetic animals. In the first experiment, a GGI (1.5-6 mL/kg/h of 10% glucose) was performed over 90 minutes in anesthetized obese Zucker diabetic fatty (ZDF) rats (N=8, fasting BG=212±24 mg/dL [mean±sem]). Blood and urine (via catheter) were sampled every 5 minutes. In untreated rats, the relationship between BG and UGE was well-described by a threshold relationship (Figure) with RT_G=415±12 (mean±sem). To assess the effect of CANA, ZDF rats were treated with either vehicle or CANA 1 mg/kg (N=6/group), infused with insulin (3 U/mL, 0.7 mL/kg/h) for 60 minutes to lower BG to 25±1 mg/dL, and then given the GGI. CANA preserved the threshold nature of the relationship between BG and UGE (Figure), lowering RT_G to 94±10 mg/dL in the CANA-treated rats, with minimal splay observed. Vehicle-treated rats had virtually no UGE in this experiment. These results demonstrate that CANA directly and markedly lowers RT_G while preserving the threshold nature of the UGE vs BG relationship. Because only minimal amounts of UGE occur in CANA-treated animals when BGG, treatment is expected to provide a low risk for hypoglycemia whenever RT_G remains above the hypoglycemic threshold.



1091-P

Meta-Analysis of the All-Cause Mortality in Premixed Insulin Treated Patients

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Purpose: To compare the risk of all cause mortality in premixed insulin treated patients with that in patients treated with other anti-diabetic medicaions. Methods: We searched the following databases for primary studies during the stipulated periods of time: MEDLINE® (1966 to July 2010), EMBASE® (1974 to July 2010), the Cochrane Central Register of Controlled Trials (CENTRAL; 1966 to July 2010). Qualified studies compared premixed insulin(pre-mixed human insulin or pre-mixed insulin analogues) with other anti-diabetic medications in adults with type 2 diabetes were included in the meta-analysis. These analyses were conducted by using Review Manager, version 4.2. Results: Totally 135 published original studies were identified.

47 qualified studies were included in the analysis. No statistically significant differences was found in all-cause mortality (OR = 1.27; 95%CI: 0.75 to 2.16) between premixed insulin groups(n= 6871) and group treated with other anti-diabetic medications(n=6642). Compared with basal insulin therapy group(n=3161), no statistically significant differences was found in all-cause mortality (OR = 2.12; 95%CI: 0.83 to 5.38) in premixed insulin group(n=3213). Compared with basal-bolus insulin therapy group(n=1564), no statistically significant differences was found in all-cause mortality (OR = 0.99; 95%CI: 0.37 to 2.63) in premixed insulin group(n=1656). Compared with bolus insulin therapy (n=463), no statistically significant differences was found in all-cause mortality (OR = 0.78; 95%CI: 0.29 to 2.14) in premixed insulin group(n=385). Compared with non-insulin anti-diabetic agents therapy group(n=1454), no statistically significant differences was found in all-cause mortality (OR = 1.42; 95%CI: 0.43 to 4.65) in premixed insulin group (n=1926). Conclusion: No statistically significant differences were found between premixed insulin treated patients and patients treated with other medications in terms of all-cause mortality.

1092-P

Metabolism of Insulin Glargine after Subcutaneous Injection of Therapeutic Dose in Type 2 Diabetes Mellitus

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After subcutaneous (sc) injection *in vivo*, the long-acting insulin analog glargine (GLA) undergoes a sequential cleavage of the carboxy terminus of the B-chain forming metabolites M1 and M2 that lack the di-arginine (M1 after removal of the two arginines, M2 with additional deamination of threonine at position B30). M1 and M2 have the same metabolic properties as human insulin (HI) and do not differ from HI in affinity for IGF-IR. Currently, there are no data about dynamics and relative percentage of plasma M1 and M2 vs GLA after sc dose in patients with type 2 diabetes (T2DM). GLA, M1, and M2 plasma concentrations were determined from samples obtained from a single-center, 32h euglycemic glucose clamp study, where 18 subjects with T2DM received a single sc dose of 0.4 U/kg GLA after one week of daily administration. Data from 9 subjects and 31h glucose clamp, are here reported (mean±SD: BMI 29.3±3 kg/m^2; A1C 7.4±0.0%, diabetes duration 13±10 yrs). GLA, M1, and M2 were extracted using immunoaffinity columns and quantified by a specific liquid chromatography tandem mass spectrometry assay, without cross-reactivity to endogenous human or other insulins. The limit of quantitation (LOQ) was 0.2 ng/ml (~33 pmol/l). GLA was detected in 5 of the 9 subjects and only at a few time points; M2 was not detected at all, whereas M1 was detected in all subjects. M1, but not GLA, was detected at baseline (median: 44 pmol/l; 25th to 75th percentile: 19 to 131 pmol/l), likely reflecting GLA injected 24h before. In fact, 24h post-injection values were similar to baseline values (60; 52 to118 pmol/l). The median GLA PK-AUC$_{0\text{-}31}$ was 171 pmol · h/l (0 to 314) and M1 PK-AUC$_{0\text{-}31}$ was 2166 pmol · h/l (1622 to 4955). GLA Cmax was 40 pmol/l (0 to 48) and M1 Cmax was 129 pmol/l (75 to 207). After sc injection of a therapeutic dose, GLA is minimally detectable in blood with low peak concentration and up to only 9 hours (3.5 to 14.5), whereas its metabolite M1 accounts for most (~90%) of the plasma insulin concentration up to 31 h. Additional studies using a higher dose of GLA might provide further insights into the metabolism of GLA in T2DM.

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1093-P

Micro(mi) RNA Profiling of Endothelial Progenitor Cell (EPC) Populations in Type 2 Diabetics (T2D): A Tool for Optimization of Autologous Cell Therapy

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Diabetic EPCs are typically dysfunctional; however, identifying the least dysfunctional population of EPCs in an individual would improve success of autologous cell therapy for revascularization. We showed in T2D, high endogenous TGF-β1 levels within CD34$^+$ EPCs are responsible for their reduced growth and poor reparative potential. Transient inhibition of TGF-β1 or plasminogen activator inhibitor-1 (PAI-1), the major gene product of TGF-β1 activation, enhances vascular reparative function of CD34$^+$ cells isolated from T2D. miRNAs, a class of short non-coding RNA molecules which form microribonucleoprotein complexes that target diverse growth, differentiation and fibrotic genes for repression or activation, are linked with several disease conditions such as diabetes and cancer. Using Pathway-focused miRNA arrays, we determined and contrasted the miRNA expression signatures in different EPCs populations (CD34$^+$cells, early EPCs (eEPCs) and late outgrowth EPCs (OECs)) from the same patient. T2D were compared to age- and sex- matched nondiabetics. Stringent comparisons showed that the levels of each miRNA were different in three EPC populations. We observed marked changes in miR-146a, which is involved in TGF-β1/ PAI-1 regulation and validated PAI-1 inhibition by over-expressing miR-146a, which promoted cell proliferation, migration, and survival by increasing activity of PI3 kinase *in vitro* (p<0.001). Interestingly, in one particular diabetic, eEPCs not only expressed greatest levels of the PAI-1/TGF-β1 regulating miR-146a, miR 21, miR29a, miR181b, but exhibited greatest proliferative potential, compared to CD34$^+$ and OECs, suggesting that in this diabetic individual, eEPCS might represent the ideal progenitor population for autologous cell therapy. Our results suggest that analyses of miRNA signature and specifically levels of key miRNAs that regulate TGF-β1/PAI-1 may serve as a tool to identify the best progenitor population for autologous cell therapy for an individual and TGF-β1/PAI-1 modulating miRNAs may offer a promising therapeutic strategy for restoring vascular reparative function in dysfunctional diabetic cells.

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1094-P

Monotherapy with the Once Weekly Long-Acting GLP-1 Analog LY2189265 for 12 Weeks in Patients with Type 2 Diabetes: Dose-Dependent Effects on Glycemic Control in a Randomized, Double-Blind, Placebo-Controlled Study

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We evaluated the dose-dependent effects of once-weekly LY2189265 (LY), a glucagon-like peptide-1 (GLP-1) analog, on glycemic control (hemoglobin A1c) in patients with type 2 diabetes treated with life-style measures. This was a double-blind, placebo controlled study in 164 patients (at entry, mean±SD; age 57±9 years; BMI 32.1±4.8 kg/m^2; and hemoglobin A1c (HbA1c) 7.2±0.6%) who were antihyperglycemic medication-naïve or had discontinued metformin monotherapy. Patients entered a 4 to 8–week lead-in period. Those with qualifying HbA1c values (≥6.5% to ≤9.5%) were randomized (baseline HbA1c between 7.6±0.7% and 7.8±0.8%) to once-weekly subcutaneous injections of placebo or LY (0.1 mg, 0.5 mg, 1.0 mg, or 1.5 mg) for 12 weeks, followed by a 4-week safety follow up.

At week 12, statistically significant dose-dependent reductions in HbA1c (LS mean±SE) were observed across LY2189265 doses (p<0.001). HbA1c reductions in LY0.5, LY1.0 and LY1.5 treatment groups were statistically significantly greater than the placebo group (-0.89±0.12%, -1.03±0.11%, and -1.04±0.13% vs. 0.01±0.13%, respectively, all p<0.001). Dose-dependent reductions in fasting blood glucose were also observed (from -37.5±4.8 mg/dL for LY1.5 mg to -3.8±4.4 mg/dL for placebo, p<0.001). A significant dose-dependent weight loss was demonstrated across LY2189265 doses (p=0.005), but none of the groups were different from the placebo group. The most common adverse events were nausea, diarrhea, and nasopharyngitis.

In conclusion, treatment of patients with type 2 diabetes for 12 weeks with LY2189265 as monotherapy resulted in dose-dependent reductions in HbA1c and blood glucose with an acceptable safety profile of all doses of this long-acting GLP-1 analog.

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1095-P

Morning Hyperglycemia: Breakfast or Dawn Phenomenon

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Morning hyperglycemia, dawn phenomenon (DP), is reported to begin about 0400 h and end about 0800 h, at the start of breakfast. Utilizing the level action of basal insulin treatment provided by glargine (IG), we evaluated the termination of action of the DP by breakfast meal omission.

The subjects' (n=37) IG (2100–2200 hr) doses were titrated to a 24 hour continuous glucose monitoring, (CGM) basal glucose target >4 hr post-meal and at meal times by daily alternate meal omission to <130 mg/dl but <10%, <70 mg/dl. After 2 days of a constant IG dose, the mean 24 hr basal glucose data was reconstructed by cut and pasting the omitted meal periods. In addition, a 7 point self monitored blood glucose (SMBG) (before and 2 h after meals and at bed time) was done both with meals and with meal omission.

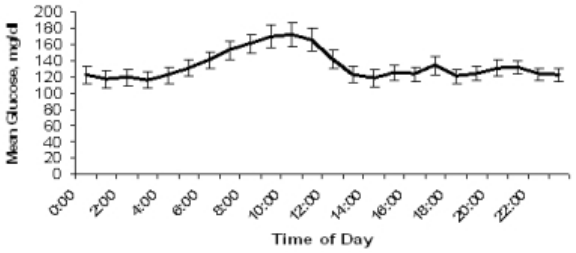
The mean (SD) age was 44 (17) years; duration of diabetes, 12 (10) years; and Hb A1c, 7.41 (0.74) %. The hourly mean (SE) CGM basal glucose is shown. The SMBG comparison between breakfast meal and its omission

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

demonstrated a before meal glucose of 148 (67) and 151 (69) (p>0.1) and after meal glucose of 185 (67) and 177 (88) (p>0.1) mg/dl, respectively. The basal mean SMBG glucose after lunch was 113 (53) mg/dl.

The DP rises at 0400 h, peaks at 1000 h and returns to baseline at 1300 h. The DP contributes a major share to the 'breakfast' meal hyperglycemia. DP pretreated with a pre-programmable pump step-up in basal rate hours before the dawn phenomenon has previously been shown to suppress the breakfast time increase in glucose and the higher morning bolusing for the carbohydrate meal content.



Supported by: Eli Lilly and Company

1096-P

National Differences in Glycemic Control 6 Months after Initiation of Basal Insulin in Patients with Type 2 Diabetes: A Subanalysis of the FINE Asia Database

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FINE Asia is a prospective, observational registry undertaken to evaluate basal insulin initiation in patients with type 2 diabetes mellitus in Asia inadequately controlled by oral antihyperglycemic agents. This subanalysis compared findings by individual participating countries. The primary efficacy end point was change in A1C from baseline to Month 6 after basal insulin initiation. Secondary end points included change in fasting blood glucose (FBG) from baseline to Month 6, responses rates (A1C and FBG), average insulin doses, and hypoglycemic events.

The study enrolled 2921 patients from 11 Asian countries (countries with small patient numbers are pooled as Southeast Asia). After starting basal insulin (NPH insulin, insulin glargine, or insulin detemir), overall A1C decreased from 9.8±1.6% to 7.7±1.4% at Month 6; 33.7% patients reached A1C < 7%. Findings for glycemic control at Month 6 varied greatly by country (Table), with a low of 10.6% and a high of 75.4% of patients in Taiwan and China, respectively, reaching A1C target. The increase in insulin dose ranged from 0.5 U in Pakistan to 6.0 U in Thailand. Rates of hypoglycemia also varied, with 2.2% and 15.9% of patients in India and China experiencing at least 1 event.

National data from the FINE Asia study show widely varying degrees of glycemic control in patients depending on their country, with China having the highest percentage of patients reaching goal A1C but also having the highest rate of hypoglycemia.

Country	n	Baseline A1C, % (SD)	Δ A1C, % (SD)	Patients With A1C <7, %	Patients Reaching FBG <110 mg/dl, %	Δ Total Daily Insulin Dose, U (SD)	Patients With Hypoglycemia, %
China	491	9.4 (1.6)	-2.6 (1.5	75.4	54.8	1.2 (4.6)	15.9
India	681	9.4 (1.2)	-2.3 (1.2)	59.8	46.1	1.7 (5.1)	2.2
Korea	291	9.7 (1.6)	-1.6 (1.8)	18.2	20.6	0.8 (4.8)	7.9
Pakistan	139	10.1 (1.3)	-2.6 (1.6)	59.0	74.1	0.5 (3.1)	10.8
Taiwan	417	10.2 (1.7)	-1.3 (2.0)	10.6	26.6	2.4 (9.0)	5.8
Thailand	448	10.2 (1.9)	-2.1 (2.0)	24.8	27.9	6.0 (8.6)	8.7
SE Asia[a]	212	10.5 (1.9)	-2.5 (2.2)	34.4	25.0	2.8 (7.0)	8.5

[a]Bangladesh, Hong Kong, Indonesia, Singapore, and Vietnam

Supported by: sanofi-aventis

1097-P

Novel Inhibitory Activity of a *Schizandra arisanensis* Stem Extract Against Cytokine-Mediated Cytotoxicity towards Insulin-Secreting Cells

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The objective of the current investigation was to explore the bioactivities of an ethanolic extract of *Schizandra arisanensis* stem (SA-Et) and isolated constituents against interleukin (IL)-1β and interferon (IFN)-γ mediation of beta cell death and abolition of insulin secretion. By employing BRIN-BD11 cells, the effects of SA-Et administration on cytokine-mediated cell death and abolishment of insulin secretion were evaluated by a viability assay, cell cycle analysis, and insulin assay. The associated gene and protein expressions were also measured. In addition, the bioactivities of several peak compounds collected from the SA-Et were tested against cytokine-mediated beta cell death. Results revealed that SA-Et dose-dependently ameliorated cytokine-mediated beta cell death and apoptosis. In addition, schiarisanrin A and B isolated from the SA-Et possessed a dose-dependent protective effect against cytokine-mediated beta cell death. However, neither cytokine-mediated IκBα degradation nor STAT-1α phosphorylation were inhibited in the presence of the SA-Et. On the other hand, SA-Et provided some insulinotropic effects which appeared to re-activate the abolished insulin exocytosis in cytokine-treated BRIN-BD11 cells. In conclusion, this is the first report on *Schizandra arisanensis* ameliorating cytokine-mediated beta cell death and dysfunction via antiapoptotic and insulinotropic actions. C_{19} homolignans appeared to be responsible for the observed beneficial actions.

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1098-P

WITHDRAWN

1099-P

WITHDRAWN

1100-P

Pioglitazone Treatment Improves Muscle Oxidative Capacity and Lowers Muscle Lipid Content in Diabetic Rats

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Pioglitazone is a PPAR-γ agonist that redirects lipids from ectopic sites into subcutaneous adipose tissue and is hypothesized to improve mitochondrial function in skeletal muscle. This study assessed whether the insulin-sensitizing effect of pioglitazone is accompanied by improved skeletal muscle mitochondrial function and intramyocellular lipid (IMCL) levels in Zucker diabetic fatty rats using ^{31}P and ^{1}H magnetic resonance spectroscopy (MRS).

Twelve-week old non-diabetic fa/+ and diabetic fa/fa rats were treated with either pioglitazone (30 mg/kg/day in water, n=6) or water as a control (n=6), for 14 days by oral gavage. After treatment, in vivo ^{1}H and ^{31}P MRS were performed on the tibialis anterior muscle using a 6.3T MR scanner. IMCL content was expressed as percentage of the water signal. ^{31}P spectra were obtained before, during and after muscle contractions induced by electrical stimulation. The phosphocreatine (PCr) recovery rate constant (k_{PCr}) was used as a measure of in vivo muscle oxidative capacity.

Fasting plasma glucose levels were 3-fold higher in untreated fa/fa rats compared with untreated fa/+ rats (17.0±0.9 and 4.7±0.3 mM, respectively). Treatment with pioglitazone significantly lowered fasting glucose in the fa/fa group (12.6±4.7 mM), but had no effect in fa/+ rats. IMCL content was 7-fold higher in untreated fa/fa rats compared with fa/+ rats (0.56±0.1 and 0.08±0.03 %, respectively). Pioglitazone treatment lowered IMCL content in fa/fa rats by 50% (0.28±0.1 %), but after treatment IMCL levels in fa/fa rats were still 3-fold higher than in fa/+ rats. k_{PCr} was significantly lower in untreated fa/fa rats compared with fa/+ rats (0.48±0.06 and 0.65±0.07 min^{-1}, respectively). Treatment with pioglitazone normalized k_{PCr} in fa/fa rats (0.60±0.06 min^{-1}) to the values of fa/+ rats, whereas it had no effect in fa/+ rats.

In conclusion, 2 weeks of treatment with pioglitazone lowered fasting glucose levels and IMCL content and increased in vivo muscle oxidative capacity in diabetic rats. This suggests that the insulin-sensitizing effect of pioglitazone is brought about by improvement of muscle mitochondrial function and partial normalization of IMCL.

1101-P

Primary Care Physician Treatment Response to A1c Data

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Published evidence implies that primary care physicians may be less likely to treat to goal than subspecialists. Records of 343 patients with diabetes managed by 10 community based primary care physicians in a major urban community were evaluated for documentation of at least two A1c measures during the evaluation period. Baseline glycemic goal was established at A1c of <7%. In cases where goal was not met, we evaluated if actions were taken to optimize treatment.

Paper based records were used at 100% of practices. 269 patients (78.43%) had paired visits with complete records. At baseline, average A1c was 7.7%, mean age was 61.4 yrs, 51% of the patients were male, and 53% did not meet goal. For those not meeting goal, pharmacotherapy changes were documented in 42% of cases resulting in significantly reduced A1c (baseline, 9.0; follow-up, 8.3; p=0.006). Adjusted odds of taking action increased by 84% if A1c was ≥7.0. While gender did not have a significant association with actions to optimize therapy (p=0.546), there was a trend for less aggressive intervention with increasing age (p=0.066).

Management actions demonstrate a trend towards treatment intensification in 55 (91.7%) of 60 patients with complete documentation for paired visits. Treatment intensification included agent addition or change, dose change, or insulin added or optimized. However, 82 patients (58%) who were above goal did not receive treatment change suggesting that only about half of the patients in this sample benefited from treatment intensification. While in many cases primary care physicians implement needed treatment changes to optimally manage patients with diabetes, this study provides an opportunity to further explore determinants of appropriate treatment change in this patient-physician setting.

1102-P

Protection Against Diabetes-Induced Myocardial Injury and Capillary Basement Membrane Thickening in OVE Transgenic Mice by Myocardial Specific Overexpression of Metallothionein

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Individuals with diabetic cardiomyopathy (DC) often experience impaired cardiac function as a result of reduced contractility, or hypertension-induced athero- or arteriosclerosis. This may be due to focal myocardial disorganization characterized by disrupted myofibrils and randomly located mitochondria in an edematous sarcoplasm. Microvascular injury, with or without basement membrane (BM) thickening, also is common, and hyperglycemia-driven reactive oxygen species (ROS) are believed to contribute to such damage. To address this hypothesis we utilized light and transmission electron microscopy to demonstrate myocardial morphology in the left ventricles of 350 day-old control (FVB) and age-matched, transgenic diabetic (OVE) mice, transgenic (MT) mice that specifically overexpress the antioxidant protein metallothionein in the myocardium, and double transgenic (OVEMT) mice. We also employed unbiased electron microscopic stereometry and "orthogonal intercepts" to demonstrate random myocardial capillary BM thickening. Our data show that myocardial capillary BMs from OVE diabetic mice (61.43 nm ±8.97 S.D.)

were significantly thickened compared to BMs from FVB (49.75 nm ±6.36 S.D.) and MT (47.50 nm ±5.20 S.D.) mice.

Importantly, capillary BMs in double transgenic OVEMT mice were significantly protected (45.88 nm ±5.63 S.D.) against diabetes-induced thickening. This strongly suggests that hyperglycemia-induced oxidative

For author disclosure information, see page 785.

stress induces damage at the level of endothelial cells. We hypothesize that in OVEMT mice, myocardial MT overexpression provides sufficient antioxidant activity to scavange free radicals in perivascular spaces, reducing local ROS injury, incipient microvascular damage and the capillary BM thickening that results from such injury. In future experiments, transgenic mice overexpressing antioxidants specifically targeted to endothelial cells may provide a more efficient cardioprotective intervention against myocardial capillary BM disease.

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1103-P

Rationale and Design of the CAROLINA Trial: An Active Comparator CARdiOvascular Outcome Study of the DPP-4 Inhibitor LINAgliptin in Patients with Type 2 Diabetes at High Cardiovascular Risk

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As there are no adequately sized active-comparator, head-to-head cardiovascular (CV) outcome trials in type 2 diabetes (T2D), the impact of different glucose-lowering therapies on CV burden remains unclear. The CAROLINA trial is a head-to-head, event-driven, multi-center, randomized, double blind, active comparator study designed to assess the impact of the DPP-4 inhibitor linagliptin (5 mg/day), compared with the sulfonylurea glimepiride (up to 4 mg/day), on CV events in 6000 mildly hyperglycemic T2D patients being on no or specified background medication and at elevated CV risk. We hypothesize a CV benefit with linagliptin, and the primary outcome will be time to the first occurrence of a CV event (CV death, nonfatal myocardial infarction (MI), stroke and hospitalization for unstable angina), adjudicated by a blinded independent committee. At an estimated annual CV event rate of 2%, 631 events will be required to provide 91% power to yield the upper limit of the adjusted 95% CI for a hazard ratio <1.3 at a one-sided α level of 0.025 assuming equal risks. Hierarchical testing for superiority will follow if non-inferiority is achieved. Secondary endpoints include treatment durability (need for rescue add-on to sustain HbA1c ≤7.0%), change from baseline in glycemic control, renal function parameters, hypoglycemic event rates and body weight. Sub-studies will evaluate the impact of the interventions on glycemic variability, β-cell function, cognitive function, silent MI and CV biomarkers. The CAROLINA trial is the first head-to-head active-comparator DPP-4 inhibitor CV outcome trial powered to demonstrate potential reductions in CV events and provide clinically relevant CV safety data on linagliptin compared with glimepiride in T2D patients.

Figure. Glycemic and CV inclusion characteristics for the CAROLINA trial - any one CV criterion under A, B, C or D will suffice for participation.

Glycemic Entry Criterion	CV Entry Criteria			
HbA1c:	A: Pre-existing CV disease (age 40-85 years)	B: Specified diabetes end-organ damage (age 40-85 years)	C: Advanced age	D: Multiple (≥2) CV risk factors (age 40-85 years)
A: 6.5-8.5%: if treatment naive or mono- or dual therapy with metformin and/or α-glucosidase inhibitor	Myocardial infarction (≥6 weeks prior inclusion)	Moderately impaired renal function (eGFR 30-59 mL/min/1.73 m²)	Age ≥70 years	T2D duration >10 years
	≥50% stenosis on angiography of left main coronary artery or ≥ two major coronary arteries	Albuminuria (albumin: creatinine ratio ≥30 µg/mg)		Systolic blood pressure (BP) >140 mmHg (or ≥ one BP lowering agent)
B: 6.5-7.5%: if treatment with SU/glinide in mono- or in dual therapy with metformin or α-glucosidase inhibitor	Percutaneous coronary intervention ≥6 weeks prior to inclusion	Proliferative retinopathy (neovascularization or laser coagulation therapy)		Current daily cigarette smoking
	CABG ≥4 years prior to inclusion or recurrent angina pectoris following CABG			LDL cholesterol ≥135 mg/dL (3.5 mmol/l) (or specific lipid abnormality agent)
	Ischemic or hemorrhagic stroke ≥3 months prior to inclusion			
	Peripheral occlusive arterial disease			

Supported by: Boehringer-Ingelheim Pharmaceuticals, Inc.

1104-P

Reduction in Postprandial Glucose with Dapagliflozin in Type 2 Diabetes

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Increases in postprandial blood glucose levels (PPG) contribute significantly to overall glycemic load and development of complications with type 2 diabetes (T2DM). Controlling PPG is an important component in overall glycemic control. Dapagliflozin (DAPA), a sodium-glucose cotransporter 2 (SGLT2) inhibitor, inhibits renal reabsorption of filtered glucose and induces urinary glucose excretion. As glucose excretion is proportional to the filtered load, DAPA may help in managing PPG surges. The effect of DAPA on PPG was assessed in 3 clinical trials in subjects with T2DM; a 12wk dose-ranging study of DAPA alone (MB102008–MT; A1c 7-10%) and two 24wk double-blind (DB) placebo (PBO)-controlled trials with 24wk DB extensions evaluating DAPA as an add-on to glimepiride (D169000005–GLM; A1c 7-10%) or pioglitazone therapy (MB102030–PIO; A1c 7-10.5%). PPG was measured 2h after a 75-g oral glucose challenge. Baseline (BL) fasting plasma glucose levels ranged from 145 to 153 mg/dL, 172 to 175 mg/dL, and 161 to 168 mg/dL in the MT, GLM and PIO studies respectively. PPG was reduced in all DAPA groups across the studies compared with PBO (Table). Mean reductions in PPG observed with DAPA in the GLM or PIO studies were sustained for up to 48 wks. In each study DAPA was generally safe and well tolerated. Events of hypoglycemia were reported at a similar rate to PBO in the PIO study, showed small increases in the GLM and MT studies (with the exception of the 5 mg dose) and did not result in discontinuations. In summary, sustained mean reductions in PPG levels were observed when DAPA was administered as MT or in combination with GLM or PIO.

PPG levels mg/dL

			DAPA (mg/d)		
	Duration	PBO	2.5	5	10
MT					
N	12	54	59	58	47
BL PPG (SD)		265.5(84.2)	255.0(72.0)	268.8(68.7)	274.1(87.4)
2-h PPG mean change (SD)		-20.3(38.5)	-53.4(60.0)	-58.0(49.3)	-71.5(77.1)
GLM					
N	24	109	126	117	132
BL PPG (SD)		158.6(58.8)	140.4(68.2)	151.2(64.2)	157.3(69.0)
2-h PPG adj. mean change (SE)		-6.0(5.0)	-37.5(4.7)[c]	-32.0(4.8)[b]	-34.9(4.6)[a]
PIO					
N	24	112	N/A	116	115
BL PPG (SD)		293.6(81.2)		284.8(98.5)	308.0(92.8)
2-h PPG adj. mean change (SE)		-14.1(6.4)		-65.1(6.3)[a]	-67.5(6.4)[a]

[a]P<0.0001 [b]P=0.0002 [c]Nominal P<0.0001

Supported by: AstraZeneca and Bristol-Myers Squibb

1105-P

Renal Impairment Has No Relevant Effect on Long-Term Exposure of Linagliptin in Patients with Type 2 Diabetes Mellitus

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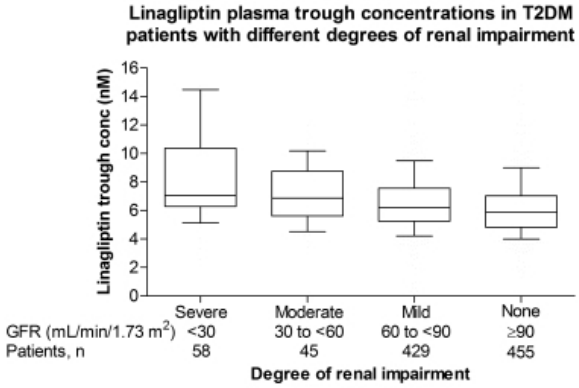
Linagliptin (LIN) is a potent and selective dipeptidyl peptidase (DPP-4) inhibitor with a primarily non-renal route of excretion. This may be particularly relevant for patients with type 2 diabetes mellitus (T2DM) who have, or are at high risk of developing, renal impairment (RI). It was assumed that progressive impairment of renal function would have a minor effect on the steady state exposure to LIN. This pooled analysis used steady state trough concentrations of LIN from patients with T2DM who participated in the global Phase III program investigating LIN 5 mg once daily for 24-52 weeks. Steady state trough concentrations have previously been shown to correlate closely with steady state exposure (AUC) independent of dose, concomitant treatment, and concomitant disease, and were, therefore, considered adequate for monitoring long-term exposure. LIN plasma concentrations were available from a total of 987 patients. These were classified by their eGFR (based on MDRD) to have normal renal function (GFR ≥90 mL/min/1.73 m^2; n=455), mild RI (GFR 60 to <90 mL/min/1.73 m^2; n=429), moderate RI (GFR 30 to <60 mL/min/1.73 m^2; n=45), or severe RI (GFR <30 mL/min/1.73 m^2; n=58). In patients with T2DM and normal renal function, the geometric mean LIN trough concentration was 5.9 nM (39.7% gCV); in patients with mild, moderate, or severe RI, LIN trough concentrations were 6.2 nM (54.7% gCV), 7.2 nM (41.4% gCV), and 8.0 nM (46.0% gCV), respectively (figure).



This corresponds to a maximum increase in trough exposure by 35% in patients with severe RI compared with patients with normal renal function. In patients with T2DM, RI had only a minor effect on the long-term exposure of LIN. Therefore, adjustment of the dose based on renal function and additional drug-related monitoring of GFR may not be required for LIN.

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1106-P

Restoration of Acute Insulin Response after CSII Predicted Long Term Euglycemia without Medication in Patients with Newly Diagnosed Type 2 Diabetes

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Acute insulin response(AIR) is impaired in type 2 diabetes mellitus (T2DM). Our previous studies showed that short term continuous subcuntaneous insulin infusion (CSII) therapy resulted in 12-month euglycemia without medication in hypoglycemic drug naïve patients with newly diagnosed T2DM. But the mechanism remained unclear. We aim to explore the relationship between AIR and euglycemic time in such kind of patients.

We enrolled 188 patients. All patients were hypoglycemic drug naïve, received CSII and maintained glycemic control(defined as fasting blood glucose(FBG)<6.0mmol/L and 2-h postprandial blood glucose (2hPG) <8.0mmol/L)for 2 weeks. and then were given life style intervention without hypoglycemic medication and followed up for 12 months. Intravenous glucose tolerance test(IVGTT) was done before and after CSII. AIR was calculated as the trapezoidal area of insulin concentration. Peak/basal insulin ratio(PBR) is calculated as peak insulin concentration during IVGTT divided by insulin concentration before glucose administration. Remission is defined as euglycemia (FBG≤7mmol/L and 2hPG≤10mmol/L) without hypoglycemic medication. The relationship between AIR measurements and remission was assessed.

The overall remission rate in 12th month was 51%. Proportional hazard analysis showed that, adjusted for age, sex, body mass index and triglyceride, AIR and PBR after CSII are independent prognostic factors for 12-month maintenance of remission (for AIR after CSII (pmol/L per min), upper tertile(>800) vs middle tertile(300~800) RR=2.58 P<0.001, middle tertile vs lower tertile(<300) RR=2.04 P=0.011); for PBR after CSII, >2 vs <2 RR=2.43 P=0.016).

Our study indicated that restoration of acute insulin response after short term CSII predicted long-term euglycemia without medication in patients with newly diagnosed T2DM.

1107-P

Safety and Efficacy of a Universal Nursing-Run Intravenous Insulin Guideline in Non-Critically Ill Patients

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The objective of this study is to determine the safety and efficacy of a universal nursing-run intravenous (IV) insulin guideline on medical and surgical wards.

The insulin infusion guideline could be ordered on any unit at the study institution since 2006. The target glucose was 100-150 mg/dl. Administrative data was used to identify patients who received insulin infusions between 2005 through 2010. Patients in the medical or surgical ICU were excluded. All cardiac beds have interchangeable critical and noncritical care status, and therefore, these patients were included.

A total of 12,380 discrete insulin drip "runs" were identified, 6,496 of which arose from cardiology floors. In the year following implementation of the infusion guideline, there was a significant decrease in time to glucose <150 mg/dl (6.5 vs 5.6 hours, p=0.003) and median glucose (162 vs 153 mg/dl, p<0.001), and this effect persisted through 2010. There was no change in hypoglycemic events from 2005 to 2006 (0.5 vs 0.6 per 24 hours, p=0.65). Cardiac floors had significantly shorter time to 150 mg/dl (4.8 vs. 6.5.hours, p<.001), lower median glucose (140 vs. 164 mg/dl, p<0.001), and fewer hypoglycemic events (0.25 vs. 0.81, p<0.001) compared to other floors. When analyzed by nutrition status, 8446 (68%) had an order for "nothing by mouth", 459 (3.7%) were eating and received concurrent subcutaneous (SQ) rapid acting insulin, 1895 (15.3%) were eating without concurrent rapid acting insulin, and 1580 (13%) were receiving enteral tube feeds. Compared to those who received nothing by mouth, patients in the other 3 feeding groups had significantly longer time to glucose <150 mg/dl, higher median glucose, and more hypoglycemic events. The effect of feeding status persisted regardless of whether SQ prandial insulin was provided, although the numbers were small for that subgroup.

Nursing-run IV insulin infusions can be implemented safely and effectively outside of the intensive care unit, although metrics vary by service and/or patient characteristics. Patients who are receiving oral or enteral nutrition have more difficulty achieving glycemic targets, warranting further study.

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1108-P

Saxagliptin (SAXA) Add-On Therapy Improves Glycemic Control in Patients (Pts) with Poorly Controlled Type 2 Diabetes (T2D) on Insulin (INS) Alone or INS Combined with Metformin (MET)

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SAXA, a potent, selective dipeptidyl peptidase-4 (DPP-4) inhibitor, was evaluated as add-on therapy in pts with poorly controlled T2D on INS alone or INS combined with MET. In this phase 3b, double-blind trial, adults with A1c 7.5-11% on stable baseline therapy (INS 30-150 U/d ± MET) for ≥8 wk at screening were stratified by MET use and randomly assigned 2:1 to receive SAXA 5 mg or placebo (PBO) once daily for 24 wk. During the study, pts were advised to maintain stable INS doses, but these could be decreased to reduce risk of hypoglycemia. Pts with hyperglycemia or with substantially increased INS had a rescue visit and remained in the study on a flexible INS regimen. MET dose could not be changed. The primary efficacy endpoint was change in A1c from baseline to wk 24 (or rescue). Pts (n=455, 68% with MET use) had a mean age of 57 y, mean T2D duration of 12 y, and mean baseline A1c of 8.7%. Baseline characteristics were balanced between groups. At wk 24, SAXA significantly reduced A1c, postprandial glucose (PPG) AUC, and 120-min PPG, and numerically reduced fasting plasma glucose (FPG), from baseline compared with PBO (Table). The difference in adjusted mean A1c change for SAXA compared with PBO was similar, regardless of MET treatment. Hypoglycemia was reported in 18.4% and 19.9% of pts in the SAXA and PBO groups, respectively (confirmed hypoglycemia: 5.3%, 3.3%). Adverse events reported in ≥5.0% of pts were urinary tract infection (SAXA, PBO: 5.9%, 6.0%), influenza (3.0%, 6.6%), and pain in extremity (1.6%, 6.0%). In summary, SAXA 5-mg add-on therapy improves glycemic control in T2D pts on INS alone or INS combined with MET and is generally safe and well tolerated.

Adjusted Mean Change From Baseline at Wk 24 (LOCF)

Endpoint	SAXA 5 mg + INS n = 304	PBO + INS n = 151
A1c, % (SE)	-0.73 (0.054)*	-0.32 (0.074)
PPG AUC, mg*min/dL (SE)	-4549 (687.7)†	-719 (981.6)
120-min PPG, mg/dL (SE)	-27.2 (4.35)‡	-4.2 (6.08)
FPG, mg/dL (SE)	-10.1 (2.87)	-6.1 (3.98)

*Δ = -0.41%, *P* <.0001
†Δ = -3830 mg*min/dL, *P* =.0011
‡Δ = -23.0 mg/dL, *P* =.0016

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Guided Audio Tour poster ADA-Funded Research

1109-P

Saxagliptin (SAXA) vs Glipizide (GLIP) as Add-On Therapy to Metformin (MET) for Type 2 Diabetes (T2D): Assessment of HbA_{1c}, Hypoglycemia, and Weight Gain

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Hypoglycemia and weight gain are known risks of sulfonylurea therapy and impediments to safe and effective T2D management. SAXA, a selective DPP-4 inhibitor, has a low incidence of hypoglycemia and is weight-neutral. In a multicenter, randomized, double-blind study, adults with HbA_{1c} 6.5–10% were given SAXA 5 mg/d (n=428) or GLIP titrated from 5-20 mg/d (n=430) as add-on to MET for 52 wks. The proportion of patients with adverse events (excluding hypoglycemia) in the 2 treatment groups was similar. A post hoc analysis of this head-to-head study examined: 1) the difference in the frequency of hypoglycemic events between the SAXA and GLIP groups by baseline HbA_{1c} categorical groupings; 2) the proportion of patients with baseline HbA_{1c} 7–8.5% achieving HbA_{1c} levels <7% without hypoglycemia and; 3) the proportion of patients achieving either HbA_{1c} levels <7% (excluding patients with baseline HbA_{1c} <7%) or HbA_{1c} reductions ≥0.5% without hypoglycemia or weight gain. More GLIP-treated patients experienced hypoglycemic events (36.3% vs. 3.0%). In a Kaplan-Meier analysis, the difference between the proportion of hypoglycemic events in the SAXA and GLIP groups increased the closer baseline HbA_{1c} was to 7%. The addition of SAXA to MET in patients with baseline HbA_{1c} 7–8.5% resulted in more patients achieving HbA_{1c} <7% without hypoglycemia compared to the addition of GLIP (Table). More patients treated with SAXA vs GLIP achieved HbA_{1c} <7% without hypoglycemia or weight gain. More patients also achieved HbA_{1c} reductions ≥0.5% without these side effects (Table). When compared to GLIP therapy, addition of SAXA to MET results in more patients achieving HbA_{1c} targets without hypoglycemia and weight gain.

Parameter (last observation carried forward)	SAXA 5 mg+MET, n/N (%)	GLIP+MET, n/N (%)
Baseline HbA_{1c} 7–8.5%, (N)	252	257
Achieving HbA_{1c} <7% without hypoglycemia	124/252 (49)	85/257 (33)
Baseline HbA_{1c} ≥7% (N)	323	320
Achieving HbA_{1c} <7% without hypoglycemia or weight gain	86/323 (27)	44/320 (14)
HbA_{1c} reductions ≥0.5% (N)	422	423
Achieving HbA_{1c} reductions ≥0.5% without hypoglycemia or weight gain	140/422 (33)	62/423 (15)

1110-P

Saxagliptin vs Glipizide as Add-On Therapy to Metformin for Type 2 Diabetes Mellitus (T2DM): Long-Term Safety and Efficacy

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This multicenter, randomized, double-blind study compared the long-term safety, tolerability, and efficacy of saxagliptin (SAXA), a selective DPP-4 inhibitor, vs glipizide (GLIP) when given as add-on therapy to metformin (MET) in adults with T2D. Adults with HbA_{1c} >6.5-10% (on stable MET ≥1500 mg/d) were randomly assigned to SAXA 5 mg/d (n=428) or GLIP titrated from 5-20 mg/d (mean dose 15 mg/d; n=430) for 52 weeks, followed by a 52-week long-term extension phase. Baseline mean HbA_{1c} was 7.7% in both groups and 36% of patients (n=312) completed the full 104 weeks of treatment. SAXA plus MET was well-tolerated; 67% vs 73% of patients had ≥1 adverse event (AE) and few patients (5% vs 6%) discontinued due to AEs for SAXA vs GLIP, respectively. Most common adverse events (≥5% in any group) were nasopharyngitis, upper respiratory tract infection, diarrhea, bronchitis, back pain, and hypertension. Assessment at 104 weeks showed that SAXA was similar to GLIP in lowering HbA_{1c} when added to MET. In the repeated measures analysis, adjusted mean change from baseline HbA_{1c} was -0.4% in both groups; the between-group difference was 0.0% (95% CI: -0.2 to 0.1). Similar mean reductions were also seen in fasting plasma glucose (FPG) at 104 weeks. SAXA treatment resulted in a lower proportion of patients with hypoglycemia (3.5% vs 38.4% with GLIP; 95% CI for difference: -39.8% to -30.0%) or with symptomatic confirmed hypoglycemia (finger-stick blood glucose ≤50 mg/dL; 0% vs 9.1% with GLIP; 95% CI for difference: -12.2% to -6.6%). There also was a divergent impact on body weight (mean change from baseline [repeated measures] -1.5 kg with SAXA vs 1.3 kg with GLIP; 95% CI for mean difference: -3.3 to -2.2) and a smaller rise in HbA_{1c} from week 24 to week 104 (adjusted mean change, 0.004% vs 0.008% with GLIP; 95% CI for mean difference: -0.005% to -0.002%). In conclusion, this long-term study of SAXA added to MET demonstrated similar reductions in glycemic parameters (HbA_{1c} and FPG) with a lower risk of hypoglycemia and otherwise similar safety profile, reduced body weight, and a smaller rise in HbA_{1c} over time compared with GLIP added to MET.

1111-P

Short Term Continuous Subcuntaneous Insulin Infusion in Patients with Newly Diagnosed Type 2 Diabetes Mellitus May Delay the Natural Progression of Diabetes

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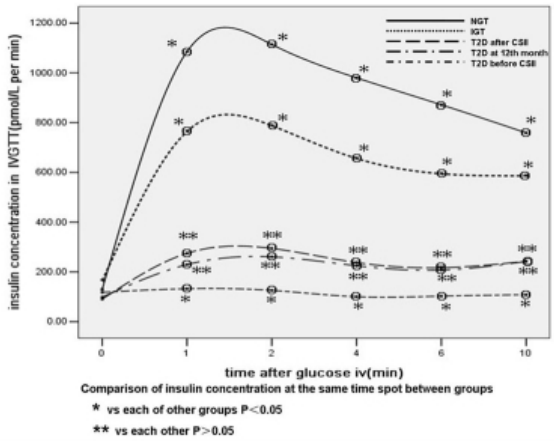
Acute insulin response (AIR) declines as patients progress from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) and ultimately to type 2 diabetes mellitus (T2DM). Our previous studies showed that intensive insulin therapy by continuous subcuntaneous insulin infusion (CSII) induced 12-month euglycemia without hypoglycemic medication in drug naïve patients with newly diagnosed T2DM. This study aimed to explore the extent of restoration of AIR in patients with newly diagnosed T2DM after short term CSII and at 1-year follow-up.

We enrolled 64 NGT volunteers, 67 IGT patients and 40 newly diagnosed T2DM patients who had received 2-week CSII therapy once diagnosed, maintained euglycemia (defined as fasting blood glucose<7.0mmol/L and 2-h postprandial blood glucose<10.0mmol/L) for 12 months with only lifestyle intervention without hypoglycemic medication. Intravenous glucose tolerance test was performed at baseline in all participants and was done immediately after and at 12th month since CSII in T2DM patients. AIR measurements were calculated and compared between groups.

AIR value(pmol/L per min) were 7604(interquatile range(IQR)3380), 4693 (IQR 3219), -53(IQR 346),

1283(IQR 847) and 1466(IQR 1407) in NGT, IGT, T2DM before CSII, T2DM after CSII and T2DM at 12th month, respectively. Differences were statistically significant between each 2 groups except for that between T2DM after CSII and T2DM at 12th month (all P<0.05). AIR lines were shown in attached figure.

Our study indicated that short term CSII therapy in newly diagnosed T2DM maybe delayed the natural progression of T2DM, pulling them back towards IGT stage. AIR restoration and its maintenance may be responsible for long term euglycemia without medication in these patients.



1112-P

Significantly Decreased Risk of Cancer in Patients with Diabetes Mellitus on Metformin: *A Systematic Review and Meta-Analysis*

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Several meta-analyses have shown that diabetes mellitus affects the risk of cancer incidence and mortality, and metformin reportedly reduces the risk. We performed a search of MEDLINE and the Cochrane Library for pertinent articles as of January 7, 2011, and included them for a qualitative review and a meta-analysis to analyze the risk of incidence and mortality of all cancer in diabetic subjects who are taking metformin.

Among diabetic subjects (n=71,851) in 3 cohort studies and 2 case-control studies, 3,184 cancer cases were reported (4.1% incidence in cohort studies). The cancer mortality was 4.5% among diabetic patients (n=19,832) in 3 cohort studies. The pooled adjusted risk ratio (RR) of cancer incidence was significantly lower (RR, 0.58; 95%CI, 0.45 - 0.76) for metformin users.

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Metformin was also associated with significantly decreased RR of mortality across all cancer types (RR, 0.67; CI, 0.51 - 0.87).

Our analysis suggests that metformin use is associated with lower cancer risk. Since diabetes increases the risk of cancer, its prevention should be an important component of clinical management and our findings would point to an additional effectiveness of metformin as the first-line therapy for diabetes.

Supported by: Japan Ministry of Health, Labour and Welfare and Japan Diabetes Foundation

1113-P

Sitagliptin Added to Ongoing Metformin Therapy in Chinese Patients with Type 2 Diabetes Significantly Enhances Glycemic Control

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Addition of the DPP-4 inhibitor sitagliptin to metformin was shown previously in non-Chinese patients with type 2 diabetes (T2DM) to significantly improve glycemic control and to be well tolerated. The aim of the present study was to assess the efficacy and tolerability of sitagliptin added to ongoing metformin therapy (1000 or 1700 mg/day) in Chinese patients with T2DM and inadequate glycemic control (A1C $\geq$7.5% and $\leq$11%). After a metformin titration/stabilization period and a 2-wk, single-blind, placebo run-in period, 395 patients ages 25-77 yr (mean baseline A1C=8.5%) were randomized in a 1:1 ratio to receive the double-blind addition of either placebo or sitagliptin 100 mg qd to ongoing open-label metformin for 24 wk. The efficacy analysis was based on all patients with available baseline and treatment period data employing ANCOVA and the LOCF method for imputing missing values. After 24 wk, addition of sitagliptin to ongoing metformin therapy led to significant ($p<0.001$) reductions from baseline in A1C (0.82%), fasting plasma glucose (FPG) (14.4 mg/dL), and 2-hr postmeal plasma glucose (34.9 mg/dL) relative to placebo. The placebo-adjusted reductions from baseline in A1C in the sitagliptin treatment group at 24 wk were 0.8% and 0.9% for patients on metformin 1000 and 1700 mg/day, respectively ($p<0.001$ for both groups). Change from baseline in A1C and FPG reached a nadir at Wk 18 and Wk 6, respectively, and subsequently remained stable through the 24-wk treatment period. Sitagliptin was generally well tolerated, with no statistically significant differences in the incidences of hypoglycemia or gastrointestinal adverse events compared with placebo. Sitagliptin had no effect on change in body weight from baseline; however, a small mean decrease was observed with placebo (0.5 kg; $p=0.018$). In this 24-wk study in Chinese patients with T2DM and inadequate glycemic control on metformin alone, the addition of sitagliptin 100 mg qd to ongoing metformin therapy led to significant improvements in glycemic control and was well tolerated.

1114-P

Sitagliptin Exerts an Anti-Inflammatory Effect

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Sitagliptin is an inhibitor of the enzyme dipeptidyl peptidase-IV (DPP-IV), which degrades the incretins, GLP-1 and GIP, and thus increases their bio-availability. The stimulation of insulin and the suppression of glucagon secretion that follow exert a glucose lowering effect and hence its use as an anti-diabetic drug.

Since DPP-IV is expressed as CD26 on cell membranes and since CD26 mediates pro-inflammatory signals, we hypothesized that sitagliptin may exert an anti-inflammatory effect. Twenty two patients with type 2 diabetes were randomized to receive either 100 mg daily of sitagliptin (n=12, mean age: 54.4±4 years; mean BMI: 34.8±1.3kg/m^2; mean HbA1c:7.6±0.1%) or placebo (n=10, mean age: 55.7±4.5 years; mean BMI: 35.1±1.5kg/m^2; mean HbA1c:7.9±0.3%) for 12 weeks. Fasting blood samples were obtained at 0, 2, 4, 8 and 12 weeks. There was no significant change in fasting blood glucose concentrations while HbA1c fell significantly from 7.6±0.1% to 6.9±0.3% in patients treated with sitagliptin. Fasting GLP-1 concentrations increased significantly by 63±20% (from 9.1±2.8 to 15.8±4.0pM) following sitagliptin treatment. In addition, the mRNA expression in MNC of the pro-inflammatory cytokine, TNFα, the receptor for endotoxin,TLR-4, and pro-inflammatory kinases, JNK-1 and IKKβ fell by 39±10%, 23±11%, 19±8% and 17±9%, respectively, while that of the chemokine receptor CCR-2 fell by 24±8% ($P<0.05$, all). This was accompanied by a significant fall of plasma concentrations of CRP, IL-6 and free fatty acids by 24±7%, 24±8% and 19±11%, respectively ($P<0.05$, all). In addition, the expression of CD26 in MNC was suppressed by 23±7% following sitagliptin treatment. While these effects are consistent with a potent anti-inflammatory effect of sitagliptin and may potentially contribute to the inhibition of atherosclerosis, the suppression of CD26 expression is surprising since we recognize sitagliptin as an inhibitor of DPP-IV action but not its production. We conclude that sitagliptin exerts a potentially beneficial anti-inflammatory effect. Its relationship to CD26 and DPP-IV requires further investigation.

Supported by: NIH

ADA-Funded Research

1115-P

Study of Once-Daily Levemir (SOLVE™) 1: Clinical Inertia in People with Type 2 Diabetes Being Initiated on Insulin Therapy in Real-Life Clinical Practice

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SOLVE is a 24-week international cohort study involving 10 countries evaluating the safety and effectiveness of once-daily insulin detemir in insulin naive people with T2DM treated with one or more oral antidiabetic drugs (OADs). Recently published guidelines encourage the earlier use of insulin, and continued targeting of HbA1c values <7.0%. Cross-sectional baseline data from the interim analysis provides insights into the timing of insulin initiation in real-life clinical practice in relation to recommended glycemic goals.

Enrolled participants (n=12,989) had a mean age 61 ± 11 years, 53% male, and T2DM duration 9.9 ± 7.0 years. Prior to the initiation of once-daily insulin detemir, mean HbA1c was 9.0 ± 1.6%, with 45% having an HbA1c ≥ 9.0%, and 25% ≥ 10.0%. Mean pre-insulin HbA1c was highest in Turkey (9.8 ±1.8%), UK (9.7 ± 1.7%), Israel (9.3 ± 1.6%), and Italy (9.2 ± 1.5%); and lowest in China (8.2 ± 1.8%), Poland (8.4 ± 1.2%), Spain (8.8 ± 1.4%), and Canada (8.9 ± 1.6%). The mean pre-insulin FBG of the total cohort was 191 ± 59 mg/dl.; with substantial differences between countries ranging from 233 ± 77 mg/dl (Turkey) to 159 ± 36 mg/dl (Poland). Only 14% of participants initiating insulin therapy had HbA1c levels of < 7.5%. The proportion of patients with HbA1c ≥ 9.0% ranged from 54% (Israel) to 23% (Poland). Prior to insulin initiation, patients had received OAD therapy for mean 8.7 ± 6.7 years. Biguanides and sulphonylureas were the most commonly prescribed oral agents in all participating countries. Mean starting dose of insulin detemir for the total cohort was 0.16 ± 0.09 IU/kg, ranging from 0.10 IU/kg (UK) to 0.21 IU/kg (Spain).

Despite consensus guidelines, there is considerable clinical inertia with respect to initiating appropriate insulin therapy, with nearly 50% of patients having HbA1c > 9.0%. SOLVE underlines the importance of understanding practice habits, identifying regional and global barriers to care with the ultimate goal of appropriately intensifying therapy and achieving glycemic control earlier in the course of T2DM in the real world setting.

Supported by: Novo Nordisk A/S

1116-P

Successful Use of Omalizumab in an Inadequately Controlled Type 2 Diabetic Patient with Severe Insulin Allergy

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In a patient with severe systemic IgE-mediated insulin allergy not responding to desensitization therapy alone, we tested whether additional treatment with omalizumab (Xolair), a monoclonal antibody against IgE, is favourable in respect to allergic symptoms.

A 62-year old patient with type 2 diabetes for 16 years developed a severe anaphylactic shock upon i.v. administration of insulin. The patient's medical history comprised allergic reactions to an unknown agent as a child. The diagnostic work-up revealed a type 1 IgE-mediated insulin allergy by positive skin-prick tests and highly elevated insulin-specific IgE levels by ImmunoCAP-Assay. Because of unsatisfactory glycemic control, a specific desensitization and maintenance therapy with Levemir was performed, which led only to a transient improvement of allergic symptoms. Based on body weight and total serum IgE-levels, i.m. treatment with omalizumab was started (300mg) every four weeks and desensitization repeated 6 months after initiation of omalizumab. Under this regime, allergic symptoms disappeared completely. Insulin doses could be increased without reappearance of allergic symptoms and glycaemia improved. We tapered omalizumab according to allergic symptoms; currently a dose of 300mg every 8 weeks allows full control of the allergic symptoms.

For author disclosure information, see page 785.

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Insulin allergy is a very rare adverse reaction to insulin. As normoglycemia is not always reached under oral antidiabetic medication alone, desensitization therapy is an attractive way to treat patients with disabling allergic symptoms. Unfortunately, drug desensitization is not always successful. Our report describes for the first time that patients with severe IgE-mediated insulin allergy can be treated with omalizumab enabling the use of exogenous insulin.

1117-P

Switching from Exenatide to Liraglutide Increases the Proportion of Patients Achieving A1c Targets

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The once-daily glucagon-like peptide-1 (GLP-1) analog liraglutide provides glycemic control with weight loss and low risk of hypoglycemia in a substantial number of patients. In the 26-week LEAD-6 trial, liraglutide provided greater A1c reduction than twice-daily exenatide (both with metformin and/or sulfonylurea). After 26 weeks, patients (n=389) entered a 14-week extension, where all patients used liraglutide 1.8 mg daily. Switching to liraglutide further improved A1c, HOMA-B, bodyweight, and SBP. There was also an increase in the proportion achieving glycemic control: from 45 to 58% for ADA A1C target (<7%), and from 24 to 41% for AACE target (≤6.5%). Post hoc analysis based on response to exenatide provides further insight into benefits of liraglutide. Of patients who reached ADA target with exenatide, 89% remained at target with liraglutide, with a further 0.3% mean reduction in A1c. Of patients who failed to reach ADA target with exenatide, 32% were subsequently able to reach target with liraglutide, with mean 0.8% further reduction in A1c. For AACE A1c target, 93% of patients reaching target with exenatide remained at target with liraglutide, with a further mean A1c reduction of 0.3%. Of patients who failed to reach target with exenatide, 25% subsequently reached target with liraglutide, with 0.7% A1c reduction. In conclusion, some patients who respond inadequately to exenatide may benefit from switch to liraglutide. Patients who respond well to exenatide can also further benefit from the once-daily liraglutide regimen with improvements in glycemic control.

	Patients at target after switch to liraglutide			Patients not at target after switch to liraglutide		
After exenatide treatment (n=182)	**% of patients (n)**	**A1c change, %; ±SD**	**A1c change, min; max**	**% of patients (n)**	**A1c change, %; ±SD**	**A1c change, min; max**
ADA (<7%)						
Patients at target; 45% (n=82)	89 (73)	-0.3±0.4	-1.1;0.5	11 (9)	0.5±0.1	0.3;0.7
Patients not at target; 55% (n=100)	32 (32)	-0.8±0.5	-2.1;-0.1	68 (68)	-0.2±0.7	-2.1;1.7
AACE (≤6.5%)						
Patients at target; 24% (n=42)	93 (39)	-0.3±0.4	-1.1;0.4	7 (3)	0.3±0.2	0.1 ;0.5
Patients not at target; 76% (n=140)	25 (35)	-0.7±0.4	-2.1;-0.1	75 (105)	-0.2±0.6	-2.1;1.7

1118-P

Switching from Sitagliptin to Liraglutide, in Combination with Metformin, Improves Treatment Satisfaction in Patients with Type 2 Diabetes

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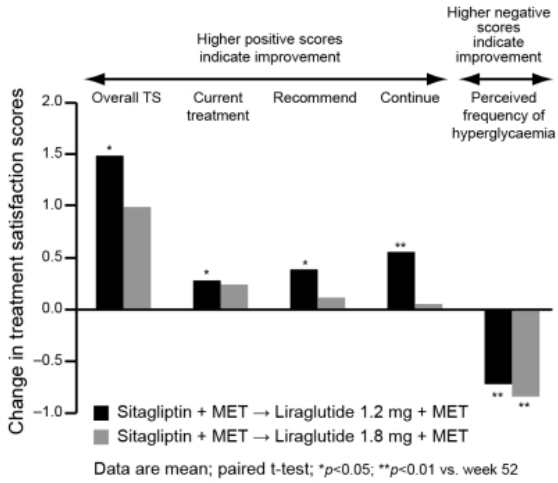
Previously, we have shown that 1-year treatment with liraglutide (LIRA) 1.2 mg or 1.8 mg OD led to superior glycemic control and weight loss vs sitaglipin (SITA) 100 mg OD, both added to metformin (MET) ≥1500 mg. During a 26-week extension period patients treated with SITA randomly switched to LIRA 1.2 or 1.8 mg, resulting in further A1c reductions and weight loss (A1c: -0.24%, -0.45%; weight: -1.6 kg, -2.5 kg for SITA→LIRA 1.2 and 1.8 mg, respectively). Treatment satisfaction (TS) was evaluated using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at 52 and 78 weeks (SITA→LIRA 1.2 mg, n=54; SITA→LIRA 1.8 mg, n=48) to assess the impact of switching from an oral therapy to an injectable one. Overall TS was calculated by adding satisfaction scores for 'current treatment', 'convenience', 'flexibility', 'understanding', 'recommend', and 'continue'. Higher scores indicated improved TS. For evaluation of perceived frequency of hyper- and hypoglycemia, lower scores indicate improvement. Changes in TS scores were analyzed by paired *t*-test. Overall TS improved in both groups of subjects who switched from SITA to LIRA (Figure) and was driven largely by the categories 'recommend' and 'continue'; no statistical difference was observed between LIRA 1.2 mg and 1.8 mg after the switch. 'Convenience', 'flexibility', 'understanding' and 'perceived hypoglycemia' were unchanged after switching from oral to injectable treatment. Thus, the switch from an oral therapy to an injectable did not negatively affect treatment satisfaction; on the contrary patients who switched to LIRA had an increase in overall TS (significant for 1.2 mg). The greater treatment satisfaction with liraglutide may be facilitated by weight loss and the improved treatment efficacy or perception thereof.

Figure: Change in mean TS scores from Week 52 to Week 78 for patients switching from sitagliptin to liraglutide



Data are mean; paired t-test; *p<0.05; **p<0.01 vs. week 52

1119-P

Switching from the DPP-4 Inhibitor Sitagliptin to the Human GLP-1 Analog Liraglutide Further Improves Glycemic Control and Weight Loss in Patients with Type 2 Diabetes

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In patients with T2D using metformin, a 52-week trial showed that the addition of liraglutide (1.2 or 1.8mg/day) produced significantly greater reductions in A1c, fasting plasma glucose (FPG) and bodyweight than the addition of sitagliptin (100mg/day). After 52 weeks, sitagliptin-treated patients were randomized (1:1) to liraglutide 1.2 or 1.8mg (via weekly dose escalation of 0.6mg), while patients originally randomized to liraglutide continued unchanged for another 26 weeks. Of 436 patients completing 52 weeks, 419 (96%) entered the extension and 381/419 (91%) completed 78 weeks. While 52 weeks of sitagliptin reduced baseline A1c by -0.9%, switching to liraglutide further decreased A1c by 0.2–0.5% enabling more subjects to reach A1c<7% (Table). Switching to liraglutide also further significantly reduced FPG and bodyweight. Overall diabetes treatment satisfaction questionnaire scores increased after switching from oral sitagliptin to injectable liraglutide (p=0.017, liraglutide 1.2mg). 78 weeks of continued liraglutide treatment (1.2 mg, 1.8mg) reduced A1c (-0.9, -1.3%), FPG (-1.3, -1.7mmol/L) and weight (-2.6, -3.1kg) from baseline with low rates of minor hypoglycemia (0.156, 0.130 events/patient/yr). One major hypoglycemic event occurred during the extension in a patient originally randomized to liraglutide 1.2mg, while minor hypoglycemia rates remained low. 21% patients in each switch group experienced nausea, which was transient. Switching from sitagliptin to liraglutide increased patient proportions reaching A1c<7.0% from ~30% to ~50% and improved weight, albeit with a transient rise in gastrointestinal reactions.

		Sita→Lira 1.2 N=67	Sita→Lira 1.8 N=68
A1c (Wk 52), %		7.23±0.9	7.6±1.2
ΔWks 52–78 (%)#		-0.2±0.1*	-0.5±0.1**
Patients with A1c<7.0%, %	Wk 52	29.5	29.5
	Wk 78	49.2	50.0
FPG (Wk 52), mmol/L		8.6±1.7	9.2±2.1
ΔWks 52–78 (mmol/L)#		-0.8±0.2**	-1.4±0.3***
Bodyweight (Wk 52), kg		92.8±20.6	91.6±18.7
ΔWks 52–78 (kg)#		-1.6±0.4***	-1.6±0.4***
Minor hypoglycemia (Wks 52–78) Rate, events/patient/yr		0.031	0.060

FAS LOCF; Wk 52: mean±SD; Δ=change, mean±SE; #paired *t*-test; *p<0.01, **p<0.001, ***p<0.0001

1120-P

The Addition of Sitagliptin to Metformin and Pioglitazone Therapy Enhances Glycemic Control in Patients with Type 2 Diabetes

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The efficacy and safety of sitagliptin, a dipeptidyl peptidase-4 inhibitor, were assessed in patients with type 2 diabetes and inadequate glycemic control (A1C ≥7.5% and ≤11%) while on dual combination therapy with metformin (>1500 mg/day) and pioglitazone (≥30 mg/day). After a metformin and pioglitazone titration/stabilization period for up to 14 weeks and a 2-week, single-blind, placebo run-in, 313 patients ages 22-78 years (mean baseline A1C = 8.7%) were randomized (1:1) to receive the addition of placebo or sitagliptin 100 mg q.d. for 26 weeks. After 26 weeks, the addition of sitagliptin led to significant ($p<0.001$) mean reductions relative to placebo in A1C (0.7%), fasting plasma glucose (FPG) (17.5 mg/dL), and 2-hour post-meal plasma glucose (40.0 mg/dL). In the subgroup of patients with baseline A1C ≥9.0%, the mean changes from baseline in A1C were 1.6% and 0.8% for the sitagliptin and placebo groups, respectively ($p<0.001$ for the between-group difference of 0.8%). Sitagliptin was generally well tolerated. The incidences of symptomatic hypoglycemia were 7/157 [4.5%] and 6/156 [3.8%] in the sitagliptin and placebo groups, respectively ($p=0.786$ for the between-group difference). There were no episodes of hypoglycemia requiring medical assistance in the sitagliptin group compared with 2 episodes in the placebo group. Both treatment groups showed small mean increases from baseline in body weight of 1.2 kg at Week 26. In this 26-week study, the addition of sitagliptin 100 mg q.d. to dual combination therapy with metformin and pioglitazone led to significant improvements in glycemic control and was generally well tolerated in patients with type 2 diabetes and inadequate glycemic control.

1121-P

The BeAM Factor: An Easy-to-Determine, Objective, Clinical Indicator for When To Add Prandial Insulin vs Continued Basal Insulin Titration

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In treating T2D, it is often unclear when titration of basal insulin (BI) is maximized and prandial insulin should be added. We propose the adoption of an easily obtained measure to assist with such treatment decisions. Ideally, BI therapy should match hepatic glucose production and maintain a narrow BG range, including overnight. Large differences between Bedtime and AM ("BeAM" factor) BG during treatment suggests that BI may have reached maximal titration and that prandial insulin should be introduced to correct for PPG excursions to help achieve target A1C. BeAM was examined using data pooled from 6 RCTs of insulin glargine (GLA) vs a comparator added to OAD therapy in adults with T2D. Insulin was titrated to achieve FG ≤100 mg/dL. 1699 patients were included; 42% female, 95% white, mean age 59(9) y, A1C 8.7%, and duration of diabetes 9(6) y. BeAM increased over 24 wks of treatment (table). Mean change in BeAM was greater in pts receiving BI (GLA or NPH) vs other treatments (OADs or other insulin, LS mean dif 36.5 mg/dL, $P<0.0001$). Regardless of treatment, patients nearing target FG ≤100 mg/dL had an even greater increase in BeAM; the proportion of patients with BeAM >50mg/dL increased from 27% at baseline to 47% at wk 24. A larger BeAM at wk 24 was associated with reduced likelihood of attaining A1C≤7.0% ($r^2=0.160$ all; $r^2=0.187$ BI; $P<0.0001$ for both) and increased risk of nocturnal ($r^2=0.152$, $P<0.0001$), but not overall, hypoglycemia. Patients on BI with a BeAM >55 mg/dL were less likely to approach A1C ≤7.0%. This analysis suggests that patients on BI with a BeAM factor >55 mg/dL may not benefit from continued BI titration and addition of prandial insulin should be considered to correct glucose excursions and achieve glycemic goals.

BeAM Factor (bedtime BG – morning FG), mean (SD)			
	Baseline, mg/dL	Week 24, mg/dL	Change, mg/dL
All patients (n=1699)	24.6 (55.8)	40.9 (55.1)	16.3 (73.1)
Basal insulin patients (n=1261)	25.3 (57.9)	52.4 (53.3)	27.0 (72.8)
24 week pre-breakfast glucose >80 and <120 mg/dL (n=431)	30.0 (56.2)	58.3 (46.8)	32.3 (68.1)
Relationship of BeAM and A1C at 24 weeks			
	A1C	BeAM Least squares mean (SE)	*P* value difference from <6.5
All patients (n=1699)	<6.5	34.5 (2.65)	—
	≥6.5 to <7.0	41.2 (2.57)	0.0570
	≥7.0 to <7.5	46.0 (2.86)	0.0021
	≥7.5 to <8.0	51.3 (3.46)	<0.0001
	≥8.0	58.9 (3.56)	<0.0001
Basal insulin patients (n=1261)	<6.5	41.8 (3.06)	—
	≥6.5 to <7.0	49.2 (2.95)	0.0685
	≥7.0 to <7.5	54.9 (3.28)	0.0024
	≥7.5 to <8.0	64.1 (4.05)	<0.0001
	≥8.0	69.7 (4.22)	<0.0001

Supported by: sanofi-aventis US

1122-P

The Combination of Colesevelam Plus Sitagliptin Enhances Glycemic Control in a Rat Diabetic Model

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Bile acid sequestrants have been shown to reduce glucose levels in patients with type 2 diabetes. We previously reported that the bile acid sequestrant colesevelam HCl (Welchol) induced the release of GLP-1 and improved glycemic control in insulin-resistant rats. In the present study, we tested whether adding sitagliptin (Januvia), which prolongs bioactive GLP-1 half life, to colesevelam would result in better glycemic control. The type 2 diabetes rat model: male Zucker diabetic fatty (ZDF) rats were assigned to 4 groups: diabetic model without treatment (untreated models); treated with 2% colesevelam (COL) or 0.4% sitagliptin (SIT) alone; or combination of colesevelam and sitagliptin (COL+SIT). All rats were fed Purina diet #5008 without (untreated models) or with the incorporated different medications in the diet.

After 4 wks of treatment, the fasting glucose [prior to oral glucose tolerance test (OGTT)] improved in the COL ($p<0.001$) and COL+SIT ($p<0.001$) groups but not in the SIT group. The glucose area under the curve (AUC) was reduced by 27% ($p<0.05$) and 40% ($p<0.001$) in the COL and COL+SIT groups respectively, compared with the untreated model group. Plasma insulin AUC in the COL and COL+SIT (both $p<0.05$), and bioactive GLP-1 AUC in the COL, SIT, (both $p<0.01$) and COL+SIT ($p<0.001$) groups were increased than the model group.

After 8 wks the glucose AUC was not significantly reduced in either COL or COL+SIT groups compared with untreated model. Increasing only the SIT dose by 50% (0.6% SIT) in the diet did not improve glycemic control in the SIT group but did reduce the glucose AUC in the COL+SIT group at both week 4 and week 8 ($p<0.001$). We hypothesize that combination of colesevelam with sitagliptin extends the half life of the induced bioactive GLP-1 and results in better improvement of glycemic control in the diabetic rat model. This study suggests that combination therapy (COL+SIT) might be complementary for reducing glucose levels in diabetes.

1123-P

The DPP-4 Inhibitor Linagliptin Delays Onset of Diabetes and Preserves Beta-Cell Function in Non-Obese Diabetic NOD Mice

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Recent data indicate that dipeptidyl peptidase (DPP)-4 inhibitors have both anti-inflammatory and beta-cell sparing effects in animal models of type 1 diabetes. Though reduced pancreatic T-cell migration and altered cytokine production are considered important for the onset of type 1 diabetes, the precise mechanism and effects on the pancreatic cell pool are not fully understood. In an attempt to evaluate the effects of the DPP-4 inhibitor linagliptin (LIN) on pancreatic inflammation and beta-cell mass, we examined the progression of diabetes in non-obese-diabetic (NOD) mice over a 60-day period with terminal stereological assessment of cellular

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pancreatic changes. Sixty female NOD mice (10 weeks of age) were included in the study and fed a normal chow diet or a diet containing LIN (0.083 g LIN/kg chow; corresponding to 3–10 mg/kg, po) throughout the study period. Bi-weekly plasma samples were obtained to determine onset of diabetes (blood glucose >11 mmol/l). At termination, the pancreas was removed and a terminal blood sample obtained for assessment of active glucagon-like peptide (GLP)-1 levels. At the end of the study the incidence of diabetes was significantly lower in LIN-treated mice (9 of 30 mice affected) compared with the controls (18 of 30 mice, p=0.021). Beta-cell mass, identified by insulin immunoreactivity, (vehicle 0.18±0.03 mg; LIN 0.48±0.09 mg, p<0.01) and total islet mass (vehicle 0.40±0.04 mg; LIN 0.70 ±0.09 mg, p<0.01) were greater in LIN-treated mice. There was a tendency for LIN to reduce peri-islet infiltrating lymphocytes (vehicle1.06±0.15; LIN 0.79±0.12 mg, p=0.17). As expected, active plasma GLP-1 was higher with LIN at termination. In summary, these data demonstrate that LIN is able to delay the onset of diabetes in the type-1-diabetic NOD mouse. The pronounced beta-cell sparing effects observed indicate that DPP-4 inhibition not only protects beta cells by increasing active GLP-1 levels, but may also exert direct or indirect anti-inflammatory actions.

1124-P

The DPP-4 Inhibitor Linagliptin Increases Active GLP-2 and Decreases Colonic Cytokines in a Mouse Inflammatory Bowel Disease Model

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Recent data support an anti-inflammatory role for dipeptidyl peptidase (DPP)-4 inhibitors in animal models of inflammatory bowel diseases. They may act via T-cell regulation or inhibition of degradation of glucagon-like peptide-2 (GLP-2), which favors proliferation and repair of the colon mucosa. This study investigated the anti-inflammatory effects of linagliptin in a model of acute dextran sulphate sodium DSS-induced colitis in Balb/c mice. Following 9 days' treatment with linagliptin (1 mg/kg and 3 mg/kg, plus DSS, n=9–10), vehicle (+DSS, n=10), or control (–DSS, n=5), hemoccult, stool consistency, clinical score, colon length, cytokine production (TNF-α, INF-γ, IL-6, MCP-1) from colon cultures, as well as systemic DPP-4 activity, and GLP-2 levels were determined. Linagliptin treatment did not significantly alter colon length, histology, hemoccult, or stool consistency; all of which were significantly worsened in vehicle-treated (+DSS) vs control (–DSS) animals. However, clinical scores (the means of the final scores of rectal bleeding, stool consistency, and changes in weight) were significantly decreased (p=0.045) with 3 mg/kg linagliptin. In addition, TNF-α and INF-γ were significantly reduced (p<0.01) with both linagliptin doses, IL-6 was somewhat reduced with the higher dose (p=0.07), but effects on MCP-1 were less pronounced. The 3 mg/kg dose also significantly increased plasma levels of active GLP-2 (89.0±18.5 pg/ml, p=0.0089) vs vehicle (36.3±5.8 pg/ml), accompanied by a reduction of DPP-4 activity (p<0.001), and GLP-2 was undetectable in control animals. In summary, linagliptin significantly reduced pro-inflammatory cytokines, elevated active GLP-2 levels, and reduced clinical changes in DSS-treated animals. However, modulation of the cytokines alone may not be sufficient to protect fully from DSS colitis, which primarily destructs the colonic epithelium. The effects of DPP-4 inhibitors should be explored in a chronic model of colitis with immune-cell- and cytokine-dependent inflammation and tissue destruction.

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1125-P

The Effect of Insulin Detemir on Fat Distribution and Weight Parameters in Overweight and Obese Subjects with Type 2 Diabetes

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A 26-week, multicentre, open-label, randomized, parallel-group trial assessed change in trunk fat mass as measured by double energy X-ray absorptiometry (DEXA) in overweight and obese type 2 diabetes subjects treated with insulin detemir (IDet) or NPH insulin. Patients received once-daily IDet (n=24, mean age 60.6 years, 54.2% male, mean A1C 8.3 %, mean body mass index [BMI] 32.2 kg/m^2, mean waist circumference 107.7 cm) or once-daily NPH insulin (n=35, mean age 63.7 years, 45.7% male, mean A1C 8.3 %, mean BMI 34.0 kg/m^2, mean waist circumference 110.0 cm) with all receiving insulin aspart at main meals. Patients taking oral antidiabetic drugs were excluded, except for those taking metformin, who continued on their existing regimen. At 26 weeks the mean (SD) percentage change in trunk fat mass was -0.38% (10.97) in the IDet group and -0.06% (12.57) in the NPH group (p=0.85). There was no significant difference between IDet (2.59% [12.39]) and NPH (3.09% [8.30]) in terms of mean percentage change of whole-body fat mass. Mean change in body weight was 0.89 kg (4.30) with IDet vs. 1.90 kg (2.79) with NPH (p=0.20). Differences were noted for change in waist circumference at week 8 (-1.05 cm [5.21 SD, IDet group] vs. 1.34 cm [3.67 SD, NPH insulin group], p=0.0173) and week 12 (-0.9 cm [4.90 SD, IDet group] vs. 1.04 cm [3.47 SD, NPH insulin group], p=0.045), but these were not maintained at study end. Mean reductions in A1C from baseline were -0.79 % (1.06) and -0.73 % (1.16) in the IDet and NPH groups respectively (p=ns). Mean number of overall hypoglycemic episodes during the trial was 6.42 (9.45) in the IDet group and 15.31 (20.90) in the NPH insulin group (p=0.02). Mean daily dose for IDet was 0.41 (0.14) U/kg, and for NPH 0.47 (0.17) U/kg. In summary, compared with NPH treatment, IDet resulted in a small reduction of waist circumference, a similar reduction in A1C and fewer episodes of hypoglycemia.

1126-P

The Effect of Liraglutide on Gastric Emptying and Body Weight Is Not Mediated by Vagal Afferents nor the Area Postrema

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Glucagon-Like Peptide-1 (GLP-1) analogs are emerging as important drugs for the treatment of diabetes. Apart from their insulinotropic and glucagonostatic effects GLP-1 analogs also inhibit gastric emptying and reduce food intake and bodyweight. It is still unclear which GLP-1 receptors mediate these effects. GLP-1 receptors are located in several central areas known to be directly involved in energy homeostasis. Since both vagal afferents and area postrema neurons express GLP-1 receptors and are accessible to peripherally circulating GLP-1 we speculated that these receptor populations could mediate the gastric inhibitory and/or the body-weight lowering effects of the once-daily GLP-1 analog liraglutide. The study involved 2 groups of 32 male SPD rats further subdivided into 4 groups (veh sham, lira sham, veh surgery, lira surgery). The surgery groups underwent either a selective vagal deafferentiation (SDA, severed left afferent rootlets coupled with a subdiaphragmatic ablation of the posterior trunk) or an area postrema lesion (APx). After 10 days of recovery the acute effect of liraglutide (0.1 mg/kg, sc) on gastric emptying was assessed using an acetaminophen release assay. Hereafter all animals continued into a 14 days bi-daily dosing study (0.2 mg/kg, sc). Interestingly, neither SDA nor APx affected the ability of liraglutide to inhibit gastric emptying measured as the area under the acetaminophen curve (SDA vehicle 9579±760 vs SDA lira 3587±990 μg/ml*min, p<0.05; APx veh 8263±295 vs APx lira 3269±466 μg/ml*min, p<0.05). Similarly, the chronic dosing study revealed that liraglutide induced weight loss was independent of vagal and area postrema GLP-1 receptors. The completeness of the vagal deafferentiation and AP lesions were verified anatomically and for the vagal deafferentiation functionally as well (lack of CCK induced anorexia). In conclusion, the data shows that neither vagal nor area postrema GLP-1 receptors mediate the gastric or food intake inhibitory effects of liraglutide, and suggest that other (presumably centrally located) GLP-1 receptors are key mediators of liraglutide induced weight loss.

1127-P

The Effect of Renal Impairment on the Pharmacokinetics and Urinary Glucose Excretion of the SGLT2 Inhibitor ASP1941 in Type 2 Diabetes Mellitus Patients

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Sodium-dependent glucose co-transporter 2 (SGLT2) is primarily responsible for the reabsorption of glucose in the renal proximal tubule. ASP1941 is a novel, selective SGLT2 inhibitor that increases urinary glucose excretion (UGE), therefore reducing plasma glucose levels. This study investigated the effect of different degrees of renal impairment (RI) on the pharmacokinetics and UGE of ASP1941 in type 2 diabetes mellitus (T2DM) patients and healthy subjects (HS).

HS and T2DM patients with normal renal function (NRF) (estimated glomerular filtration rate [eGFR] ≥90 mL/min/1.73m^2), and T2DM patients with mild, moderate, or severe RI (eGFR 60–89, 30–59, and 15–29 mL/min/1.73m^2, respectively) received 100 mg ASP1941 as a single oral dose (n=8/group). Plasma concentrations of ASP1941 and its metabolites, UGE, and safety were measured for up to 120 h after dosing.

Mean exposure (AUC_{inf}) of ASP1941 was higher in T2DM patients with RI compared with HS and T2DM patients with NRF. An increased exposure in T2DM patients with moderate and severe RI was also observed for ASP1941 metabolites (all inactive). Mean half-life ($t_{½}$) of ASP1941 was ~20 h in all T2DM patient groups whereas in HS the $t_{½}$ was 15 h. Maximum ASP1941

plasma concentration (C_{max}) was comparable among T2DM groups. Baseline UGE over 20 h (UGE_{20}) was similar between T2DM groups, except for the mild RI group. Among T2DM groups, UGE_{20} after ASP1941 dosing was lower in moderate or severe RI. ASP1941 was well tolerated in all groups. In conclusion, ASP1941 exposure increased by approximately 50% in T2DM patients with moderate and severe RI, whereas $t_{½}$ was similar in all T2DM groups. The UGE after 100 mg ASP1941 was reduced in T2DM patients with moderate or severe RI compared with NRF and mild RI T2DM patients.

Statistic [mean (SD)]	HS	T2DM NRF	T2DM RI		
			Mild	Moderate	Severe
AUC_{inf} (ng.h/mL)	7326 (2037)	8241 (1812)	10506 (3165)	12104 (4906)	12687 (4840)
C_{max} (ng/mL)	1277 (360)	1456 (156)	1626 (417)	1448 (420)	1576 (404)
Baseline UGE_{20} (mmol)	0.9 (1.4)	6.2 (15.1)	19.8 (43.6)	5.9 (9.1)	9.0 (16.4)
UGE_{20} (mmol)	243 (100)	271 (108)	361 (200)	124 (94)	67 (49)

1128-P

The Effect of the Human GLP-1 Analogue Liraglutide on 24-Hour Glycemic Variations in Japanese Type 2 Diabetic, Obese Patients as Assessed by Continuous Glucose Monitoring (CGM)

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Liraglutide has been assessed for its efficacy in HbA1c lowering, but not specifically for its effect on 24-hour glycemic variations.

A total of 10 type 2 diabetic, obese patients hospitalized for glycemic control (mean age, 63.3 ± 14.0 years; males/females, 9/1; mean BMI, 32.4 ± 4.7 kg/m^2; HbA1c level, 7.6 ± 1.4% [JDS value]; urinary C-peptide level, 76.0 ± 46.8 μg/day) were given liraglutide, once stable glycemic control was achieved with diet and exercise therapy after admission. The patients were monitored by CGM for 24-hour glucose levels at baseline and during each period when liraglutide was given at a dose of 0.3 mg, 0.6 mg or 0.9 mg/day, respectively.

The mean 24-hour glucose level (mg/dl) at baseline and during each liraglutide treatment was 192.0 ± 54.4, 168.8 ± 54.4 ($P < 0.05$), 135.8 ± 39.6 ($P < 0.05$), 122.7 ± 39.7 ($P < 0.01$), respectively, demonstrating a significant decrease in glucose levels even with the 0.3 mg dose. The SD (mg/dl) of the 24-hour glucose levels at baseline and during each period of liraglutide treatment was 35.2 ± 15.9, 37.4 ± 14.9, 27.7 ± 18.3, 18.2 ± 11.9 ($P < 0.05$), with the total area for glycemic variation (mg·hr/dl) being 726.3 ± 370.8, 758.9 ± 316.8, 556.3 ± 392.4, and 351.6 ± 241.5 ($P < 0.05$) and the MAGE (mg/dl) being 81.9 ± 37.1, 89.8 ± 47.4, 70.0 ± 30.3, 48.3 ± 30.3 ($P < 0.05$), demonstrating dose-dependent decreases in these parameters, which, however, became signifincant with the 0.9 mg dose alone. The percentage of time in hyperglycemia(>180 mg/dl) at baseline and during each liraglutide treatment was 48.6 ± 44.1, 41.5 ± 40.3, 20.9 ± 27.4, and 8.2 ± 13.3, demonstrating a tendency for dose-dependent decreases in hyperglycemic episodes.

Liraglutide decreased not only the mean glucose level as equivalent to the HbA1c value but also the glycemic variations; while decreases in the mean glucose level became apparent with the 0.3 mg dose and gradually became more accentuated with greater doses, improvements in the parameters for glycemic variation became noticeable only with greater doses.

1129-P

The Efficacy and Safety of a Novel Injectable Cr-Insulin Formulation for the Treatment of Type 1 Diabetes

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This experiment was conducted to test the efficacy and safety of chromium-insulin (Cr-Ins) in the treatment of type-1 diabetes. Forty-two Wistar rats were assigned to one of 6 experimental groups: 1) healthy control: rats injected with saline 2) type-1 diabetes group: rats injected with streptozotocin (STZ, 65 mg/kg i.p.) to damage beta cells (n=35). Diabetic rats were then injected with a) no treatment, b) Zn alone (5 mcg Zn as ZnO), c) Cr alone (3.98 mcg Cr as Cr-histidinate), d) Zn-insulin (ZnO + 3 IU Ins/100 g BW), or e) Cr-insulin (Cr-histidinate + 3 IU Ins/100 g BW), daily for 26 days (n=7 per subgroup). Body weights were measured at the beginning and end of the experiment. Blood samples were collected on day -2 (beginning), 0 (STZ induction), and 4, 6, 12, and 26 for blood biochemistry. At the end of the experiment, rats were sacrificed for brain tissue GLUT 1 and 3 analyses. Data were analyzed using one-way ANOVA with LSD option for mean comparison. Body weight at the beginning of the experiment was not different across the groups. However, diabetic rats at the end of the experiment lost body weight as compared to the control rats. Diabetic rats treated with Zn-Ins and Cr-Ins lost less body weight than untreated diabetic rats. Diabetes induction was associated with decreased serum insulin and total protein, and CK levels, and increased serum glucose, urea, creatinine, and K levels, as well as AST, ALT, ALP and LDH activities. The ability of Cr-Ins to restore metabolic profile was equivalent or superior to Zn-Ins. During the experiment, injecting Cr-Ins was more effective in reducing elevated serum glucose levels than Zn-Ins. Brain GLUT 1 and 3 expressions were depressed by diabetes induction. Cr-Ins treatment was superior to other treatments in restoring cerebral GLUT expression. In conclusion, it appears that Cr-Ins is an efficacious treatment of STZ-induced type 1 diabetes, and superior to Zn-Ins in decreasing elevated blood glucose levels and restoring metabolic profiles through a dual effect of the Cr-histidinate and exogenous insulin, possibly a result of potentiated insulin action and enhanced internalization of glucose.

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1130-P

The Impact of Glucose Variability on Achievement of Glycemic Control and Risk of Hypoglycemia in Patients with Type 2 Diabetes (T2D)

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Glucose variability (GV) has been proposed as a predictor of clinical outcomes in patients with T2D. The impact of GV on glycemic control and hypoglycemia during treatment intensification is unknown. We pooled data from 6 randomized controlled clinical trials of insulin glargine (GLAR) vs a comparator (oral agents/other insulins) to determine changes in GV during a treat-to-target (FPG ≤100mg/dL) protocol and to explore the relationships among baseline GV, age, A1C, and hypoglycemia. GV was calculated from 7-point glucose profiles using standard deviation (SD) and mean amplitude of glycemic excursions (MAGE). Complete data were available at baseline and 24 weeks for 1699 pts (1026 GLAR, 673 comparator); 43% female, 95% white, mean age 59(9) yrs and duration of T2D 9(6) yrs. Mean A1C was reduced from 8.7(.95)% to 7.0(.91)% and FPG from 194(48)mg/dL to 125(38) mg/dL. GV was significantly reduced on trial in the entire cohort irrespective of treatment type (Table); younger pts (<65 yrs) experienced twice the reduction of older pts. Pts who failed to achieve A1C ≤7.0% had modestly higher baseline GV than those who reached goal. Pts who experienced ≥1 symptomatic hypoglycemic event during the study had modestly higher baseline GV than those with no hypoglycemia. Comparable associations of GV, A1C, and hypoglycemia were observed when GLAR pts were analyzed separately. Our post-hoc analysis shows a significant decrease in GV during therapy with a variety of antihyperglycemic agents, including insulin glargine, and suggests that T2D pts with elevated GV at baseline are at increased risk for hypoglycemic events and greater likelihood of failing to reach A1C ≤7.0%. Improved understanding of these relationships may lead to better treatment strategies for T2D.

Glucose Variability		
	Change from baseline, mean (SD)	*P* value
All patients (N=1699)		
SD	-4.21 (20.2)	<0.001
MAGE	-7.44 (33.2)	<0.001
GLAR (n=1026)		
SD	-3.1 (19.4)	<0.001
MAGE	-5.7 (31.3)	<0.001
Relationship to age		
SD		
Patients <65 yrs (n=1190)	-4.99 (21.1)	*P* (difference) < 0.01
Patients ≥65 yrs (n=509)	-2.40 (17.9)	
MAGE		
Patients <65 yrs (n=1190)	-8.77 (34.5)	*P* (difference) < 0.02
Patients ≥65 yrs (n=509)	-4.95 (29.5)	

Relationship of Baseline GV & A1C at 24 Weeks			
	Baseline GV, mean (SD)		LS means* for difference (*P* value)
	A1C ≤7.0% N=949	A1C >7.0% n=750	
All patients (N=1699)			
SD	42.4 (16.8)	44.5 (18.6)	-2.74 (P <0.001)
MAGE	61.7 (27.0)	64.9 (31.1)	-4.57 (P <0.001)
GLAR (n=1026)			
SD	41.7 (17.1)	43.0 (17.2)	-2.35 (P <0.03)
MAGE	60.4 (26.9)	62.5 (27.8)	-3.77 (P <0.03)

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Relationship of Baseline GV & On-Trial Hypoglycemia			
	Baseline GV, mean (SD)		LS means* for difference (*P* value)
All patients (N=1699)	≥1 hypo event, n=1035	No hypo, n=663	
SD	45.8 (18.2)	39.2 (15.8)	4.36 (*P* <0.001)
MAGE	66.6 (30.5)	57.6 (25.4)	5.38 (*P* <0.001)
GLAR (n=1026)	≥1 hypo event, n=562	No hypo, n=464	
SD	45.8 (17.6)	37.9 (15.6)	5.05 (*P* <0.001)
MAGE	66.0 (28.0)	55.7 (25.3)	6.00 (*P* <0.001)
*means adjusted for study			

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1131-P

The Impact of Insulin Use on Adherence to Oral Hypoglycemic Agents

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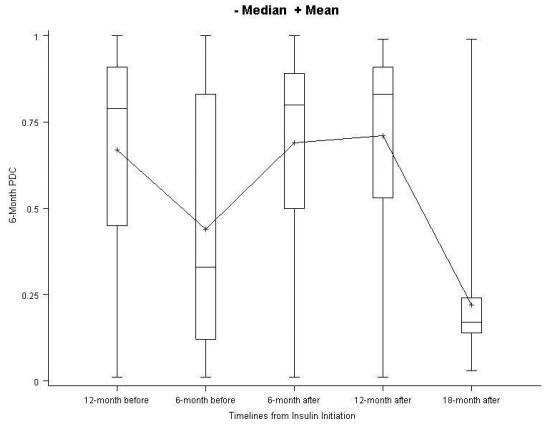
We investigated the effect of insulin use by patients with type 2 diabetes (DM2) on adherence to co-prescribed oral hypoglycemic agents (OHA). A retrospective study for the Indiana Medicaid population from January, 2001 through December, 2008 was conducted. Subjects were 18 years or older, with at least 6 months OHA therapy prior to insulin treatment, and were prescribed the same number of OHAs afterwards. OHA adherence was measured by the proportion of days covered (PDC) in each 6-month interval for one year before insulin treatment and 18 months thereafter. The OHA 6-month PDC right before and after insulin initiation was specifically analyzed for each patient. There were 8,035 subjects: 4,420 on basal insulin (69% female, mean age of commencing insulin 59 years) and 3,615 on mealtime insulin (68% female, mean age of commencing insulin 66 years). The mean duration of first time dispensing OHA to insulin initiation was 1.05 years (range 0.5-6.4 years). The mean OHA 6-month PDCs were 64% and 44% for the first and second half-year prior to insulin initiation, respectively. Since insulin initiation, the mean OHA 6-month PDCs were 69%, 71%, and 21% after 6, 12 and 18 months, respectively.



In an unadjusted mixed effects linear regression analysis, OHA 6-month PDC was significantly higher when insulin was used (β=0.24, 95% CI: 0.05-0.23; P<0.0001). Adjusting other factors, the coefficient between insulin use and OHA 6-month PDC was 0.20 (95% CI: 0.19-0.21; P<0.0001). Other factors, that significantly, yet slightly affected OHA adherence, were age (0.03, P<0.0001), African-American (-0.07, P<0.0001), and basal insulin (0.03, P<0.0001). In conclusion, OHA adherence was increased around 20% after insulin initiation among the Indiana Medicaid DM2 patients. However, this improvement was not sustained after one year.

1132-P

The Novel GPR119-Receptor Agonist PSN821 Stimulates Basal and Nutrient-Induced GIP, GLP-1 and PYY Secretion from Rat Small Intestine

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GPR119, a GPCR localised in pancreatic β-cells and enteroendocrine cells, is implicated in the regulation of blood glucose and body weight. Activation of the receptor leads to increases in intracellular cAMP triggering secretion of GLP-1 and initiating glucose-dependent insulin secretion. PSN821 is a small-molecule GPR119 agonist currently in clinical development with demonstrated efficacy in improving blood glucose control and body weight in rodent models of diabetes and obesity. Knowledge of the enteroendocrine response to PSN821 informs us of the requisite hormone profile that contributes to blood glucose lowering and body weight loss.

This study presents the gut hormone profile stimulated by PSN821 from isolated male Sprague-Dawley rat small intestine in the presence of simple sugar and mixed nutrients. Small intestine was placed into an organ bath and perfused luminally. Serosal samples were analysed for tGIP, aGLP-1 and tPYY by ELISA. PSN821 (0.03 – 10 μM) and 5 mM glucose dose-dependently stimulated the release of GIP, GLP-1 and PYY in a ratio of 1:2:10, saturating at 10 μM. When the glucose concentration was raised to 25 mM, PSN821 elevated the secretion of GIP, GLP-1 and PYY in an additive fashion and the ratio of GIP:GLP-1:PYY was maintained. Challenging the small intestine with a mixed nutrient dietary load (Ensure Plus 10, 50 and 100 % (v/v)) stimulated the release of GIP, GLP-1 and PYY dose-dependently. Co-administration of PSN821 (10 μM) and 10 % Ensure Plus stimulated the secretion of GIP, GLP-1 and PYY by 20, 10 and 14 fold, respectively and altered the ratio of GIP:GLP-1:PYY to 1:2:70. The release of GIP, GLP-1 and PYY by PSN821 (10 μM) did not increase further when Ensure Plus was raised to 100 % (v/v).

Nutrient availability modified the ability of PSN821 to stimulate gut hormone release. PSN821 and glucose stimulated gut hormone secretion in an additive fashion; a mixed nutrient load stimulated GIP, GLP-1 and PYY secretion potentially via additional pathways. Delivery of PSN821 at the time of nutrient intake could have further beneficial therapeutic effects in treating type 2 diabetes over PSN821 alone.

1133-P

The Risk of Heart Failure among Patients Receiving Exenatide Versus Other Glucose-Lowering Medications for Type 2 Diabetes: A Matched Retrospective Cohort Analysis of the GE Healthcare Electronic Medical Record Database

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Exenatide twice daily (ExBID), a GLP-1 receptor agonist, has improved cardiovascular risk factors in patients (pts) with type 2 diabetes (T2D). We hypothesized that addition of ExBID to other glucose-lowering therapies may reduce the risk of developing heart failure (HF), defined as HF diagnosis and brain natriuretic peptide>100 pg/mL. This retrospective matched cohort study used data obtained from the national Medical Quality Improvement Consortium of ambulatory medical practices (>14,000 providers) that use Centricity Office from GE Healthcare IT as their electronic medical record.

Patients w/T2D receiving a prescription for glucose-lowering therapy--ExBID, insulin (INS), and/or other (OTH) (excluding ExBID and INS) between 1 Jan 2005-30 Sept 2010 were identified (n=778,408). Therapies may have been prescribed serially or concomitantly. Pts using ExBID were randomly matched 1:1 to pts not receiving EBID based on gender, 10-y age band, follow-up time, and any use of TZDs. Odds ratios (ORs) were calculated using conditional logistic regression models with and without adjustment for weighted Charlson Comorbidity Index (CCI), a disease severity measure.

Without adjustment for CCI, the rate of HF (affected/total) among pts that received ExBID+INS+OTH was 0.52 vs 1.24 for INS+OTH (OR=0.41, 95% CI=0.34-0.51). The rate of HF among pts that received ExBID+OTH was 0.13 for ExBID pts vs 0.18 in matched controls (OR=0.69, 95%CI=0.44-1.07, NS). After adjustment for CCI, risk of HF for pts who received ExBID+INS+OTH was 57% lower vs INS+OTH (OR=0.43, 95% CI=0.35-0.53, n=50,330). With adjustment for CCI, the risk of HF for pts who received ExBID+OTH was 31% lower vs OTH (OR=0.69, 95% CI=0.44-1.07, NS, n=53,446). Finally, in a model adjusting for CCI that included all pts that received ExBID vs all non-ExBID controls, the risk of HF was 54% lower (OR=0.46, 95% CI=0.38-0.56, n=103,776).

In this analysis the addition of ExBID to glucose-lowering regimens for the treatment of T2D was associated with reduced risk of developing HF, especially among pts receiving INS.

1134-P

The Usage of Metformin Despite of Existing Contraindications in Type 2 Diabetes Mellitus (T2DM) Patients

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People with T2DM and coexisting hypoxemic conditions such as advanced congestive heart failure or renal and liver insufficiency are at high risk of developing lactic acidosis – the life-threatening side effect of metformin. The purpose of our study was to assess the frequency of metformin usage in patients with T2DM in spite of established contraindications and the prevalence of metformin-related side effects. Four hundred and twenty consecutive patients aged 29-91 years with T2DM was admitted to our department between June 2009 and November 2010 due to acute and chronic complications of diabetes or poor metabolic control. All patients were interviewed about their diabetes treatment regiment and existing

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comorbidities before hospitalization and basic laboratory tests were performed. From among 211 patients (roughly 50,0% of the entire group) with currently accepted contraindications 95 (45,0%) had been treated with metformin in a dose of 1500-3000 mg/d on an outpatient basis. Twenty nine patients (30,0%) were using metformin in the presence of advanced renal failure (defined as serum creatinine concentration higher than 135 and 110 µmol/l for males and females, respectively). Despite diagnosis of congestive heart failure at III/IV NYHA class in 57 individuals (60,0%) metformin was prescribed by general practitioners (GPs). Advanced liver dysfunction (>3-fold increase in transferases levels) was diagnosed in 16 patients (16,8%). Of note, in 27,4% patients 2 or more contraindications were present. The mean age of patients with contraindications was higher than in the entire group (68,8 ± 12,0 vs. 66,2 ± 12,3). Interestingly, no metformin-related side effects were reported by the patients using the drug before admission. Current guldelines suggest metformin use, unless contraindicated, in all patients with T2DM. Recently, the use of metformin has been proposed in patients with systolic heart failure and renal insufficiency provided that continuous monitoring is secured. However, these recommendations should be considering with caution and GPs should prescribe metformin in accordance with the current guidelines based on the label of the drug.

1135-P

Tofogliflozin, a Novel Sodium-Glucose Co-Transporter 2 Inhibitor, Improves Pancreatic and Renal Functions in Animal Models of Type 2 Diabetes

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In the treatment of type 2 diabetes (T2D) patients, maintenance of pancreatic beta cell and renal functions is just as critical as the appropriate glucose control. Tofogliflozin, a potent and selective SGLT2 inhibitor, reduces blood glucose level by increasing urinary glucose excretion. In this study, we examined whether the tofogliflozin treatment ameliorates the pancreatic beta cell and the kidney functions in db/db and KKAy mice, two T2D animal models. Tofogliflozin (0.005% and 0.015% (w/w) pellet chow, for 8 weeks) decreased plasma glucose and suppressed HbA1c in a dose-dependent manner in both db/db and KKAy mice. In the db/db mice experiment, pancreatic beta cell mass of the vehicle group was smaller than that of db/+m mice. Tofogliflozin-treated db/db mice showed larger pancreatic beta cell mass than the vehicle group which was accompanied by decreased plasma insulin, suggesting that sustained treatment with tofogliflozin prevented beta cell damage in this animal model. In both untreated db/db and KKAy mice, urine albumin/creatinine ratio (ACR), an indication of renal impairment, inevitably increased during the experiments, but that of KKAy mice was significantly higher, suggesting more severe renal impairment. In the two T2D mice models with different severity of renal impairment, tofogliflozin significantly prevented the increment of ACR and the effects were comparable to losartan, a clinically validated angiotensin II receptor blocker against progression of renal disease in T2D patients. Our findings provide evidence of the beneficial effect of long-term use of tofogliflozin on the function of beta cells and the kidney in T2D mice models. It suggests that tofogliflozin may improve pancreatic and renal functions under various pathological conditions of T2D. Further studies are required to evaluate the therapeutic usefulness of tofogliflozin for preservation of beta cells and renal function in T2D patients.

1136-P

Tofogliflozin, a Novel, Potent, and Highly Selective SGLT2 Inhibitor, Improves Glycemic Control in Diabetic Mice and Rats

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Inhibition of renal sodium-glucose co-transporter 2 (SGLT2) is a new approach for treatment of type 2 diabetes mellitus (T2D), and several SGLT2 inhibitors have been reported recently. These inhibitors have a glucose-like moiety and inhibit SGLT2 competitively, but any low selectivity to other glucose transporters or to enzymes using glucose as a substrate would raise safety concerns. We identified a new potent and selective SGLT2 inhibitor, tofogliflozin, and examined its potential efficacy and pharmacological properties as an antidiabetic agent, in terms of selectivity. Inhibitory effects of tofogliflozin on human and rodent SGLT2 were evaluated by alpha-methyl glucopyranoside uptake in cells which over-express SGLT2. Tofogliflozin competitively inhibits SGLT2, and *Ki* values for human, mouse and rat SGLT2 were 2.9, 6.4 and 15.0 nmol/L, respectively. SGLT2 selectivity ratio ($SGLT_n$ IC_{50}/SGLT2 IC_{50}) of tofogliflozin for human SGLT1, SGLT3, SGLT4, SGLT6 and SMIT were 2900, 20000, 1600, 6700 and 30000, respectively. Furthermore no physiologically relevant interaction by tofogliflozin was observed in a battery of tests examining glucose metabolism such as glucose uptake, oxidation, hepatic glucose production, glycogen synthesis, glycosidase reaction, and glucose-stimulated insulin secretion. Single oral dosing of tofogliflozin (0.1, 0.3, 1, 3 and 10 mg/kg) lowered blood glucose over 8 hours accompanied by increased glucose excretion in ZDF rats. Tofogliflozin (1, 3 and 10 mg/kg) also improved postprandial glucose excursion in a meal tolerance test with GK rats. No blood glucose reduction was observed in normoglycemic Wistar rats treated with tofogliflozin. In db/db mice, single oral dosing of tofogliflozin (0.1 to 10 mg/kg) lowered blood glucose, moreover four-week tofogliflozin treatment (0.3, 1, 3 and 10 mg/kg q.d.) reduced glycated hemoglobin, and improved glucose tolerance in the oral glucose tolerance test 4 days after the final dosing. These findings clearly demonstrate that tofogliflozin inhibits SGLT2 in a specific manner and improves the T2D pathophysiological conditions with a low risk of hypoglycemia.

1137-P

Transcription Profiling Analyses of Male ZDF Rat Tissues Following Chronic Dapagliflozin Treatment

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Dapagliflozin (Dapa) is a potent (Ki = 0.2nM), selective SGLT2 inhibitor (3000-fold vs SGLT1) which reduces renal glucose reabsorption and may provide an insulin-independent mechanism for the treatment of type 2 diabetes. We have shown that prevention of progression to hyperglycemia by Dapa treatment in prediabetic male ZDF rats improves impaired hepatic glucose metabolism and peripheral insulin sensitivity. To further understand the molecular basis of these therapeutic effects, we performed transcription profiling analyses on RNA samples from obese ZDF rats dosed for 5wk with 0.5mg/kg Dapa q.d. p.o. or vehicle. Liver, skeletal muscle and kidney tissues were harvested from both fasted and fed animals 48hr after the last dose. Comparing Dapa vs. vehicle treated animals, the greatest changes in gene expression were observed in liver. In the fasted state, Dapa treatment resulted in a significant increase in the mRNA level of hepatic steroyl coenzyme A desaturase 1 (3,000%, $p=2.4x10^{-23}$), glucokinase (270%, $p=1 x10^{-6}$) and inhibin beta C (180%, $p=6.4 x10^{-6}$), and a significant decrease in the expression of hydroxysteroid (11-beta) dehydrogenase 1 (70%, $p=1 x10^{-7}$). In the fed state, similar changes in these genes were observed. In addition, fatty acid synthase, fatty acid elongase and acetyl CoA carboxylase were elevated in expression after Dapa treatment, suggesting an impact on the genes related to fatty acid metabolism. However, there was no effect of Dapa on hepatic triglyceride levels in related studies. There was no significant impact on genes involved in metabolic pathways in skeletal muscle or kidney. In the kidney, of the renal sodium-glucose cotransporter proteins only SGLT5 gene expression was altered by Dapa after 5wk of treatment (66% increase $P<0.03$); GLUT2 gene expression was reduced by 40% ($P<0.005$), and SGLT1 expression was not changed. We conclude that the observed gene expression changes in liver arise from the prevention of hyperglycemia with Dapa in male ZDF rats, and that there is no major compensatory up-regulation of other glucose transporters in kidney upon Dapa treatment.

Supported by: AstraZeneca LP and Bristol-Myers Squibb Company

1138-P

Translational Research of Ghrelin to Diabetic Peripheral Polyneuropathy on Type 2 Diabetes Mellitus

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Peripheral polyneuropathy is the most frequent complication of diabetes, and often lower the quality of life. The effect of drugs for polyneuropathy, however, is insufficient at present.

Ghrelin, an acylated peptide produced in the stomach, increases food intake and growth hormone secretion. Ghrelin also reported to suppress inflammation, oxidative stress and cell apoptosis, and to increase blood flow and cell proliferation. We recently reported that ghrelin ameliorated experimental diabetic neuropathy in uncontrolled streptozotocin-induced diabetic mice. In the model, ghrelin improved thermal sensation, both sensory and motor conduction velocities, density of myelinated nerve fibers, plasma 8-iso-PGF2a level, and blood flow.

To investigate the pharmacological potential of ghrelin in the treatment of diabetic neuropathy, 1.0 mg/kg ghrelin was administered to 5 diabetic

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patients (4 men, 57.8 ± 3.6 years old) with polyneuropathy just before breakfast for 2 weeks. Their duration of diabetes was 15 ± 4.8 years, body mass index was 23.7 ± 2.8, and A1C was 8.3 ± 0.4%. Total symptom score (TSS) assessed by subjective symptoms including pain, burning pain, dysesthesia, and hyperesthesia, nerve conduction velocity, meal tolerance test, and various blood parameters were examined before and after the treatment. After 2 weeks, ghrelin treatment did not change appetite, body weight, and plasma glucose and insulin levels. No remarkable adverse effect was observed. The motor conduction velocity of the tibial nerve and TSS significantly improved from 34.2 ± 2.2 to 37.7 ± 2.5 m/sec and from 15.5 ± 3.6 to 9.7 ± 2.0, respectively after 2 weeks ghrelin administration. Sensory potentials of the sural nerve in two patients were not evoked before ghrelin treatment, but they could be detected after the treatment.

Plasma concentrations of tumor necrosis factor-α, 8-iso-prostaglandin F2α, high sensitivity C-reactive protein, IL-6 did not change. Although underlying mechanisms have not been fully elucidated, ghrelin could become a novel therapeutic drug for diabetic polyneuropathy.

1139-P

WITHDRAWN

1140-P

TS-071, a Novel, Potent and Selective SGLT2 Inhibitor, Induced Dose-Related Increase of Urinary Glucose Excretion and Showed Good Tolerability in Japanese Healthy Male Subjects

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TS-071 (TS) is a novel, potent and selective SGLT2 inhibitor. To assess safety, PK, and PD of TS, single dose (SD) study and 7 days multiple dose (MD) study were conducted in Japanese healthy male subjects.

In SD study, 57 subjects were randomized to TS (1, 3, 5, 9, 15 or 25mg) or placebo (PBO) and dosed under fasting condition. In a MD study, 24 subjects were randomized to TS (5 or 10 mg/day) or PBO. In order to assess the effect of food intake on PK, 5 mg was administered to the identical subjects under fasting condition and just before meal.

After SD of 1–25 mg of TS, plasma concentration increased dose-dependently and both Cmax and $AUC_{0-\infty}$ showed dose proportionality. Mean Tmax and $T_{1/2}$ were 0.67–2.25 and 9.2–13.8 hours, respectively. After MD of 5 or 10 mg/day, PK profiles on Day 7 were similar to those on Day 1. No cumulative effect was observed. At 5 mg dosing, there was no effect on the PK parameters by with or without food intake.

The urinary glucose excretion (UGE) was dose-dependently and significantly affected by TS. After SD of 25 mg, mean UGE up to 24 hours was about 70 g. After MD of 5 or 10 mg/day, 24hr-UGE on Day 7 were similar. Mean UGE rates 0–2 hours after breakfast, lunch and supper were 3.3, 3.9, and 3.4 g/hr in 5 mg/day on Day 1, and 3.7, 4.0, and 4.5 g/hr in 10 mg/day on Day 1, respectively. Similar rates were observed on Day 7 (Figure 1).

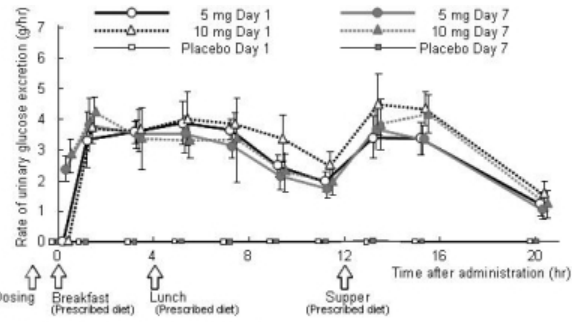

Figure 1. Urinary Glucose Excretion Rates

In both SD and MD study, there was no serious adverse event and no major safety concern. No hypoglycemia was observed. No clinically meaningful mean change compared to PBO in urine volume, electrolyte excretion, and renal function was observed.

TS showed favorable PK profiles, significantly increased UGE, and had no problem in safety and tolerability, at SD of 1–25 mg and MD of 5 and 10 mg/day for 7 days.

1141-P

Use of a New Basal Insulin with a Bolus Boost (IDegAsp) in Type 2 Diabetes: Comparison with Biphasic Insulin Aspart 30 (BIAsp 30)

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Insulin degludec (IDeg; formerly named SIBA) is a new basal insulin that forms soluble multi-hexamers upon sc injection, resulting in an ultra-long action profile. Insulin degludec/insulin aspart (IDegAsp) is a soluble insulin preparation comprising IDeg (70%) and insulin aspart (IAsp, 30%). This phase 2, 16-week, open-label, treat-to-target trial investigated the safety and efficacy of IDegAsp in people with type 2 diabetes inadequately controlled on OADs. Subjects (mean: 60 yrs old; A1C 8.5%; FPG 209 mg/dl) were randomized to twice-daily IDegAsp (n=61), an alternative formulation of IDegAsp (AF; n=59) with a higher percentage of IAsp (45%), or BIAsp 30 (n=62), all in combination with metformin (1500 or 2000 mg/day). Insulin was dosed sc before both breakfast and the evening meal and titrated to a pre-breakfast and pre-dinner PG target of 72–108 mg/dl. Mean A1C after 16 weeks (primary endpoint) was comparable for IDegAsp, AF and BIAsp 30 (6.7%, 6.6% and 6.7%). With IDegAsp, more subjects achieved A1C <7.0% without confirmed hypoglycemia (PG<56 mg/dl) in the last 4 weeks of treatment compared to AF and BIAsp 30 (67%, 53% and 40% of subjects). Mean FPG at Week 16 was significantly lower for IDegAsp vs. BIAsp 30 (treatment difference (TD): -17.8 mg/dl [95% CI: -30.2; -5.2]), and AF vs. BIAsp 30 (TD: -15.8 mg/dl [-28.4; -3.2]). No severe hypoglycemia was reported. The rate of confirmed hypoglycemia was 58% lower for IDegAsp than BIAsp 30 (2.9 vs. 7.3 episodes/patient yr; rate ratio: 0.42 [0.23; 0.75]); rates were similar for BIAsp 30 and AF (7.3 vs. 6.8 episodes/patient yr). Nocturnal confirmed hypoglycemia was less frequent for IDegAsp (7 episodes) than AF (14 episodes) and BIAsp 30 (20 episodes). The overall rate of adverse events was similar between insulins, the majority (>99%) were mild or moderate in severity, and there was no treatment-specific pattern or clustering. In conclusion, this proof-of-concept trial showed IDegAsp to be safe and well tolerated, providing comparable overall glycemic control to BIAsp 30. IDegAsp was associated with a significantly lower FPG and a significantly lower rate of confirmed hypoglycemia than BIAsp 30.

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1142-P

Use of Once Daily Liraglutide in Type 2 Diabetes: Clinical Practice and Experiences from Combination with Oral Antidiabetic Drugs or Insulin

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To study the efficacy of liraglutide (LIR) on reduction in HbA1c, weight and dose of other antidiabetic agents in type 2 patients treated with oral antidiabetic drugs or insulin.

All type 2 patients from three outpatient diabetes clinics in Copenhagen, Denmark, initiating LIR were eligible for inclusion (n = 518). Patients, who changed from treatment with another GLP-1 receptor agonist were excluded (n = 107). Data were obtained from patients treated ≥ 3 months (n = 346). 79 patients stop LIR treatment due to adverse reactions or lack of clinical response within three months of treatment. 267 patients treated for at least three months were included in the analyses.

152 patients started on LIR were treated with metformin (91%) and/or sulfonylurea (SU) (60%) at baseline. Mean observational period were 7 months (range: 3-15 months). Median dose of LIR were 1.2 mg/daily. Dose of SU were reduced in more than 20% of patients, and was stopped in 15%. At baseline BMI was 35.2 kg/m² (weight 106.4 kg) and HbA1c 8.7%. HbA1c were reduced by 1.4%, and 41% achieved HbA1c ≤ 7.0 %. Mean weight reduction were 3.5 kg.

In 115 patients LIR was added to insulin for a mean of 6.4 months (range: 3 - 14). 85% of patients also used metformin. Insulin treatment was primarily premix insulin (35%) and glargine (27%). Median LIR dose were 1,2 mg/daily (57%), and 29% treated with 1,8 mg/daily. Baseline BMI 36 kg/m² (weight 107.7 kg) and HbA1c 8.6%, and mean insulin dose were 69 IU/daily. Mean weight loss were 5.1 kg (4.8% reduction of baseline weight). HbA1c were reduced by 0.8% and 35% of patients achieved HbA1c ≤ 7.0%. Baseline insulin dose were reduced with a mean of 28 IU daily. Significantly more in the group treated with LIR 1.8 mg/daily (41 IU) than the 1.2 mg/daily group (24 IU). Insulin treatment could be ended in 21%.

Our results do not differ significantly from results in clinical controlled trials where LIR is added to oral antidiabetic agents. Liraglutide in combination with insulin lead to reduction in HbA1c, weight and in daily insulin dose, even termination of insulin in a group of patients.

1143-P

Use of Structured SMBG Facilitates Earlier Initiation of Insulin Therapy in Poorly Controlled T2DM Patients: Results from the STeP Study

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Type 2 diabetes (T2DM) is a progressive disease with relentless decline in beta cell function that often requires insulin therapy to achieve/sustain glycemic goals. Many primary care physicians are often reluctant to initiate insulin therapy even when HbA1c levels are significantly above glycemic goals. We assessed the impact of a structured self-monitoring of blood glucose (SMBG) intervention on physician prescribing patterns related to initiation of long-acting insulin (glargine, detemir or NPH) in poorly controlled type 2 diabetes patients. We analyzed data from the 483 poorly-controlled (HbA1c ≥7.5%), insulin-naïve T2DM participants of the Structured Testing Program (STeP) study, a prospective, cluster-randomized, multi-centered clinical trial that assessed the impact of structured SMBG use on changes in both HbA1c and treatment intensification.

Patients were randomly assigned to structured testing (STG) or active control (ACG). STG subjects used the ACCU-CHEKâ 360° View Blood Glucose Analysis System to collect/interpret 7-point glucose profiles over 3 consecutive days. Between-group comparisons of timing of insulin initiation and dose titrations were calculated using Fishers exact test, time-to-event analysis and a log-rank test.

Long-acting insulin was initiated in 41 (16%) STG patients and 21 (9%) ACG patients; p=0.029. Mean (SE) time to insulin initiation in STG was significantly shorter compared with ACG patients: 42.2 (0.9) vs 45.3 (0.63) weeks, respectively; p=0.011. The mean (SD) HbA1c at initiation was similar in both groups: 9.60% (1.66) STG vs 9.27% (1.39) ACG; p=0.408. During the next 3 months, 17 STG patients and 8 ACG patients received adjustments in insulin dosages; p=0.367. Mean (SD) changes in HbA1c were similar between STG and ACG patients: groups:-0.14% (1.34) vs. 0.00% (1.21), respectively; p=0.729.

Appropriate use of structured SMBG facilitates earlier initiation of insulin therapy in poorly controlled, previously non-insulin treated T2DM patients. Our findings suggest that graphical presentation of blood glucose patterns may help overcome clinician inertia associated with insulin initiation.

For author disclosure information, see page 785.

1144-P

Using Liraglutide in Combination with Insulin Therapy for Type 2 Diabetic Patients: An Early Clinical Experience Data

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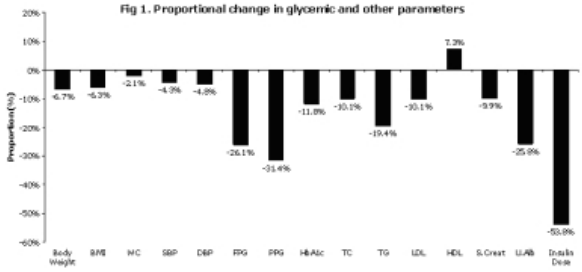
Once-daily GLP-1 analogue, liraglutide appears to be an interesting therapeutic option with multiple benefits for diabetes. Present data show the clinical profile following addition of liraglutide to existing insulin±OAD therapy in 22 type 2 diabetic patients. Mean age of patients was 58.5±7.8 years and mean duration of diabetes was 12.8±5.2 years. Prior to starting liraglutide; one patient was on Insulin + 4 OADs, 10 patients were on insulin + 3 OADs, 10 patients were on insulin + 2 OADs and one patient was on insulin monotherapy. Liraglutide was stared at 0.6 mg/day and escalated to 1.2 mg/day. After 12 weeks following liraglutide initiation there were clinically significant improvements in glycemic and non-glycemic parameters (table 1) and (figure 1).

Parameter	Baseline	After initiating Liraglutide (12 weeks	Mean difference	Significance
Body weight (Kgs)	88.2±12.4	82.3±7.6	-5.9	p<0.01
BMI (Kg/m^2)	34.3±3.5	32.2±3.1	-2.1	p<0.001
Waist Circumference(cms)	105.6±8.9	103.4±8.1	-2.2	p=ns
SBP(mmHg)	145.4±10.5	139.2±7.1	-6.2	p=ns
DBP(mmHg)	85.5±6.7	81.4±4.2	-4.1	p=ns
FPG(mg/dl)	170.7±55.4	126.1±21.5	-44.6	p<0.001
PPG(mg/dl)	268.1±74.2	184±29.5	-82.1	p=ns
HbA1c(%)	8.4±1.1	7.4±0.6	-1	p=ns
Total Cholesterol (mg/dl)	169±40.1	151.9±25.4	-17.1	P<0.01
Triglycerides(mg/dl)	224.8±41.8	181.3±19	-43.5	p=ns
LDL(mg/dl)	109.6±20.6	98.6±14.1	-11	p=ns
HDL(mg/dl)	36.2±5.7	38.9±4.8	2.7	P<0.01
S. Creatinine(mg/dl)	1.1±0.22	1±0.16	-0.1	p=ns
U.Albumin (mg/dl)	67.8±62.1	50.3±44.7	-17.5	P<0.05
Insulin Dose (U)	64.4±46	29.7±31.4	-34.7	p=ns



There was apprx. 54% reduction in insulin dose and close to a third (7/22) of patients were completely off insulin. In summary addition of liraglutide to insulin ± OADs further improves glycemic control with a clinically significant reduction in insulin dose and body weight.

1145-P

WITHDRAWN

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1146-P

Weight-Lowering Efficacy of Glucagon-Like Peptide-1 Receptor Agonists: A Meta-Analysis

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The effect of glucagon-like peptide-1 receptor (GLP-1R) agonists on weight loss has been assessed in several randomized controlled trials (RCTs).

We performed a meta-analysis of RCTs reporting body weight changes after ≥20 weeks of treatment with a GLP-1R agonist. Random effects meta-analysis was performed with results expressed as weighted mean difference (WMD) or risk ratio (RR) with 95% confidence intervals (CI). Bias was assessed based on individual components. Subgroup, sensitivity and regression analyses were performed to evaluate inter-trial heterogeneity and evidence of bias.

Included RCTs assessed 20-52 weeks of treatment with exenatide (11 trials), exenatide long acting release (LAR) (3 trials) or liraglutide (10 trials) in subjects with (21 trials) or without type 2 diabetes (3 trials). Control interventions included placebo, insulin, sulfonylurea, thiazolidinediones and dipeptidyl peptidase-4 inhibitors. Quality assessment of published trial reports and protocols revealed no evidence of bias. Random effects meta-analysis revealed a greater weight loss among subjects randomized to GLP-1R agonists (N=2,891) vs. subjects in the control group (N=2,399) (WMD: -2.91 kg; CI: -3.61 to -2.21 kg). No evidence of bias was identified (Egger's test, P=0.13). Increasing dose of GLP1R agonist and baseline body weight correlated positively with weight loss. No significant differences between liraglutide, exenatide and exenatide LAR were observed. Non-diabetic subjects had a greater weight loss (-3.25 kg; -4.22 to -2.27 kg) than patients with type 2 diabetes (-2.76 kg; -3.34 to -2.18 kg) before and after adjusting for the intervention and baseline body weight (P=0.006). Treatment with GLP-1R agonists increased the risk of nausea (RR: 4.09; CI: 3.44 to 4.86), vomiting (2.23; 1.75 to 2.89), and diarrhea (2.27; 1.80 to 2.87), but did not increase the risk of serious adverse events.

In conclusion, meta-analysis of large high-quality RCTs shows that treatment with GLP-1R agonists for at least 20 weeks leads to a substantial weight loss in subjects with or without type 2 diabetes. The intervention effect may be more pronounced in subjects without diabetes compared type 2 diabetic patients.

1147-P

Zinc Oxide Nanoparticles Show Anti-Diabetic Activity in Rats

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Role of zinc in glucose absorption, insulin secretion, insulin signaling, glucagon secretion and release of free fatty acids (FFA) from adipocytes is well documented. Since imbalance in zinc homeostasis is positively correlated with diabetes, its use in therapy becomes an attractive proposition. Several zinc complexes reported for their anti-diabetic activity are also known to be toxic, highlighting the need for safer alternatives. Here we report on zinc oxide nanoparticles (ZON) as a possible novel and safe therapy for diabetes.

Toxicity profile of ZON (~10 nm diameter) was assessed (by acute and sub-acute toxicity tests, micronucleus assay and hemolysis test) prior to its evaluation for anti-hyperglycemic activity in Streptozotocin induced type 1 and type 2 diabetic wistar rats. At the end of 4 week treatment, blood glucose levels under fasted (F) and non-fasted (NF) conditions, serum triglycerides (TG), FFA, and insulin levels were estimated. Oral glucose tolerance test (OGTT) was also performed. *In vitro* insulin secretion by rat insulinoma Rin5f cells in response to ZON was monitored.

Toxicity data obtained confirmed safety of ZON up to 300 mg/kg dose. In efficacy studies, blood glucose levels were found to reduce significantly in both type 1 diabetic (26% in F and 20% in NF) and type 2 diabetic (21% in F and 29% in NF) rats treated with ZON (10 mg/kg dose). However, increase in serum insulin levels (~70%) was seen only in type 2 diabetic rats. Significant lowering of circulating TG (44% in type 1; 48% in type 2 diabetic rats, respectively) and FFA (41% in type 1; 15% in type 2 diabetic rats, respectively) levels suggested beneficial effects of ZON on lipid metabolism. Similarly, significantly diminished $AUC_{glucose}$ values in both type 1 (22%) and type 2 (28%) diabetic rats indicated considerable improvement in glucose intolerance. Enhanced insulin secretion could be a major mechanism of antidiabetic activity as evident from observed ZON induced dose-dependent (1 - 10 µg/ml) increase in insulin levels (~1.5 – 3.5 folds) in Rin5f cells. These exciting results warrant further evaluation of ZON as a possible therapeutic agent.

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CLINICAL THERAPEUTICS/NEW TECHNOLOGY—TREATMENT OF INSULIN RESISTANCE

[*See also: Presidents Poster 417-PP, page A116.*]

Guided Audio Tour: Clinical Therapeutics—Treatment of Insulin Resistance *(Posters 1148-P to 1155-P), see page 13.*

1148-P

Use of Pioglitazone vs. Placebo in Addition to Standard Insulin Treatment in Patients with Type 2 Diabetes Mellitus Requiring Hemodialysis Treatment

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The aim of this study was to investigate the effect of additional pioglitazone (PIO) vs. placebo treatment on total daily insulin requirements and the overall metabolic status in type 2 diabetes patients with renal failure requiring hemodialysis. This was a prospective multi-centre, randomized, double-blind study in 37 patients with Type 2 diabetes and end stage renal failure (12 women, 25 men, age(mean±STD): 69±8 yrs., BMI: 30.9±4.2 kg/m², HbA1c: 7.5±0.9 %, disease duration: 11.8±8.5 yrs.). Efficacy parameters were collected before dialysis after an overnight fast at baseline and after 6 months and included total daily insulin dose, HbA1c, fasting blood glucose, insulin, adiponectin, lipids, NT-proBNP and ultra filtrate volume. Application of PIO resulted in a significant decrease of the daily insulin dose by 35 % (p<0.05 vs. baseline; placebo: -10 %., n.s.), and improvement in HbA1c (-0.59±0.85 %, p<0.01; placebo: +0.30±1.21 %, n.s.), fasting glucose (-24 %, p<0.05 vs. 10 %, n.s.), insulin (-5 %, n.s. vs. + 58 %, p<0.05), adiponectin (+80 %, p<0.01 vs. -14 %, n.s.), and triglycerides (-30 %, p<0.01 vs. +19 %, p<0.05). Slight improvements with PIO or no changes were seen with HDL, LDL, NTproBNP and the ultra filtrate volume. Absolute values at baseline and endpoint for selected parameters are provided in the Table.

	pioglitazone	pioglitazone	placebo	placebo
	baseline	6 months	baseline	6 months
daily insulin dose [IU]	64.0±48.9	44.2±34.7*	55.4±33.0	51.1±28.2
HbA1c [%]	7.42±0.90	6.95±0.94*	7.72±0.92	8.02±1.00
Glucose [mg/dL]	168±49	125±49*	165±41	165±56
Adiponectin [mg/L]	9.2±6.2	17.2±7.3*	9.8±5.9	9.4±5.8
Triglycerides [mg/dL]	316±208	235±110*	241±96	293±157
NT-proBNP [ng/mL]	5.1±8.8	7.9±13.6	5.1±7.4	8.5±15.1
Ultra filtrate volume [L]	2,50±0,86	2,61±0,91	2,74±1,00	3,01±1,05

Without changing the ultra filtrate volume, additional PIO treatment to standard insulin therapy resulted in a decrease of the daily insulin dose and

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an improvement of glycemic control, lipid metabolism and the cardiovascular risk profile in patients with type 2 diabetes requiring hemodialysis.

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1149-P

A Study To Assess the Metabolic Effects of Ranolazine When Added to Ongoing Non-Insulin Medical Therapy in Subjects with Type 2 Diabetes Mellitus (T2DM)

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Ranolazine is a first-in-class antianginal agent with anti-ischemic effects that inhibits the cardiac late sodium current. Prior studies supported a HbA1c lowering effect by ranolazine in patients (pts) with chronic angina and T2DM (post hoc analysis of the CARISA study; total n=823, 23% DM pts), as well as in pts with DM, coronary artery disease (CAD), and acute coronary syndromes (pre-specified subset analysis of the MERLIN TIMI-36 study; total n=6560, 34% DM pts).

In this double-blind study, 80pts with HbA1c 7-11% (on non-insulin medical therapy) were randomized to placebo or ranolazine ER (1000mg BID) for 12 weeks. The effect of ranolazine on HbA1c, 2-hour postprandial glucose (PPG), and fasting serum glucose (FSG) was determined.

Mean baseline HbA1c was 8.5% and 8.4% for the placebo and ranolazine groups, respectively. Ranolazine significantly reduced placebo-corrected HbA1c by 0.53%, and the reduction was even greater in pts with higher baseline HbA1c levels. Ranolazine also reduced placebo-corrected PPG levels in all pts, with a 35.8mg/dL reduction in the PPG subgroup with baseline FSG>140mg/dL. Although not statistically significant, ranolazine also lowered FSG levels in all pts; a greater placebo-corrected reduction was observed in the FSG subgroup with baseline FSG>140mg/dL.

In summary, in T2DM pts, we confirm prior observations in pts with CAD and T2DM that ranolazine significantly improves HbA1c when added to existing non-insulin anti-DM therapy. Compared to FSG, greater placebo-corrected reductions in PPG were observed, particularly in the subset of pts with FSG>140mg/dL.

Change From Baseline at 12 wks	Full Analysis	Least Squares Mean*			P-value
	N	Placebo	Ranolazine	Ranolazine - Placebo	
HbA1c (%) - all subjects	78	-0.08	-0.61	-0.53	0.010
⇐7.5	21	0.02	-0.29	-0.30	0.179
>7.5	57	-0.11	-0.73	-0.62	0.023
>10	10	-0.32	-2.35	-2.03	0.065
2-hour PPG (mg/dL) - all subjects	71	-11.2	-26.6	-15.4	0.234
- PPG subgroup with baseline FSG>140mg/dL	43	-5.7	-41.4	-35.8	0.037
FSG (mg/dL) - all subjects	79	4.5	2.0	-2.5	0.879
- FSG subgroup with baseline FSG>140mg/dL	48	4.9	-7.8	-12.7	0.256

*Analysis of Covariance models (ANCOVA)

1150-P

Efficacy and Safety of the Partial PPARγ Agonist Balaglitazone Compared with Pioglitazone and Placebo: A Phase III, Randomised, Parallel-Group Study in Patients with Type 2 Diabetes on Stable Insulin Therapy

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Treatment of patients with full PPARγ agonists is associated with weight gain, heart failure, peripheral oedema and bone loss. However, the safety of partial PPARγ agonists has not been established in a clinical trial.

The BALLET trial aimed to establish the glucose-lowering effects and safety parameters of the partial PPARγ agonist balaglitazone in diabetic patients on stable insulin therapy.

409 subjects from 3 countries with type 2 diabetes on stable insulin therapy were randomised to 26 weeks of double-blind treatment with once daily doses of 10 or 20mg balaglitazone, 45 mg pioglitazone, or matching placebo (n≥99 in each group). The primary endpoint was the efficacy of balaglitazone 10mg and 20mg versus placebo on the absolute change in HbA_{1c}. Secondary endpoints included levels of fasting serum glucose (FSG), and changes in body composition and bone mineral density as measured by DXA, with comparison to pioglitazone 45mg. Clinicaltrials.gov identifier: NCT00515632.

In the 10 and 20mg balaglitazone groups, and in the pioglitazone 45mg group, significant reductions in HbA_{1c} levels were observed (-0.99%, -1.11% and -1.22% respectively ($p<0.0001$)) versus placebo.

FSG was similarly reduced in all treatment arms. DXA analyses showed balaglitazone 10mg led to less fat and fluid accumulation and no change in bone mineral density, when compared to pioglitazone.

In the balaglitazone 10mg treated group clinically relevant reductions in HbA_{1c} and glucose levels were observed, although it appeared to be less potent that pioglitazone 45mg. On the other hand significantly less fluid and fat accumulation were observed, highlighting this drug candidate for further studies.

1151-P

Deactivating Acetyl-CoA Carboxylase (ACS) Alters Metabolic Fate of Glucose and Fatty Acids but Fails To Ameliorate Obesity or Insulin Resistance: Pharmacological and Gene Knockout Studies in Rodents

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Effects of suppressing ACC function on in vivo substrate fluxes, insulin resistance and obesity were studied in rodents. We used a dual ACC1/2 inhibitor (ACCi), in several animal models spanning a range of baseline levels of de novo lipogenesis (DNL) and insulin sensitivity. In Sprague Dawley (SD) rats fed a virtually fat-free diet under conditions of an insulin/glucose infusion (a model of enhanced DNL), ACCi dose dependently reduced hepatic DNL (based on ^{14}C-glucose incorporation into lipid) and simultaneously increased hepatic glycogen stores and total insulin levels compared to vehicle controls. In SD rats fed a fat diet rich in polyunsaturated fatty acids (a model of suppressed DNL and insulin resistance), ACCi lowered liver and adipose tissue malonyl-CoA levels and enhanced the whole body clearance of available FFA into oxidation (based on production of ^{3}H-water from a ^{3}H-palmitate infusion). However, this was not associated with an increase in whole body FFA oxidation due to a simultaneous reduction in plasma FFA levels. Repeated oral dosing of ACCi (100µmol/kg/day) for one week reduced hepatic TG levels but did not affect whole body insulin sensitivity (assessed using hyperinsulinemic glucose clamps) or body weight gain. In ob/ob mice, ACCi (20µmol/kg b.i.d, 6 days) decreased liver TG content but actually worsened glucose control (increased fasting plasma glucose and glycated albumin) and raised plasma TG levels without affecting body weight. Finally, effects of genetic inactivation of ACC2 were examined. Deletion of exons 17 and 18 of ACC2 resulted in a drastic reduction in embryonic survival. ACC2 knockdown was therefore performed using an inducible approach in adult animals chronically fed a high fat diet. Conditional ACC2 depleted animals had indistinguishable energy expenditure, food intake, body weight gain and glucose tolerance compared to controls. In conclusion, our results based on both pharmacological and genetic approaches in rodents, do not support the idea that ACC suppression is a useful principle for correction of obesity or insulin resistance.

1152-P

Valsartan-Induced Improvement of Insulin Sensitivity Is Not Mediated by Changes in Microvascular Function in Individuals with Impaired Glucose Metabolism

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Individuals with impaired glucose metabolism (IGM) are at high risk to develop type 2 diabetes (T2DM). Inhibition of the renin–angiotensin system by an angiotensin receptor blocker may delay the onset of T2DM via improvement in insulin sensitivity. The underlying mechanisms may include ARB-induced improvement in microvascular structure and function, which might increase glucose and insulin delivery to insulin-sensitive tissues. We hypothesized that functional and structural capillary density is impaired in insulin resistant subjects with IGM versus BMI-matched controls and that treatment with valsartan (VAL) will improve insulin sensitivity and microvascular function.

In this randomized-controlled trial, individuals with IGM (n=48, 52% males; mean±SE age 56.7±1 yrs; BMI 28.8±0.5 kg/m^2; BP 130/84±2/1 mmHg) underwent a hyperinsulinemic-euglycemic clamp to assess insulin sensitivity (M-value) and capillaroscopy to examine baseline skin capillary density (BCD), capillary density after arterial occlusion (PRH) and capillary density during venous occlusion (VEN) before and after 26-wks VAL treatment or placebo (PLB). 16 BMI-matched normoglycemic individuals (63% males; age 54.4±1.8 yrs; BMI 27.5±0.7 kg/m^2; BP 122/78±2/2 mmHg) served as controls.

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Compared to NGM, IGM were more insulin resistant (P<0.001) and microvascular function variables were diminished by approximately 20-30% (all P<0.001). Univariate associations were found for microvascular function parameters (BCD, PRH, VEN) and M-value (all P=0.004). The relations were independent of age, gender and BMI. VAL vs. PLB improved insulin sensitivity (P=0.034) and lowered blood pressure, whereas microvascular function remained unchanged.

In conclusion, in insulin resistant individuals with IGM impaired functional and structural capillary density was inversely associated with insulin sensitivity. VAL therapy improved insulin sensitivity but did not affect functional and structural capillary density, indicating that other mechanisms may be stronger determinants in the observed VAL-mediated insulin sensitizing effect.

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1153-P

A Malonyl-CoA Decarboxylase (MCD) Inhibitor Suppresses Fatty Acid Oxidation, Has Anti-Diabetic/Anti-Obesity Actions but Promotes Ectopic Lipid Deposition in Rodents

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Effects of inhibiting MCD on in vivo substrate fluxes and the potential of this principle to induce beneficial metabolic alterations in the context of obesity/diabetes were examined in rodents. Acute effects of a MCD inhibitor (MCDi) on in vivo whole body and tissue specific free fatty acid (FFA) metabolism were studied using tracer methods in adult male lean and obese Zucker rats. Tissue rates of FFA utilization (Rf*) and storage were estimated using [9,10-^{3}H]-(R)-2-bromopalmitate and [U-^{14}C]-palmitate FFA tracers. In lean Zucker rats, MCDi induced several systemic metabolic alterations compared to vehicle treated controls: increased muscle and liver malonyl-CoA (MCA), increased plasma FFA levels, reduced plasma FFA clearance and decreased ketone body (KB) levels, decreased hepatic Rf* and in contracting muscles FFA uptake was redirected towards storage rather than oxidation. In contrast, in obese Zucker rats MCDi did not change FFA levels, FFA clearance rate, KB levels or hepatic Rf*, despite a large increase in hepatic MCA. MCDi did however induce a suppression of Rf* in contracting skeletal muscle and a redirection of FFA uptake towards storage in liver and heart. Effects of repeated dosing (7 days), at two dose levels, of MCDi were studied in the diabetic ob/ob mice. Repeated dosing with the high dose MCDi resulted in reduced body weight gain (possibly a result of a MCDi induced increase in hypothalamic MCA), as well as reductions in plasma glucose, fructosamine, TG and KB levels compared to vehicle controls. However, these positive effects were accompanied by lipid accumulation in the heart and liver. In the low dose group, tissue lipid accumulation was observed in the absence of positive metabolic effects. In conclusion, our results suggest that MCDi diverts FFA to storage rather than oxidative metabolism in muscles and liver in vivo. In the ob/ob mouse treated for 1 week with an MCD inhibitor, anti-obesity and anti-diabetic effects were induced, however, these actions occurred together with tissue lipid accumulation.

1154-P

Visceral Obesity Is a Negative Predictor of Remission of Diabetes after Bariatric Surgery

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Our aim was to investigate the impact of Roux-en-Y gastric bypass (RYGB) on abdominal fat depots after surgery. We also aimed to identify preoperative anthropometric and clinical parameters that predict the remission of diabetes after RYGB.

Fifty morbidly obese patients with type 2 diabetes underwent RYGB. Visceral and abdominal subcutaneous fat area was assessed using computed tomography before and 6 and 12 months after RYGB. Remission was defined as glycated hemoglobin (A1C) level <6.5% for 1 year or more without the use of medication.

The visceral-to-subcutaneous fat ratio decreased from 0.60 ± 0.30 to 0.53 ± 0.29 (P = 0.001) after 6 months and decreased further to 0.44 ± 0.28 (P = 0.006) after 12 months. Thirty-four of the 50 patients (68%) had remission of diabetes (remission group). Compared with patients in the nonremission group, patients in the remission group had a shorter duration of diabetes and lower preoperative A1C level, and were less likely to use insulin preoperatively. Preoperative body mass index did not differ, but abdominal fat distribution differed significantly between groups. The visceral-to-subcutaneous fat ratio was greater in the nonremission group (0.79 ± 0.29 vs. 0.53 ± 0.26, P = 0.003). The preoperative visceral-to-subcutaneous fat ratio was an independent predictor of the remission of diabetes after bariatric surgery.

RYGB affected visceral fat preferentially in morbidly obese patients with type 2 diabetes. The visceral-to-subcutaneous fat ratio was a significant and independent predictor of the remission of diabetes after RYGB.

1155-P

High Glucose Condition Reduced the Expression of Low-Density Lipoprotein Receptor-Related Protein 1 (LRP1), and Rosiglitazone Up-Regulated LRP1 Expression in Human Brain Microvessel Endothelial Cells

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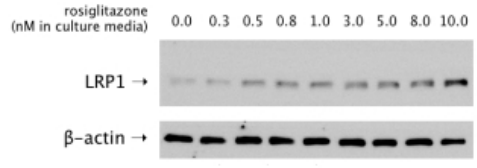
Low-density lipoprotein receptor-related protein 1 (LRP1) serves as a transporter for amyloid β in the brain capillaries, thus playing an important role in clearing amyloid β from brain across the blood brain barrier (BBB). In this regard, LRP1 has been reported to be critical in the pathogenesis of Alzheimer's disease (AD) and an important therapeutic target in AD. In this study, we investigated the effect of high glucose condition and rosiglitazone treatment on LRP1 expression in human brain microvessel endothelial cells (HBMECs)

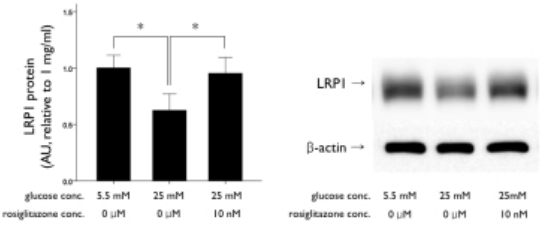
HBMECs were incubated in normal or high glucose condition (5.5 vs. 25 mM in culture media) with or without rosiglitazone treatment (0 vs. 0.5 μM in culture media). The LRP1 expression was assessed by immunoblot.

Rosiglitazone increased LRP1 expression in HBMECs in dose dependent manner.



The effect of rosiglitazone on LRP1 expression in HBMECs. Western blot analyses for LRP1 were performed in HBMECs with various concentration of rosiglitazone. LRP1 = low-density lipoprotein receptor- related protein 1; HBMEC = human brain microvascular endothelial cell

LRP1 expression was reduced in HBMECs incubated in high glucose condition, and rosiglitazone treatment recovered this reduced LRP1 expression.



The effect of rosiglitazone on LRP1 expression reduced by high glucose condition in HBMECs. Western blot analyses for LRP1 were performed in HBMECs with various concentration of glucose (5.5 and 25 mM in culture media) and rosiglitazone (0 and 10 nM in culture media). LRP1 = low-density lipoprotein receptor- related protein 1; HBMEC = human brain microvessel endothelial cell; AU = arbitrary unit; * $p < 0.05$

In conclusion, hyperglycemic condition might reduce the expression of LRP1 in the brain capillaries and impair the clearance of amyloid β across the BBB. PPARγ agonists could recover the reduced LRP1 and the clearance of amyloid β from brain. Therefore, PPARγ agonists could be a therapeutic option in AD with diabetes.

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1156-P

Comparison of Pioglitazone vs Metformin and Effects of the Combination of Both on Cardiovascular Risk Factors in Type 2 Diabetes with Stable Insulin Therapy: The PIOCOMB Study

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Patients with long term type 2 diabetes with stable insulin therapy still exhibit a high cardiovascular (CV) risk. Here we analyzed specific effects of add-on therapy with pioglitazone in comparison with metformin and their combination in patients with acceptable HbA1c control with basal insulin

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glargine on biomarkers of CV risk. In this double blind randomized active comparator controlled trial at two study centres 121 patients with type 2 diabetes were included. Inclusions: stable insulin treatment with basal insulin glargine, HbA1c > 6.5% < 8.5%, age 30-75 years.

The patients were 63.0 (± 7.5) years old, BMI 32.2 (± 5.3), HbA1c 7.34 (± 0.53), insulin glargine dosage 36.2 (± 20.9) units, hsCRP 3.21 (± 2.54). Comorbidities: hypertension 87,6%, CVD 19%. After a run in phase of >2 weeks with glargine monotherapy titrated to FBG < 7.8 mmol/l patients were randomized to either (1) bid 850mg metformin (2) bid 15mg pioglitazone or (3) 30mg pioglitazone plus 1.7g metformin for a treatment phase of 6 months. We measured Matrix Metal Proteinase 9 (MMP-9) as primary objective, hsCRP, PAI-1, NFKB, adiponectin, insulin, HbA1c and 8 epiprostaglandin F2 (PGFα).

Tab. 1 Course of Efficacy Parameters – Absolute Values

Efficacy Parameter [Unit]	1: Metformin (n=39)		2: Pioglitazone (n=37)		3: MET + PIO (n=37)	
	Baseline	LOCF	Baseline	LOCF	Baseline	LOCF
Fasting glucose [mmol/L]	7.97 ± 1.98 (8.10); 39	7.32 ± 1.90 ** (6.79); 39	8.73 ± 2.58 (8.40); 37	7.34 ± 1.58 ** (6.99); 37	8.21 ± 1.96 (7.81); 37	6.52 ± 1.48 ** (6.33); 37
HbA_{1c} [%]	7.33 ± 0.53 (7.30); 39	7.23 ± 0.66 (7.10); 39	7.35 ± 0.54 (7.20); 37	7.19 ± 0.73 (7.20); 37	7.34 ± 0.55 (7.30); 37	6.85 ± 0.75 ** (6.70); 37
HOMA-S [mmol*mU/L²]	3.87 ± 3.89 (2.38); 39	4.14 ± 3.84 b (2.64); 39	4.60 ± 3.93 (2.93); 37	2.39 ± 1.79** (1.85); 37	3.40 ± 3.73 (1.97); 35	1.80 ± 1.30 ** (1.22); 35
MMP-9 [ng/mL]	601.7 ± 317.0 (544.8); 39	651.3 ± 365.3 a (543.3); 39	535.0 ± 214.9 (533.7); 37	480.9 ± 232.4 ** (443.2); 37	581.8 ± 260.7 (504.5); 37	514.0 ± 219.5 (474.3); 37
hs-CRP (≤10) [mg/L]	3.22 ± 2.43 (2.32); 33	2.99 ± 2.42 a (2.00); 33	3.30 ± 2.73 (2.49); 35	2.57 ± 2.07 ** (1.50); 35	2.62 ± 1.79 (1.99); 34	1.78 ± 1.06 ** (1.46); 34
NFkB [RLU]	1.248 ± 0.756 (0.785);38	1.228 ± 0.688 (0.805);38	1.024 ± 0.630 (0.745);36	0.992 ± 0.588 (0.705);36	1.172 ± 0.707 (0.760);35	1.154 ± 0.703 (0.750);35
PAI-1 [ng/mL]	71.2 ± 23.5 (70.0); 39	61.2 ± 27.7 * (54.4); 39	71.4 ± 25.7 (76.3); 37	62.0 ± 29.9 * (59.7); 37	70.9 ± 27.8 (76.0); 36	53.3 ± 30.4 ** (54.5); 36
Adiponectin [mg/L]	4.43 ± 2.61 (4.16); 39	4.33 ± 2.34 b (4.00); 39	4.29 ± 2.69 (3.85); 37	13.20 ± 8.81 ** (11.49); 37	4.83 ± 3.08 (4.11); 37	13.42 ± 7.69 ** (10.94); 37
PGFa [ng/mmol]	164 ± 89 (147); 38	186 ± 99 (168); 38	171 ± 131 (130); 36	186 ± 114 (144); 36	140 ± 46 (133); 37	162 ± 94 (138); 37
Mean insulin consumption; [units]	35.2 ± 17.1 (32.0); 38	37.7 ± 19.6 b (35.2); 38	34.5 ± 16.9 (33.0); 35	27.2 ± 14.6 ** (25.9); 35	35.4 ± 20.3 (32.4); 37	29.4 ± 20.9 ** (24.2); 37

a = p<0.05, b < 0.01 for Met vs. Pio
* = p<0.05, **<0.01 for within group comparison

No serious adverse events were observed. Hypoglycemic episodes were seen in 21.4% vs. 20.0% vs. 28.2%, weight change was -0.7kg vs. +4.3kg vs. +2.7kg and peripheral edema were observed in 11.9% vs. 40.0% vs.20.5% in groups 1, 2 and 3. The addition of pioglitazone but not metformin significantly reduces MMP-9 and hsCRP and increased insulin sensitivity and adiponectin independent from glycemic control. The triple combination of pioglitazone with metformin resulted in better HbA1c without added effect on inflammation and fibrinolysis. Pioglitazone is suggested to be a rational add on therapy to basal insulin in patients with high CV risk.

1157-P

Diacerhein Increase Survival and Improves Sepsis Induced Insulin Resistance in Rats

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Sepsis induces insulin resistance and hyperglycemia is a major risk factor for increased morbidity and mortality in sepsis and the maintenance of normoglycemia has been shown to reduce morbidity and mortality. Here, we studied the effect of diacerhein, a potential new therapeutic agent with properties differing from those of existing nonsteroidal anti-inflammatory drugs, in the treatment of sepsis induced insulin resistance. Sepsis was induced by cecal ligation and puncture surgery (CLP) in male Wistar, they were treated with diacerhein or placebo 3 hours after surgery and then once a day. Serum glucose and inflammatory cytokines levels were assessed 24 hs after CLP. Liver and adipose tissue was excised for protein expression analyses by Western Bloting. A second group was used to evaluate the survival rate. The effect of diacerhein on survival of septic animals was investigated in parallel with insulin signaling and its modulators in liver and adipose tissue. Sepsis was observed to lead to reduction in insulin signaling, a phenomenon which was attenuated by diacerhein. Diacerhein improves survival in septic rats and this improvement is accompanied by a marked improvement in insulin signaling, characterized by an increase in Akt activation. Sepsis induced an increase in the expression/activation of JNK and also in IKK/NF-κB activation, and blunted insulin-induced insulin signaling in liver, and adipose tissue; diacerhein reversed these alterations in parallel with a decrease in circulating levels of inflammatory cytokines. In conclusion, our results show that diacerhein treatment improves survival in sepsis accompanied by a reduction in tissue activation of inflammatory pathways and in parallel improves insulin resistance and tissue insulin signaling and seems to offer a novel therapeutic or prophylactic strategy to sepsis and probably other situations of insulin resistance.

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1158-P

Divergent Effects of Treatment of Polycystic Ovary Syndrome with Anti-Diabetic Agents on Insulin Action and Circulating Inflammatory Cytokine Levels

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Low-grade inflammation, including increased tissue content of neutrophils, is a feature of obesity and the Polycystic Ovary Syndrome (PCOS). The relationship between circulating levels of cytokines and insulin action in PCOS was investigated before and after 6 months of treatment with Pioglitazone (Pio, 45 mg/day, n=12) and again after an additional 6 months with metformin (2000 mg/day) added to all subjects. Compared to age and BMI-matched normal cycling subjects (n=7), there was a tendency ($p<0.1$) for circulating levels of IL-6 and macrophage inflammatory protein 1B (MIP1B) to be lower in obese PCOS subjects; levels of IL-8, IL-10, TNFα,GROα, and MCP1 were similar between groups. At baseline, levels of TNFα, IL-6 and MIP1B were associated with measures of fasting glycemia in PCOS subjects, while IL-6 and IL-8 were associated with measures of maximal insulin action (glucose disposal rate (maxGDR)). Following Pio treatment, changes in IL-6, IL-10 and TNFα levels were significantly correlated with reductions in fasting insulin. While Pio treatment increased maxGDR (5.91±0.50 to 7.44±0.70 mg/kg min, p=0.011), no associations were found between Pio effects on maxGDR or cytokine levels. Metformin alone (n=6) did not have any effect on levels of the cytokines studied. Adding metformin to Pio did not have any additional effect on either cytokine levels or measures of fasting glycemia and insulin action. A function of IL-8 and GROα is neutrophil recruitment. Pio treatment resulted in a reduction in the content in skeletal muscle of CD15, a marker for neutrophils, (81 ± 10% of baseline, p=0.12). In Summary: 1) The circulating levels of a number of inflammatory cytokines are similar in obese women with and without PCOS. 2)Whole body insulin action is improved by Pio treatment in the absence of significant changes in the levels of selected cytokines. Thus, altered responses to inflammatory cytokines/chemokines such as neutrophil recruitment into skeletal muscle rather than reductions in cytokine levels may be a novel mechanism of insulin sensitizing effects of Pio in individuals with PCOS.

Supported by: Dept of Veterans Affairs Medical Research Service

ADA-Funded Research

1159-P

Effect of Adding Pioglitazone and/or Metformin to Insulin Treatment on Blood Pressure and Renal Function in Patients with Diabetes Mellitus Type 2—Results from the PIOCOMB-Study

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The aim of the PIOCOMB study was to evaluate the effect of adding pioglitazone and/or metformin to ongoing insulin treatment in T2DM.

A total of 121 patients on stable insulin treatment were randomized to receive additional treatment with 850mg metformin bid (group A; n=42; age: 64.2±7.3 years, duration of diabetes: 12.3±6.8 years), 15mg pioglitazone bid (group B; n=40; age: 61.5±7.1 years, duration of diabetes: 9.8±5.8 years), or the combination of both (group C; n=39; age: 63.3±7.9 years, duration of diabetes: 10.0±5.7 years). At baseline and after six months blood pressure profiles were recorded, venous blood was taken for the measurement of creatinine and a 24 h urine sampling was performed (albumin/creatinin ratio). GFR was calculated by the use of the Cockroft Gault formula.

As shown in the table, addition of oral treatment decreased HbA1c only in group C ($p<0.001$). Mean 24 h diastolic blood pressure declined in group B (p=0.001), which was mainly caused by a diurnal diastolic blood pressure reduction (p=0.0001) and less pronounced during the night. In addition, a slight, albeit non-significant reduction in the diastolic 24 h blood pressure measurements could be observed in group C (p=0.06). The albumin/creatinin ratio declined in group B ($p<0.01$) and tended to decrease in group C (p=0.09).

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

	A Baseline	A LOCF	B Baseline	B LOCF	C Baseline	C LOCF
HbA1c (%)	7.33± 0.53	7.23±0.66	7.35±0.54	7.19±0.73	7.34±0.55	6.85±0.75
Mean syst. RR (mmHg)	131±12	132±12	133±10	131±12	132±12	131±11
Diurnal syst. RR (mmHg)	134±13	136±14	137±11	134±13	135±12	134±12
Noct. syst. RR (mm Hg)	123±12	123±13	121±13	122±13	125±13	123±12
Mean diast. RR (mmHg)	72±9	73±10	75±8	72±9	74±7	72±7
Diurnal diast RR (mmHg)	74±10	75±11	78±8	74±9	76±7	74±8
Noct. diast. RR (mmHg)	65±7	66±9	66±8	65±9	68±8	67±7
GFR (ml/min)	114.2±34.2	115.8±38.9	116.9±33.7	115.3±36.6	118.7±47.3	117.2±47.9
Alb/Crea Ratio (mg/mmol)	1.14±0.76	1.72±3.12	3.47±14.55	1.19±1.00	1.89±3.14	1.54±1.61

Pioglitazone but not metformin improved blood pressure control and albuminuria in patients with stable insulin glargine treatment.

Supported by: Unrestricted Grant from Takeda Pharmaceuticals

1160-P

Impact of a Pioglitazone/Glargine vs. Metformin/Glargine on Laboratory Biomarkers of β-Cell Dysfunction, Insulin Resistance, and Chronic Systemic Inflammation

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A common approach to start insulin therapy in patients with type 2 diabetes is the addition of basal insulin to the existing oral therapy. The goal of this analysis of the PIOcomb study was to investigate the impact of six month of therapy with pioglitazone plus insulin glargine (PI) in comparison to metformin plus insulin glargine (MI) treatment, and to triple therapy (PMI) on glycemic control (HbA1c) and on the BEVAIR biomarker panel for insulin sensitivity and beta-cell function (intact proinsulin), endocrine visceral lipid tissue activity (adiponectin), and chronic systemic inflammation (hsCRP). A total of 121 patients participated in the prospective double-blind study (47 women, 74 men, age: 63±8 yrs., disease duration: 11.1±6.2 yrs., BMI: 32.2±5.3 kg/m^2, HbA1c: 7.3±0.5 %). They received an optimised and individualised insulin regimen with insulin glargine (titration) and were randomised to additional therapy with pioglitazone (2 x 15 mg/day) or metformin (2 x 850 mg/day), or a combination of both drugs. The changes in glycemic control and the other observation parameters from baseline are provided in the Table.

	MI	PI	PMI
HbA1c [%]	-0.11±0.67	-0.15±0.69	-0.49±0.69*
intact proinsulin [pmol/L]	-3.5±15.2	-2.5±4.6	-2.0±3.0*
total adiponectin [mg/L]	-0.1±0.8	8.9±6.9*	8.6±5.2*
hsCRP [mg/L]	-0.2±2.1	-0.7±1.7	-0.8±1.3*

*: p<0.05 vs. MI

There was no difference in the number of hypoglycaemic episodes between the treatment arms. A reduction in intact proinsulin indicating reduced β-cell stress was seen with all treatments and may be related to the insulin glargine therapy. Reduced endocrine activity of the visceral lipid tissue and reduced chronic systemic inflammation was only seen in the pioglitazone treatment groups.Addition of metformin and/or pioglitazone to a basal insulin therapy with insulin glargine provided stable metabolic control in all cases. A significant improvement in insulin resistance and cardiometabolic syndrome, as indicated by related biomarkers (BEVAIR panel) was seen in the treatment arms with pioglitazone only.

Supported by: Takeda Pharmaceuticals

1161-P

Pharmacodynamic Effects of AZD4017, a Selective 11beta-HSD1 Inhibitor, in Liver and Adipose Tissue

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11beta-hydroxysteroid dehydrogenase type 1 (11BHSD1) converts inactive cortisone to the active glucocorticoid cortisol and is mainly expressed in liver and adipose tissue (AT). It is anticipated that the highly selective, competitive 11BHSD1 inhibitor AZD4017 will act as an insulin sensitizer. The aim was to quantify inhibition of 11BHSD1 indirectly in AT using an-ex-vivo method and in the liver by measuring conversion of oral prednisone to prednisolone in plasma and the ratio of cortisol/cortisone metabolites in urine. 45 healthy adult male volunteers participated in a multiple ascending dose study of AZD4017. 75-1800 mg per day (n=6 for each dose) and placebo (n=15) were administered for 9 days. An oral prednisone (10 mg) challenge was administered at baseline and at end of treatment. Abdominal subcutaneous biopsies were taken at baseline, day 1 and 9 and 11BHSD1 activity in AT was measured *ex vivo* by conversion of added 3H-cortisone to 3H-cortisol measured by HPLC.

After oral administration, AZD4017was rapidly absorbed and had nearly dose-proportional increase in exposure. Inhibition of 11BHSD1 enzyme activity in AT after single doses AZD4017 (approx up to 50% decrease vs baseline, p<0.05) was observed but there was a loss of this effect after 9 days. Transcript levels for the enzymes 11BHSD1, 11BHSD2 and H6PDH in AT were unaltered. The generation of prednisolone decreased dose-dependently (up to >90%, p<0.05) after both single and multiple dosing and there was a decrease in the ratio of urinary cortisol to cortisone metabolites, indicating inhibition of liver 11BHSD1 activity. Serum ACTH and DHEA-s were increased (approx 50%), but generally within the reference range. Serum testosterone and cortisol were unchanged. Triglycerides and total and LDL cholesterol tended to decrease vs. placebo. There was no safety concern except for a few subjects who had slightly increased liver enzyme levels. The results confirm that AZD4017 consistently inhibits liver 11BHSD. Importantly, inhibition in AT seem not to be sustained after multiple dosing and a time-dependent desensitisation in adipose to 11BHSD1 inhibitors could have implications for their therapeutic use in T2DM.

1162-P

Remission of Type 2 Diabetes after Billroth-II Gastrectomy on Patients of Gastric Cancer

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Currently, more and more data indicate type 2 diabetes of obese patients remission after bariatric surgery, especially Roux-en-Y gastric bypass (RYGBP). However, there are no clear pathophysiological mechanisms involved in the rapid resolution of type 2 diabetes. Even more, limited studies are performed on non-obese type 2 diabetic patients. With these questions in mind, glucose and insulin, together with the circulating levels of total glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), were measured by an oral glucose test (OGTT) before and 3 moths after Billroth-II gastrectomy in three groups of gastric cancer: (1)diabetes mellitus (DM), with body mass index (BMI) 23.40±2.06kg/m^2(n=9); (2)impaired glucose tolerance (IGT), with BMI 23.17±2.90kg/m^2(n=7); (3)normal glucose(NG), with BMI 21.17±2.72kg/m^2(n=7). Total AUC 0–120 min for outcome variables were calculated using the trapezoidal method. Three moths after surgery, no patients in DM group required hypoglycemic medication, with fasting glucose (FBG) and 2 hour glucose (2hBG) decreased (7.78±2.15mmol/l to 6.48±0.83mmol/l, p=0.110 and 15.60±3.01mmol/l to 8.39±3.19mmol/l, p<0.001, respectively), and glycate haemoglobin (HbA$_1$C) lowed to 6.19±0.53% from 6.84±0.89% (p=0.077). In IGT group, 2hBG significantly decreased (9.68 0.94mmol/l to 7.23 2.21mmol/l, p=0.019). The glucose fluctuated in normal range in NG group. Before surgery, there were respectively no differences of AUC GLP-1, AUC PYY and AUC insulin among the three groups (p=0.091, p=0.288 and p=0.094). After surgery, GLP-1 peak levels increased in the three groups with no significance, but PYY peak levels significantly increased by 16.74±13.06 pmol/l in DM group (p=0.045), and PYY AUC significantly rised in all the three groups (p<0.001, p=0.001 and p=0.004). There was a positive correlation between GLP-1 AUC changes and PYY AUC changes (r=0.733, p=0.025) and also between GLP-1 AUC changes and insulin AUC changes (spearman's ρ=0.75, p=0.020). In summary, blood glucose can be improved by Billroth-II gastrectomy in non-obese type 2 diabetes and IGT patients, may be related to potential mediator of greater GLP-1 and PYY release after surgery.

1163-P

The Relationship of Prediabetes to Acute Postoperative Cardiothoracic Surgery Outcomes

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Patients with diabetes have more complications after cardiothoracic surgery (CTS), but it is unclear whether this is true for patients with prediabetes (PDM). We evaluated whether patients with untreated PDM defined by preoperative hemoglobin A1c (HbA1c) screening have different outcomes after CTS as compared to those with a normal HbA1c. We screened 1040 patients without a history of diabetes who underwent surgery from

January 2008 to December 2009. PDM was defined as an HbA1c of 5.7-6.4%, while non-diabetes (NDM) was defined as an HbA1c <5.7%. Major exclusion criteria included: no HbA1c value within 3 months prior, an HbA1c value >6.4%, anemia, heart or lung transplant, or ventricular assist device placement. All patients were initially treated with intravenous (IV) insulin postoperatively with a target glucose of 90-120 mg/dL. Outcomes were extracted from the STS National Database and UCLA electronic records. The primary outcomes were postoperative 3 day glucose average (postop 3BG), amount of IV insulin used, length of stay (LOS) and a composite of postoperative complications (including renal, pulmonary, infectious, neurologic, reoperation, death, and readmission). Statistical analysis included t-tests and Chi-square tests. There were an equivalent number of patients in NDM and PDM groups with equivalent postop 3BG. However the amount and time of IV insulin required was significantly greater in the PDM group. Length of stay (LOS) and composite complications were also greater in the PDM group, although these differences were not statistically significant. This may be due to small sample size. Alternatively, equivalent glucose control with more aggressive insulin therapy in the PDM group may negate any deleterious effect of PDM.

	NDM (n=169)	PDM (n=162)	p-value
Age (years)	58.2 (16.4)	66.4 (12.2)	<0.001
Male (#(%))	109 (65%)	108 (67%)	0.76
Postop 3BG (mg/dL)	130.6 (14.9)	131.9 (12.9)	0.41
Total IV insulin used (units)	100.5 (84.9)	139.4 (108.8)	<0.001
Time on IV Insulin (hours)	37.7 (19.4)	45.1 (20.4)	<0.001
Episodes Hypoglycemia <40 mg/dL (#(%))	1 (0.6%)	2 (1.2%)	0.97
LOS (days)	8.5 (4.6)	9.7 (7.2)	0.067
Composite Complications (#(%))	40 (24%)	55 (34%)	0.052

HEALTH CARE DELIVERY—ECONOMICS

[*See also: Presidents Posters 418-PP to 419-PP, page A116.*]

Guided Audio Tour: Health Care Costs for Type 1 Diabetes and Reducing Health Disparities *(Posters 1164-P to 1171-P), see page 11.*

1164-P

The Economic Burden of Illness of Type I Diabetes in a Health Maintenance Organization (HMO) Setting in the United States

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The economic burden of illness during the early stages of type 1 diabetes (T1D) is poorly characterized. The objective was to estimate the direct medical cost of managing T1D among children, adolescents and adults during the first year following onset.

We estimated the diabetes-related costs incurred during the first year of T1D using retrospective administrative and clinical data from Kaiser Permanente Northwest (KPNW). A diagnosis of T1D was based on information from the KPNW diabetes registry between 1999 and 2005, and confirmed by a clinician. Average per-subject costs were stratified by age: 8 to 12 years (children); 13 to 18 years (adolescents); and 19 to 35 years (adults). Direct medical costs included: physician visits, hospitalizations and emergency visits with a diabetes-related diagnosis code; diabetes-related laboratory tests; insulin, needles, syringes and other diabetic supplies. Costs were calculated in 2008 dollars from the perspective of KPNW, and descriptive statistics were used to summarize the data.

A total of 129 subjects with incident T1D were identified: 33 children; 32 adolescents; and 64 adults. Over 90% of children and adolescents and 45.3% of adults were hospitalized during the incident year, with most hospitalizations occurring at the time of diagnosis. Less than 25% of subjects were hospitalized after diagnosis. The proportion of subjects with emergency room visits was 39.4% among children, 31.3% among adolescents, and 40.6% among adults. The direct medical cost per subject was $8,748 (95% confidence interval [CI]: $7,252 to $10,243) among children; $13,659 (95% CI: $7,593 to $19,726) among adolescents; and $7,992 (95% CI: $6,033 to $9,850) among adults. The largest cost driver was hospitalizations, accounting for between 38.2% and 59.5% of total annual costs. Several high-cost hospitalizations in the adolescent cohort contributed to their higher cost.

To our knowledge, this is the first US-based study that presents estimates of the disease-related costs of T1D for children, adolescents and adults in their incident year, and it identifies a substantial economic burden, particularly among adolescents.

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1165-P

Improvements of Glucose Control Seen in Children with Type 1 Diabetes in Rwanda, Africa

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Many children and youth with diabetes in the developing world die quickly or remain in poor control due to lack of access to all the components of diabetes care. The International Diabetes Federation, with Australian Diabetes Council and HOPE *worldwide* administer the Life For a Child (LFAC) program, which provides insulin, syringes, glucose monitoring and education for children and youth with diabetes. One of the objectives of this program is to track the status and improvements of the youth supported by this program. In Rwanda the program is assisted by the University of Pittsburgh Graduate School of Public Health, Department of Epidemiology, with students assisting the Association Rwandaise des Diabetiques (ARD) in the LFAC program requirement of an annual assessment of each child in the program These assessments contain data collected on items such as: date of birth, number of daily injections, daily units of insulin, height, weight, blood pressure, eye function, HbA1c, microalbuminuria, and neuropathy.

As of November 2010, 288 youth have had HbA1c testing completed at least once. Of these, 135 have two or more readings with a follow up interval of 3 – 16 months (mean of 10 months). The mean HbA1c for these children fell from 11.5% at the first visit to 10.6% at follow-up. This represents a decrease of 0.91% over an average of 10 months of follow up (p <0.001). The percentage with HbA1c >14% (maximum reading for DCA Advantage) also fell from 36.5% to 22.0%. However, improvement was not universal and though 76 (56.3%) had a lower second HbA1c (average decrease 2.3% [range 0.1 – 6.6%]), 35 (25.9%) had a higher second HbA1c (average increase 1.5% [range 0.1 – 6.1%]). No change at all was seen in 24 (17.8%) (all but 5 were for readings >14%).

Encouragingly, even within the short follow up time, significant improvements in glycemic control are apparent in this population. However, diabetes control remains a challenge and future plans include assessing different treatment regimens, adapted to this setting, to further improve control.

1166-P

Medical Home in Childhood Type 1 Diabetes (T1D): Associations with Less Parental Work Restriction and Less Financial Strain

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The American Academy of Pediatrics defines the medical home as care that is accessible, family centered, coordinated, comprehensive, continuous, compassionate, and culturally effective. The medical home has been shown to reduce the impact of many childhood chronic diseases on families although its effect in T1D requires further study.

We assessed the association of the medical home with family impact in 583 youth, aged 0-17 years, with T1D and no other chronic conditions, identified from the 2005-06 National Survey of Children with Special Healthcare Needs. Family impact domains included parental work restriction, excessive medical expenses, financial strain (defined as need for added income or presence of financial problems), and substantial time caring for child's T1D (see table). In this random telephone survey, parent/guardian responses indicated the presence or absence of both family impacts and the medical home (e.g. coordinated and family centered care, etc., as operationally defined by the Maternal and Child Heath Bureau).

Overall, 75% of families with T1D reported family impact. In the 50% of families endorsing a medical home, only 69% reported family impact while 84% without a medical home reported impact (p=.01)(see table). After adjusting for child's age, sex, race, home language, poverty level, insurance, parent education, and number of adults in the home, families with a medical home had less work restriction (OR 0.41, p=.002) and less financial strain (OR 0.4, p=.001). The medical home was not associated with medical expenses or time demands.

The majority of families experience substantial impacts. The medical home is associated with less work hour restriction and less financial strain in families of youth with T1D, supporting its importance for this group.

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

% of Families Endorsing Impacts	Any Family Impact	Work Hour Restriction	Financial Strain	Out of Pocket Expenses >$1000	≥11 Hours/ week Caring For Child's T1D
Families of Youth with T1D (n=583)	75%	35%	38%	41%	24%
Families with Medical Home (50%)	69%	26%	28%	41%	22%
Families without Medical Home (50%)	84%	45%	49%	42%	25%
P (with vs without Medical Home)	.01	.003	.002	.9	.6

1167-P

Improved Outcomes and Reduced Disparities in Diabetes Care for Rural African Americans

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Rural African American (AA) diabetic patients have disparate outcomes and access to state-of-the-art diabetes care is often out of reach for this vulnerable population. Previous interventions have focused on urban populations and managed systems of care. We sought to determine the effectiveness of a redesigned culturally relevant model of point-of-care supplemental diabetes care management on glycemic, BP, and lipid control. The study involved a prospective intervention in three purposively selected rural fee-for-service rural practices with historically disparate outcomes compared to usual care in five randomly selected control practices matched for practice and patient characteristics. We enrolled 727 randomly selected rural AA diabetic patients (n = 368 intervention; n = 359 control). Intervention patients received culturally-tailored supplemental care management at the point of care involving education, coaching, and medication adjustment from a team of nurse and pharmacist. Patients in control practices received usual care during the same time period. We evaluated the effect of the intervention on long-term (3-year) changes in HbA1c, BP, and lipids. Statistical analysis compared mean change in biological outcomes in bivariate and multivariate adjusted models. Demographic and clinical parameters were similar at baseline. Intervention patients had a significantly greater reduction in HbA1c at long-term follow-up (-0.6 vs. -0.10; $p < 0.05$); age and duration of diabetes were also significant predictors of change in HbA1c in the multivariate model. BP/lipid changes were greater in intervention patients and approached statistical significance. Health system savings were estimated at > $140,000 using standardized per patient cost of care differentials. Our findings demonstrate that redesigning care in rural fee-for-service practices for rural AA diabetics results in significantly improved long-term glycemic control relative to that in usual care.

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1168-P

Culturally Tailored Diabetes Program Reduces Ethnic Disparities in Asian Americans

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Ethnic disparities in diabetes care have been well described in primary care and cannot simply be resolved by referral to subspecialists. Our study examined if a culturally tailored Asian clinic program can help Asian patients achieve similar glycemic target as white patients in a diabetes clinic within the same specialty institution. The primary outcome for this retrospective study was the proportion of patients reaching A1c of ≤7% after 12 months of care. Subjects included all new Asian American (AA) patients with type 2 diabetes in the Asian clinic (n=109) and a randomly selected sample of new white patients with type 2 diabetes (n=218) who were seen at the same institution between 1/1/ 2004 and 9/30/2009. AA and whites were similar in initial A1c (8.2±0.9, 7.9±1.8%; p=0.19) but different in BMI (25.4±3.7, 32.1±6.6 kg/m^2; p<0.0001), income ($56336±31333, $64253±23186; p=0.013), and English language preference (21, 97%; p<0.02). AA and whites had a statistically comparable proportion of patients with A1c ≤7% (32.1%, 34.9%; p>0.5) at baseline and after 12 months of care (48.6%, 56.0%; p>0.5). The absolute A1c reduction was 0.85% in AA and 0.78% in whites (p=0.71). When stratified according to initial A1c from lowest to highest quartile, 96.7, 61.9, 24.0, and 15.2% of AA vs. 85.2, 58.9, 37.7, and 35.4% of whites within each quartile reached the glycemic goal at 12 months. Ethnic differences among those who failed to achieve glycemic target compared with those who did included older age in AA but younger in whites, lower education level in AA but not in whites and higher baseline A1c in AA (9.5%) than in whites (8.5%). Our results indicated that while a culturally tailored diabetes program in a specialty setting achieved a statistically similar glycemic outcome for AA compared with whites, challenges remain. Diabetic ethnic disparities only persist in AA patients with higher initial A1c who were older and with lower education, in contrast to AA with lower initial A1c. These findings call for a need to further study barriers for care and to develop a stratified treatment approach for AA patients who are especially at risk for treatment failure.

Supported by: Asian American Diabetes Fund

1169-P

Comparing Outcomes and Costs of Diabetes-Related Hospitalizations for AA/PI and Whites in Medicare

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We compared length of stay (LOS), death during stay, and costs of all diabetes-related hospitalizations between 2004-2008 for elderly (65+) Medicare beneficiaries who were Asian American/Pacific Islander (AA/PI) or White. Hawaii Health Information Corporation data, which includes all hospitalizations in Hawaii, was used. Discharge ICD-9 codes identified: (1) uncomplicated diabetes, (2) diabetes complications, and (3) diabetes-related preventable hospitalizations. Multivariate regression models adjusted for age, gender, location, co-morbidity. Out of 188,643 hospitalizations among elderly Medicare beneficiaries, 22.4% (42,265) indicated diabetes, 8.6% (16,208) indicated a diabetes complication, and 1.7% indicated a D-RPH. Among hospitalizations indicating uncomplicated diabetes, every AA/PI group (Japanese, Chinese, Native Hawaiian, and Filipino) was significantly more likely than Whites to have that hospitalization end in death even in adjusted models; odds ratios ranged from 1.18 in Japanese to 1.33 in Filipinos. Whites similarly had fewer deaths than AA/PI during hospitalizations including diabetes complications, but these were significant only in unadjusted models. Among D-RPH, Hawaiians were significantly more likely than Whites to have a hospitalization ending in death in adjusted models (OR: 3.34). Chinese had more expensive visits indicating uncomplicated diabetes than Whites and Filipinos had less expensive visits, which held in multivariate models. For D-RPH, Filipino and Japanese elderly had significantly less expensive visits than Whites even in adjusted models. Filipinos had shorter LOS for hospitalizations with diabetes complications than Whites (8.4 vs. 8.8 days), which held in adjusted models. Filipino and Japanese elderly also had significantly shorter LOS for D-RPH (8.0 and 7.7 days respectively vs. 10.2 for Whites) even in adjusted models. In this 5-year, statewide study, significant variation was seen in outcomes of diabetes-related hospitalizations, particularly in death during stay, for AA/PIs and Whites across a uniform payer (Medicare) even when age and co-mordibity were controlled.

Supported by: NIMHD

1170-P

The Role of Medication Non-Adherence in Blood Glucose Control in the Hispanic Population in Riverside Service Area

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Kaiser Permanente Riverside Medical Center (RMC) is a staff model HMO with 320,000 members of whom 21,190 have diabetes. RCM is the largest health care organizations in the Riverside County in Southern California.

Kaiser members include a diverse population including Hispanics and African Americans. Currently 12% (n=2,487) of RMC diabetes patients are monolingual Spanish speaking patients who are at higher risk due to language and cultural barriers.

We studied the ecology of the Spanish speaking patients compared to the non-Spanish speaking diabetes population. There is higher concentration of monolingual Spanish speaking members in certain cities. Currently 42% of residents in the county are of Hispanic origin. The population studied included Spanish speaking diabetes patients (n=2,489) and non-Spanish diabetes patients (n=19,201). Medication adherence in the Spanish speaking patients (69.62%) rates were lower when compared to non-Spanish diabetes population (74.41%) (P< 0.0001). Average A1c for the Spanish diabetes population was 7.4% compared to the non-Spanish speaking patients at 7.1%(P< 0.0001). Depression scores were better in the Spanish speaking group(7.28% vs 11.58%) (P< 0.0001). A sample survey indicated the following as barriers to care: physician trust, education, cost of medication and the distance to the medical center.

There is a significant reduction in medication adherence and A1c in the Spanish speaking population. A possible reason for less depression may be because the population is located in certain areas with close proximity to family and social support. Based on the data we need to focus on strategies to improve diabetes care based on the ecologic differences. We have identified medication adherence as a significant component to disparity of diabetes care.

Our next phase is to implement culturally based (ecologic) strategies to improve medication adherence. Based on our survey the following has been initiated: 1) Dedicated Spanish speaking case managers 2) Mobile nurse clinics and 3) Interactive voice messaging programs 4) Physician education program.

1171-P

Effect of Modifiable Variables on Demographic Differences in the Treatment and Glycemic Control of Type 2 Diabetes

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Identifying modifiable covariables that significantly reduce demographic disparities in controlling type 2 diabetes could inform efforts to improve health equity. This retrospective study utilized electronic health record data on 22,285 adults with type 2 diabetes seen at 110 outpatient clinics in the Southeast U.S. from 2004–2008. Demographic differences in diabetes control and modifiable covariables which reduce those disparities were quantified using descriptive and logistic regression analysis. Patients were 55.8±14.6 (SD) years old, 57.5% women, 61.0% white and 39.0% black, and had a baseline body mass index 37.7±13.5 kg/m^2 and HbA1c 7.6±1.9%. The percentage with HbA1c <7% was higher in whites than blacks (55.6% vs. 44.7%, p<0.0001) and rose with age from 45.3% at <50, to 50.0% at 50–64, and 59.6% at ≥65 years (p<0.001). White vs. black race/ethnicity (odds ratio [OR] 1.59, 95% confidence interval [CI] 1.51–1.68) and age/10 years (OR 1.20/10 years, 95% CI 1.17–1.22) were predictors of HbA1c <7% in univariable logistic regression. Three modifiable covariables including initial HbA1c, therapeutic inertia (increase dose or add medication for diabetes on at least 50% of visits when HbA1c ≥7% unless diagnosis of hypoglycemia/ hypoglycemic episodes), and visit frequency accounted for 47.9% of the variance in diabetes control. When adjusting for these modifiable covariables, the independent impact of race/ethnicity (OR 1.21 for white vs. black, 95% CI 1.13–1.30) and increasing age (OR 1.13/10 years, 95% CI 1.11–1.16) on HbA1c control declined. Greater attention to early diagnosis and treatment, ensuring regular healthcare visits and overcoming therapeutic inertia could improve diabetes control and health equity.

Guided Audio Tour: Health Care Costs and Delivery for Type 2 Diabetes
(Posters 1172-P to 1179-P), see page 11.

1172-P

Factors Associated with Proper Monitoring of Diabetes Care among the US Non-Institutionalized Population: A Retrospective Analysis of the 2007 Medical Expenditure Panel Survey (MEPS)

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Objective: To examine the rate and predictors of diabetes monitoring in the US. Methods: This cross-sectional retrospective study was conducted on a representative, non-institutionalized sample of the US population (the 2007 Household Component (HC) of the MEPS). According to the ADA 2007 practice guidelines, proper monitoring is defined as at least two A1c tests, one eye and one foot examination annually. Health status was measured by SF-12. A logistic regression model was used to examine the predictors of proper monitoring. Differences in health status and medical expenditures between patients with and without proper monitoring were examined using t-tests. Estimates were weighted to the total population (WTP). Results: Among 1,747 (WTP: 19,320,394) patients with diabetes, 80.64% had at least two A1c tests; 63.29% had an eye examination; and 67.51% had a foot examination. Thus, 63.36% patients (WTP: 14,065,289) received proper diabetes monitoring. Older patients (OR:1.021, 95% confidence interval (CI):1.012-1.030), non-Hispanic Caucasians compared with African Americans (OR:1.236, CI:0.933-1.636), patients with a higher education level (OR:1.211, CI:1.056-1.390), insurance coverage (OR:2.216, CI:1.408-3.486), use of oral anti-diabetic drugs (OR:2.935, CI:2.131-4.042) and insulin (OR:3.453, CI:2.477-4.814) were more likely to undergo the proper monitoring. Well monitored patients had a higher SF-12 Mental Component Summary score (50.09±0.37 vs. 48.51±0.45, p<0.05), but a lower SF-12 Physical Component Summary score (39.95±0.34 vs. 42.28±0.47, p<0.05). Properly monitored patients spent significantly more on total health care services ($5,243), outpatient visits ($1,023), and medications ($1,204), respectively (all p-values<0.05). Conclusion: In the US, nearly 40% patients with diabetes do not receive the proper diabetes monitoring. In addition to racial and socioeconomic disparities, anti-diabetics/insulin use, mental health status, physical health status, and health care expenditure were associated with performing monitoring. Cost-benefit of long-term monitoring should be studied.

For author disclosure information, see page 785.

1173-P

Personalization of Care for Type 2 Diabetes: A Process Control Approach

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Because severity of disease, duration, and co-morbidities varies in patients with type 2 diabetes, a single treatment strategy is not effective for all patients. In this study, we investigate how to best match various treatment approaches to different types of patients, and to assess the impact of personalized care strategies on health outcomes and cost.

We examine two treatment strategies inspired from control theory: feedback (FB) and feedforward (FF). Strategy FB makes treatment decisions based on the current patient state. Strategy FF bases decisions on the anticipated future state. We compare these two strategies with use of an existing treatment guideline, i.e., Staged Diabetes Management® (SDM). A major difference between the strategies is visit frequency (maximum # of visits for SDM=12, FF=6, FB=4). We used a previously developed care simulation model to apply the 3 strategies for 1 year to a population of 10000 simulated patients modeled after a real patient population with type 2 diabetes.

Cost effectiveness of strategies was assessed by calculating the average amount (out-patient) spent on treatment of a group to bring a patient to goal (Total Cost / Patients at Goal, CPG). As shown in Table 1, patients are grouped according to their initial A1c into: low (<8%), medium (8-10%), and high (>10%) A1c categories. SDM is the most cost-effective strategy for the patients in the high A1c group. Strategies FB and FF are the most effective for the low and medium A1c groups respectively, leading to total savings of $2.1M in treatment costs in 1 year.

We conclude that costs and clinical quality of care vary using different personalized treatment approaches. The best method (SDM, FF, or FB) varies depending on the clinical situation and baseline A1c level.

Table 1.

A1c categories (# of Patients)		FB	FF	SDM	Lowest CPG Strategy	Savings in 1 yr vs. SDM
A1c Low (7711)	% Pts at Goal	97	100	100	FB	$1.0M
	Total Cost	$4.2M	$4.4M	$5.2M		
	CPG	567	575	677		
A1c Med (1678)	% Pts at Goal	40	93	100	FF	$1.1M
	Total Cost	$1.8M	$2.5M	$3.6M		
	CPG	2668	1571	2080		
A1c High (611)	% Pts at Goal	0	33	83	SDM	0

1174-P

Integration of Services and Blood Pressure Control among Diabetic Hypertensive Patients

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Integration of services in medical practice has been defined as ability to coordinate functions and activities, including insurance, payment, and care delivery systems. We evaluated the effect of service integration on blood pressure (BP) control among diabetic patients from 28 US primary care sites. Patient clinical and demographic information was collected via retrospective chart review for a random sample of adult patients with diagnoses of hypertension and diabetes (n=2,162). BP control was defined as <130/80 mm Hg, was assessed by site, and means across sites were calculated. A modified Physician Practice Connection Readiness Survey (PPC-RS) was completed by the chief medical officer at each site; this included an integration scale that measured structure, functions, and financial risk. Total integration score was calculated as the mean of these 3 domains, with possible scores of 0 to 100; a higher score indicates better service integration. Correlations between integration scores and aggregated BP outcomes were assessed using Pearson correlation coefficients. To account for clustering of site-specific variables, generalized linear mixed models were used to assess the effect of integration score quartile on BP control.

Guided Audio Tour poster ADA-Funded Research

Mean patient age was 65 (SD 13) years and 40% (SD 12) had controlled BP. 61% of sites employed 50 or more physicians, 50% were physician-owned, and 71% had electronic medical records. Mean integration score was 46 (SD 27, range 4-93); means of subscores were 64 (SD 31) for structure, 33 (SD 43) for financial risk, and 42 (SD 28) for function. Correlation values for the total integration score trended towards significance with BP control (r=0.32, p<0.10), and the structure subscore was correlated with BP control (r=0.48, p<0.05). Sites in the highest quartile of total integration score had better BP control than those in the lowest quartile (41.4% vs 32.7%); compared to the lowest quartile, quartiles 2-4 had somewhat higher adjusted probability of BP control (p=0.16, 0.08, and 0.11, respectively). This study provides evidence that better integration of services in physician organizations is associated with improved outcomes.

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1175-P

Hypoglycemia in Adult vs Elderly Type 2 Diabetes Mellitus Patients: Risks, Costs, and Impact on Treatment Persistence

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We compared risks of hypoglycemia associated with various antidiabetic drugs, impact on treatment persistence, and estimated healthcare costs between adult and elderly patients with type 2 diabetes mellitus (T2DM).

A retrospective analysis of IHCIS/Ingenix impact claims database from 1/1999 to 9/2008 was conducted in T2DM patients aged ≥18 yr with ≥1 prescription drug claim for an oral antidiabetic (OAD) and a subgroup of elderly patients aged ≥65 yr. Hypoglycemia was identified by ICD-9 codes (ICD-9: 250.8X, 251.0X, 251.1X, or 251.2X). Relative hypoglycemia risks of various drug classes were determined using a treatment- and covariate-adjusted Cox proportional hazard regression model with time-varying covariates measured in 6-month intervals. The impact of hypoglycemia on treatment discontinuation (≥30 day gap) was evaluated using adjusted generalized estimating equations. Annual healthcare costs following OAD initiation were compared between patients with and without hypoglycemia using adjusted generalized linear models.

Of 207,748 T2DM patients identified, 30,335 were elderly. The hazard ratios for hypoglycemia risk associated with sulfonylureas, metformin and thiazolidinediones were 1.95 ($p<0.0001$), 1.08 ($p=0.0843$), and 1.22 ($p<0.0001$), respectively, in the elderly, and 1.56, 1.18, and 1.09 (all p<0.0001), respectively, in adults. The odds of treatment discontinuation for those with vs. without hypoglycemia in a given 6-month interval were greater in elderly (OR=1.35, $p<0.0001$) than adults (OR=1.26, $p<0.0001$). The difference in both all-cause and diabetes-related annual healthcare costs between patients with and without hypoglycemia were greater in elderly ($20,264 vs. $11,897 and $11,829 vs. $4,190, respectively, $p<0.0001$) than adults ($14,031 vs. $9,007 and $7,012 vs. $3,265, respectively, $p<0.0001$).

Compared to adults, elderly T2DM patients exhibit higher risks of treatment-associated hypoglycemia in most treatment groups. Risk of treatment discontinuation and healthcare costs attributable to hypoglycemia are also higher in the elderly.

1176-P

Use of a Hypoglycemia Treatment Protocol in a Military Hospital

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Background: Hypoglycemia is a barrier to intensification of insulin therapy in the hospital. Unrecognized or inadequately treated hypoglycemia predisposes to seizures, arrhythmias, and even death. Use of standardized protocols is important in military hospitals with frequent turnover related to deployments. To address this, a nurse-directed Hypoglycemia Treatment Protocol (HTP) was implemented at Wilford Hall Medical Center, Air Force facility, in November 2009 for any bedside blood glucose (BG) <70 mg/dL. Proper implementation of the HTP depended on nurse's ability to recognize hypoglycemia, initiate treatment without delay, and retest at prescribed times.

Objective: To compare hypoglycemic events managed using HTP versus no HTP.

Methods: Hypoglycemia data was collected from a data repository for all inpatients with bedside blood glucose (BG) values < 70 mg/dl. Mean BG at initiating hypoglycemic event; % reaching target BG at any time point; median time to reach target BG in minutes; final status of BG; mean duration from initial to next prescribed BG in minutes; and mean length of stay (LOS) in days. Measures of central tendency (percentages, means, or mediums) were used for descriptive analysis.

Results: A total of 260 hypoglycemic events occurred from Nov. 2009 -Aug. 2010. It was more likely to reach the target BG range with HTP use (80.28%, p<0.0001). The median time to reach target BG was statically significant when groups were compared; 52 minutes for HTP (p<0.0005) group and 79 minutes for non-HTP. LOS was statistically significant when both groups were compared: 8.01 for HTP group versus 12.08 non-HTP (p<.0.0044).

Outcomes	Without HTP (n=118)	With HTP (n=142)	P Value
Mean BG at initiating hypoglycemic event	57.54 (11.17)	57.66 (9.69)	0.93
Mean BG at next prescribed test (SD), mg/dL	119.07 (77.99)	131.97 (70.57)	0.17
Reach target BG at any time point n (%)	65 (55.08)	114 (80.28)	<0.0001
Median time to reach target BG in min	79 (153)	52 (57)	0.0005**
Final status BG n (%)			0.20
Mean duration from initial to next BG (SD) min	221.05 (176.07)	300.33 (211.93)	0.0003
Mean LOS (SD) day	12.08 (14.09)	8.01 (6.46)	0.0044

Conclusions: Findings support use of a nurse directed HTP in a military hospital.

1177-P

"Wal-Mart Effect" Is a Mixed Blessing for Diabetes Drug Prices

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Objective: The emergence of $4 generic formularies at "big-box" discount stores in 2008 prompted concerns about adverse effects of loss-leader marketing on medication prices. An investigation at the time demonstrated substantial cost-savings for price-conscious patients with diabetes for widely prescribed medications. We investigated whether aggressive pricing for generic medications has had a detrimental effect on consumer prices since its introduction.

Methods: Pricing information was available from a previous study for the 10 most-prescribed medications for patients with diabetes in 2008 (Jackness, Tamler ADA 2009 LB-49).We obtained prescription drug prices from the New York State Attorney General offices and verified with the pharmacies in December 2010.

Results: Overall, discounters (Wal-Mart, $507.40 for a 30-day supply) and mail-order pharmacies (Medco, $431.46) still underbid neighborhood retailers and convenience stores (CVS, $612.90). However, all pharmacies have adopted lower pricing for generics, leading to a 58% decrease in price differential. In contrast, the cost and price differential of non-generic medication has increased 113%, particularly at the discounters Wal-Mart and Kmart (Table 1).

Conclusion: Concerns about the long-term effects of aggressive loss-leader marketing have merit: Increased cost for brand medications has lifted overall expenditure at the discount stores that had introduced low-cost formularies. Nonetheless, mail order pharmacies and discounters continue to offer the lowest medication prices for patients with diabetes. Competitive pressures have decreased price differential for value-conscious patients overall, particularly for generics. Patients should therefore exploit the higher price differential for brands.

Table 1: Medication Pricing and Differential

Medication for 30 days / (% since 2008 change)	CVS	Rite Aid	Walgreen's	Target	Wal-mart	Kmart	Drugstore.com ^	Medco by Mail ^	Independent Pharmacy	Maximum Differential
Metformin 500mg	$3.33 (-90%)	$8.99 (-78%)	$8.99 (-73%)	$3.33 (-17%)*	$3.33 (-17%)*	$1.67 (-67%)*	$4.33 (-87%)*	$4.85 (-10%)*	$8.95 (-77%)	$7.28 (-79%)
Atorvastatin** 10mg	$120.99 (24%)	$108.09 (7%)	$102.99 (3%)	$104.49 (23%)	$99.88 (39%)	$124 (29%)	$93.32 (-13%)*	$85.57 (8%)*	$115.95 (35%)	$38.43 (8%)
Lisinopril 10mg	$3.33 (-82%)	$8.99 (-64%)	$9.99 (-50%)	$3.33 (-17%)*	$3.33 (-17%)*	$3.33 (-33%)*	$10.66 (-18%)*	$6.86 (6%)*	$8.95 (-76%)	$7.33 (-78%)
Furosemide 40mg	$3.33 (-78%)	$8.99 (10%)	$8.97 (-17%)	$3.33 (-17%)*	$3.33 (-17%)*	$3.33 (-33%)*	$2.50 (-8%)*	$1.12 (-54%)*	$8.95 (-17%)	$8.85 (-7%)
Pioglitazone** 30mg	$277.99 (64%)	$270.99 (22%)	$251.99 (13%)	$252.99 (17%)	$290.08 (22%)	$290 (37%)	$248.66 (41%)*	$209.38 (17%)*	$275.95 (30%)	$80.62 (72%)
Simvastatin 10mg	$40.29 (26%)	$8.99 (-85%)	$12.99 (-78%)	$16.49 (-58%)	$16.29 (-13%)*	$5 (0%)*	$16.66 (-17%)*	$19.46 (26%)*	$13.95 (-84%)	$35.29 (-58%)
HCTZ 25mg	$3.33 (-78%)	$8.99 (-38%)	$8.99 (-17%)	$3.33 (-17%)*	$3.33 (-17%)*	$3.33 (-33%)*	$2.39 (7%)*	$0.59 (-77%)*	$8.95 (13%)	$8.40 (-4%)
Insulin Glargine** vial	$113.99 (18%)	$102.85 (13%)	$105.99 (23%)	$102.99 (16%)	$102.88 (54%)	$132 (38%)	$111.88 (32%)*	$88.08 (11%)*	$115.95 (21%)	$43.91 (51%)
Amlodipine 5mg	$42.99 (-37%)	$8.99 (-87%)	$29.99 (-62%)	$21.99 (-61%)	$21.62 (-57%)	$3.33 (-93%)*	$6.66 (-89%)*	$11.55 (-79%)*	$7.95 (-89%)	$39.66 (37%)
Atenolol 25mg	$3.33 (-78%)	$8.99 (-38%)	$8.99 (-38%)	$3.33 (-17%)*	$3.33 (-17%)*	$3.33 (-33%)*	$4.00 (1%)*	$4.00 (38%)*	$7.95 (-9%)	$5.66 (-33%)
Total Generic	$99.93 (-49%)	$62.93 (-72%)	$90.91 (-60%)	$55.13 (-53%)	$54.56 (-38%)	$23.32 (-71%)	$47.20 (-58%)	$48.42 (-46%)	$63.68 (-76%)	**$76.61 (-58%)**
Total Brand name	$512.97 (28%)	$481.93 (16%)	$460.97 (13%)	$460.47 (18%)	$492.84 (32%)	$546 (39%)	$453.86 (23%)	$383.04 (13%)	$507.85 (30%)	**$162.96 (113%)**
Total Cost	$612.90 (5%)	$544.86 (-15%)	$551.88 (-14%)	$515.6 (2%)	$507.4 (17%)	$69.32 (18%)	$501.06 (0%)	$431.46 (0.7%)	$571.5 (-13%)	**$181.44 (-25%)**

* Pricing based on 90 day plan, ** Brand name medication, ^ Shipping and handling not included

Clinical Diabetes/Therapeutics POSTERS

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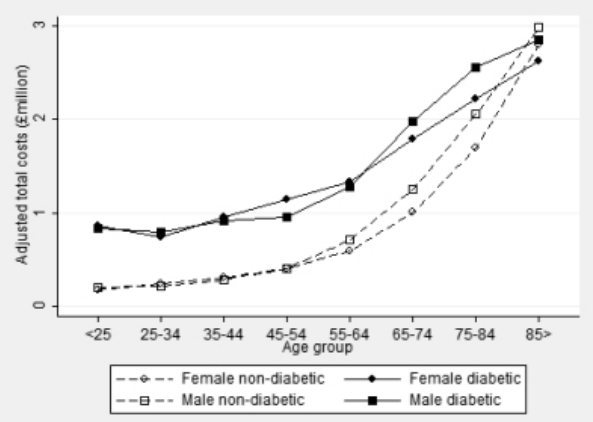
1178-P

WITHDRAWN



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1179-P

Relative Cost of Inpatient Care for People with Diabetes in Scotland: A Study from the SDRN Epidemiology Group

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The rising prevalence of diabetes worldwide has increased interest in the cost of diabetes. We have already ascertained that people with diabetes (4% of the Scottish population of 5.1million) account for 9.8% of the 1.2million total hospital admissions, and 13% of the total inpatient expenditure of £2.9billion. We investigated inpatient costs for all people with diabetes in Scotland relative to the non-diabetic population in 2007 using national diabetes (Scottish Care Information–Diabetes Collaboration (SCI-DC)) and hospital admission (Scottish Morbidity Record 01) data. Inpatient stay costs for people with and without diabetes were estimated using 2009/10 National Tariff.

The crude rate of admission in people with diabetes was 546 admissions per 1000 person years (analysing 108,610 admissions) compared to 224 admissions per 1000 person years in the non-diabetic population (1.1 million admissions). The age and sex adjusted rate of 475 admissions per 1000 person years among people with diabetes reflects 2.1 fold greater admission rate than among the non-diabetic population. Similarly costs were 2.2 fold higher in people with diabetes after adjustment for age and sex. The largest proportionate increase in rates of admission were in the youngest age groups (age<25) where admission rates were increased 4.4 fold in males and 4.9 fold in females. Similarly relative costs (Figure) were increased most markedly in the youngest ages (4.0 fold in males and 4.7 fold in females). Average cost per admission was increased in people with diabetes with the largest relative increase in those aged 35-64.

Admission rates and total costs are considerably greater for people with diabetes suggesting potential for interventions reducing admissions to be cost effective in this population.

1180-P

A Retrospective Analysis of a Pharmacist-Managed Diabetes Management Clinic within an Endocrinology Clinic

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The management of diabetes mellitus (DM) and its co-morbidities often requires case management and multiple clinic visits with a provider. In order to address the long wait times in a busy county hospital Endocrinology practice, a program was piloted where patients requiring intensive diabetes management were referred by an endocrinologist to a clinic run by a pharmacist working with a collaborative practice agreement. The practice agreement allows the pharmacist to titrate insulin and oral antihyperglycemics with a preapproved algorithm. It also allows lipid and blood pressure (BP) lowering medications to be modified. The pharmacist makes decisions regarding the frequency of follow-up the patients require.

Between 4/20/10 and 11/2/10, 25 patients were referred to the clinic, with 19 patients seen at least once. Three patients had Type 1 and 16 had Type 2 DM with a mean baseline A1c of 10.5±2.1%. During the 6-month follow-up period, there were a total of 59 visits to the pharmacist clinic, amounting to 3.1 visits per patient. Eleven patients were on insulin pre-referral, 1 on oral agents, and 7 were on both. Post referral, the patients remained on the same medications, but due to dose titration, the mean A1c at the end of the analysis period was 8.7±1.4% (p=0.03 compared to pre-referral). 95% of patients were on anti-hypertensive medications during the study period; mean 2.6 drugs pre-referral and 2.8 post referral (p=0.69). Mean BP was 134/78±18/12 mmHg pre-referral and 135/73±19/10 mmHg at the time of the last visit (p=0.5). With lipid lowering medications, 73.6% were on a statin pre-referral with a mean low-density lipoprotein (LDL) of 103±43 mg/dL. At the 6-month analysis time point, 78.9% of patients were on a statin (p=0.09 compared to pre-referral) with a mean LDL of 87±56 mg/dL (p=0.7 compared to pre-referral).

We conclude that a pharmacist-run clinic, in collaboration with endocrinologists, is a successful model for the case management and reducing A1c of difficult-to-treat patients with diabetes in a county hospital setting and could be a useful model for other practices to manage a high diabetes patient volume.

1181-P

Advancing Practice Excellence among Solo and Small Group Practices in the Care and Management of Patients with Type 2 Diabetes

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Solo and small group practices (< 6 physicians) are the invisible backbone of primary care in the United States even though they represent 74% of all primary care providers. In California, primary care physicians provide 85% of adult diabetes and other chronic disease care making it critical to involve these physicians in efforts to improve diabetes care and management. The California Medical Association Foundation conducted the Diabetes Quality Collaborative (DQC), a 24 month prospective initiative to determine the impact of disease registry support, team-based care and implementation of practice-created Diabetes Quality Action Plans (DQAP) on clinical quality indicators for patients with type 2 diabetes. Because of the lack of health information technology available in the solo and small practice setting,

For author disclosure information, see page 785.

each participating practice (n = 24) received an incentive valued at $2,600 which included a two-year license for the DocSite Disease Registry, a PDA with a 1 year medical license for a medical software program and a stipend for collecting and reporting patient data through chart extraction. Through the DQC, participating practices received site visits, check-in calls, office hours, training, technical assistance and resources (available in-person and via the web) to provide support in maximizing the use of the registry, developing a prepared and proactive team, implementing their DQAP and conducting small tests of change. Using a pre/post design, data were collected at baseline and at year 2. The data represent 1,941 patients with type 2 diabetes. Improvements were obtained in percentage of patients at HbA1c goal < 7% (41% to 48%), at LDL goal <100mg/dL (44% to 52%), receiving routine foot exams (24% to 35%) and dilated eye exams (14% to 19%). Solo and small practices participating in the DQC were able to achieve improvements in the care and health of their patients with type 2 diabetes. With the onset of health care reform and its focus on patient outcomes, solo and small practices will need to be included in any initiatives to improve diabetes care, with interventions tailored to meet the needs of this practice type.

1182-P

An Administrative Data-Based Foot Risk Index for Lower Extremity Amputation

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Objectives: Our objects in this study were to derive a foot risk index using administrative data based on the International Working Group on the Diabetic Foot clinical risk classification scheme, and to evaluate its association with risk of initial lower extremity amputations.

Methods: This is an analysis of merged Veterans Health Administration administrative and Medicare inpatient and outpatient claims data for a historical cohort of Veterans Health Administration users with diabetes. We classified individuals with diabetes, aged 67 and over in 1999, into seven foot risk categories of different severity derived from the International Working Group on the Diabetic Foot risk classification. We evaluated the associations between foot risk category and different levels of initial lower extremity amputation through 2004 using Cox proportional hazard models.

Results: Of 255,534 individuals with diabetes, 54.8% had a documented foot condition in 1999; 6,869 had an initial lower extremity amputation through 2004. We found increased rates of initial lower extremity amputations as foot risk increased. The hazard ratios for risk of amputation ranged from 1.18 (1.04-1.33) for the lowest foot risk category to 8.34 (7.80-8.91) for the highest foot risk category, when compared to individuals without defined foot conditions. Findings were consistent with and without adjustment of other independent variables.

Conclusions: An administrative data-derived foot risk category was associated with risk of initial lower extremity amputations in a risk level-dependent pattern.

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1183-P

Blood Glucose Testing Constitutes 20% of Total Pharmacy Costs in the USA in Patients with Diabetes on an Insulin Regimen

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Self-Measured Blood Glucose (SMBG) is an essential part of titrating and monitoring an insulin-based treatment regimen. However, little is known about the real-life frequency and costs associated with SMBG in relation to the specific regimen, and what SMBG expenditure is compared to other treatment costs. The present study used the IMS LifeLink Health Plan Claims Database, which have medical and pharmacy claims for more than 71 million unique patients from 102 health plans across the USA. Patients were included in the analysis if: they had 2+ prescriptions for insulin (any type) during the period from January 1, 2007 through June 30, 2009; they had 18+ months of data (6 months for baseline data + 12 months for outcomes data); they had a diagnosis for type 1 or type 2 diabetes; they were persistent with insulin therapy throughout the 12-month follow-up period. Patients were excluded if: they were <4 years old; they had incomplete claims data; their insulin type could not be adequately categorized. 74,936 patients met the inclusion and exclusion criteria. All analyses were stratified by gender, age group, type of diabetes, insulin regimen (basal only, premixed, basal-bolus), type of health plan/payer, geographic region, total healthcare costs for all conditions during the patient's 6-month baseline period, Charlson Comorbidity Index, daily average consumption of insulin. The analysis demonstrated that SMBG (strips, lancets etc.) constitutes 20.2% ($602 of $2,975) of the total annual diabetes-related pharmacy costs (strips, insulin, needles, OAD etc.). Relative cost of SMBG was 15.3% ($399 of $2607) for basal only, compared with 22.2% for basal/bolus ($812 of $3666) and 15.1% for pre-mixed insulin ($395 of $2617). In conclusion, this study shows that SMBG constitutes a large part of the treatment costs for insulin users. New generations of insulin with simpler, user-friendly dosing options and simpler titration are warranted in order to enable relevant cost savings.

1184-P

Care Management Processes and Blood Pressure Control among Diabetic Hypertensive Patients in US-Based Physician Group Practices

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Care management processes (CMP) may be implemented in health systems to improve chronic disease quality of care. We evaluated the relationship between the use of CMP and blood pressure (BP) control among diabetic patients from 28 US-based physician organizations. Clinical and demographic data was collected via retrospective chart review for a random sample of patients aged >17 years with diagnoses of both hypertension and diabetes (n=2,162). BP control was defined as <130/80 mm Hg; "uncontrolled" patients exceeded goal BP by 10 mmHg SBP or 5 mmHg DBP. To assess CMP use, a modified Physician Practice Connection Readiness Survey (PPC-RS) was completed by the chief medical officer at each site. The PPC-RS measures health system organization, delivery system redesign, decision support, clinical information systems, and self-management support. Total PPC score was calculated as the mean of these 5 domains, with possible scores of 0 to 100; a higher score indicates more use of CMP. BP control was assessed by site and means across sites were calculated. Correlations between PPC scores and aggregated BP outcomes were assessed using Pearson correlation coefficients. Mean patient age was 65 (SD 13) years and 51% were female; 39.5% (SD 12) had controlled BP, and 31.7% (SD 9) had uncontrolled BP. Mean total PPC score across sites was 55 (SD 19, range 24-94), with highest scores for health system organization (mean=81.0, SD 29), followed by design support (mean=60, SD=29), clinical information systems (mean=57, SD=16), self-management support (mean=39, SD=26), and delivery system redesign (mean=39, SD=25). Sites in the highest quartile of total PPC score had somewhat better BP control than those in the lowest quartile (42.2% vs 37.0%, p=NS). Correlation values for both total PPC score and the clinical information systems subscore trended towards significance with uncontrolled BP, though correlations were not significant at p<0.05 (r=-0.29 and r=-0.33, respectively). While this study provides some evidence that CMP are associated with better outcomes, further research in this area is warranted.

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1185-P

Cost Effectiveness of a TeleHealth-Based Diabetes Self-Management (DSME) Intervention in a Rural Community

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Lack of access to self-management education is a barrier to care for patients with diabetes in rural areas. A randomized, controlled, clinical trial evaluated the cost-effectiveness of a 12-month remote DSME program that increased the availability of a CDE, a dietitian, and provided remote-camera retinal screening to patients with diabetes in rural community in South Carolina.

Adults with type 2 diabetes were randomized (n=165; 85 intervention and 80 usual care).

The intervention was conducted in-person and remotely in single and group formats. Usual care consisted of one education session by a CDE lasting about 15 minutes followed by approximately 4 hours of education by a health educator. Data were collected prospectively on clinical outcomes, health utilities, resource utilization, and costs.

DTC Per Person Cost

Usual Care		**DTC Intervention**		**Screening Eye Exam**	
Staff Time and fringe benefits	$12	Staff Time and fringe benefits	$802	Staff time and fringe benefits	$20
Transportation	$19	Transportation	$217	Equipment and Supplies	$266
Supplies and incentives	$1	Telemedicine Equipment	$225	**Total**	**$286**
Total	**$32**	Teaching Aids	$45		
		Supplies and Incentives	$99		
		Mailing and Shipping	$25		
		Total	**$1,413**		

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 785.

Cost-effectiveness may be understood in terms of its incremental cost relative to the incremental improvement in A1c, LDL-cholesterol, and eye exam rates. The incremental cost of the DTC intervention relative to usual care was $1,380 over one year. The investment of $1,380 over one year bought a 0.6% absolute improvement in A1c and a 11 mg/dL absolute decrease in LDL-cholesterol. The incremental cost of the DTC educational intervention relative to usual care was less than the annual cost of adding a third-line pharmacologic agent to improve glycemia. The cost-utility for the combined DTC educational intervention and screening eye exam compared to no intervention would then be approximately $17,000 per QALY-gained over 1 year. Interventions costing less than $50,000 per QALY-gained are generally considered being cost-effective. This investment thus represents a good value for the money spent.

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1186-P

Cross-Sectional Survey of Healthcare Access and Diabetes-Related Health Outcomes

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To examine the relationship between insurance status and diabetes-related outcomes in the US, we surveyed a panel of 3,603 subscribers to a diabetes patient newsletter in March 2010. From the 2,244 respondents (response rate=62%), we prospectively defined a subpopulation of 393 patients with type 2 diabetes (T2DM) who reported as exclusively reliant upon self-pay (SP; n=125, mean age 51±8 yrs, mean T2DM duration 9±7 yrs, median annual household income $25,000-$49,999) or employer's health insurance (EI; n=268, 51±9 yrs, 9±7 yrs, $75,000-$99,999) to finance their diabetes care (other groups in the panel, e.g., Medicare, T1DM patients, were excluded). Measures of medication use and health outcomes are summarized below. Reflecting the population surveyed, high percentages of patients self-reported as motivated to discuss their diabetes management with their doctor (66% SP; 67% EI) and as having read ≥3 diabetes resources in the past 30 days (41% SP; 46% EI).

Medication Use	SP	EI	p
Oral anti-diabetic medication	78%	78%	ns
-TZD	12%	21%	<0.01
-DPP-4 inhibitor	6%	12%	=0.06
GLP-1	2%	13%	<0.01
Insulin	37%	46%	<0.05
-Insulin analogs (% of insulin users)	80%	87%	ns
-Insulin syringe (% of insulin users)	58%	25%	<0.001
-Insulin pen (% of insulin users)	18%	41%	<0.01
Regular blood glucose monitor use	70%	79%	<0.05

Health Outcomes	SP	EI	p
A1c ≤7.0%	57%	58%	ns
A1c ≥8.0%	18%	14%	ns
Diabetes-related complications	32%	38%	ns
-Heart/circulation	12%	20%	ns
-Eyes	11%	14%	ns
-Nerves	8%	11%	ns
-Kidney	5%	9%	ns
Hypoglycemia: mild (mean events/past 30 days)	1.8	2.1	ns
Hypoglycemia: severe (mean events/past year)	0.7	0.8	ns

EI patients were more likely than SP patients to use certain diabetes medications (TZDs, DPP-4s, GLP-1s), but had similar glucose control as assessed by A1c and similar rates of diabetes-related complications. While limited by the self-reported, cross-sectional nature of our study, these results suggest that some patients may achieve similar diabetes-related health outcomes regardless of insurance status. Given the population surveyed, we suggest the further study of behavioral and motivational factors to improve upon the cost-effectiveness of diabetes management.

For author disclosure information, see page 785.

1187-P

Encounter Frequency and Blood Glucose, Blood Pressure and Cholesterol Control in Patients with Diabetes

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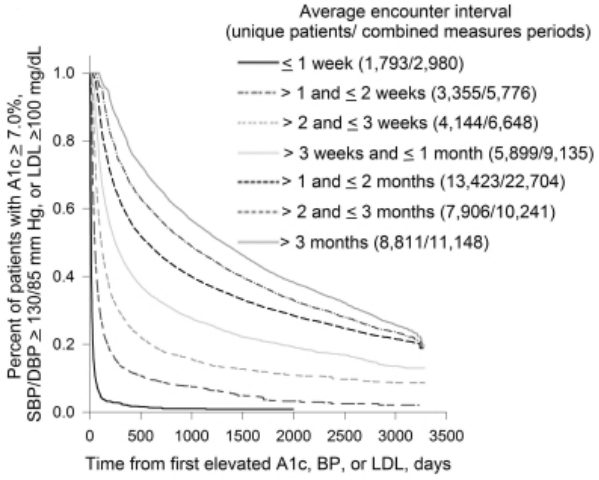
Rapid control of hyperglycemia, hypertension, and hyperlipidemia improves clinical outcomes. Studies suggest that more frequent provider encounters may lead to faster control but there are no guidelines for how frequently patients with diabetes should be seen.

We conducted a retrospective cohort study of 26,496 patients with diabetes and elevated A1c, blood pressure (BP), and/or LDL treated in primary care practices at two teaching hospitals for at least two years between 1/1/2000 and 1/1/2009 to determine optimal frequency of provider encounters for patients with diabetes.

Median time to combined (A1c, BP and LDL) control (Figure 1) rose progressively as encounter frequency decreased from 14 days for patients with mean encounter frequency of ≤ 1 week, to 113 days for mean encounter frequency between 2 and 3 weeks, to 561 days for mean encounter frequency between 1 and 2 months, and to 1,303 days for mean encounter frequency > 3 months ($p < 0.0001$). In multivariable analysis, doubling of the time between physician encounters led to a 32% increase in median time to combined A1c, blood pressure and LDL control ($p < 0.0001$). Time to treatment targets decreased progressively as encounter frequency increased up to once every two weeks for most targets and all the way to weekly encounters for hyperglycemic patients on insulin and hypertensive patients.

Biweekly provider encounters are associated with fastest achievement of A1c, blood pressure, and LDL targets for patients with diabetes. More frequent encounters may be helpful for hyperglycemic patients on insulin and patients with elevated blood pressure.



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1188-P

Health Care Services Use among Home Health Care Patients with and without Diabetes

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Although the use of home health care (HHC) services has become more common over the past decades, little is known about its use among people with diabetes. We used data from 4,546 HHC patients in the 2007 National Home and Hospice Care Survey to examine the prevalence of diabetes (any mention) among the HHC population and compare utilization of selected health services and outcomes between patients with and without diabetes. Ten HHC services—nursing aid visits, skilled nursing visits, medical services, personal care/therapy, counseling services, help from agency staff in taking/preparing medications, pain management strategy, aid devices, assistive devices, and agency services for family/friends and two adverse outcomes (hospitalization and emergent care use in the past 60 days) were compared in bivariate analyses. We used multiple logistic regression to assess the relationship between adverse outcomes and diabetes status, controlling for selected patient characteristics and home health care services.

Approximately 32% (95% CI: 28.8-34.5%) of HHC patients had diabetes in 2007. Among patients with diabetes, about 69% (95% CI: 63.5-74.8%) used blood glucose monitors. Patients with diabetes were more likely to receive medical services (90.9% vs. 83.8%; p=0.002), counseling and/or

psychosocial services (29.1% vs. 22.2%; p=0.005), help from agency staff with medications (38.0% vs. 31.8%; p=0.043), and to use aid devices (80.7% vs. 72.9%; p=0.012) than those without diabetes. No significant associations were observed between diabetes status and hospitalization (adjusted odds ratio [AOR] =0.93, 95% CI: 0.71-1.23) or emergent care use (AOR=1.01, 95% CI: 0.68-1.49). We found that: nearly one-third of patients served by HHC agencies have diabetes; the use of blood glucose monitors may be suboptimal; and patients with diabetes use more of some HHC services than patients without diabetes, but patients with diabetes did not have significantly more emergent care use or hospitalizations. Given the high prevalence of diabetes among these HHC patients, compliance with evidence-based diabetes management should be assessed.

1189-P

Impact of Adherence to Guidelines on Glycemic Control and Chronic Complications in Type 2 DM Patients in Turkey

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Current clinical practice guidelines on diabetes mellitus (DM) has been published in 2009 by The Society of Endocrinology and Metabolism of Turkey (SEMT). Ongoing ADMIRE Project is designed to examine the clinical practice pattern regarding the adherence to guidelines and evaluate the effect of implementation activities addressed to physicians' awareness. Results of first (retrospective) phase had been published before. In this abstract, results of second (prospective) phase are presented.

180 physicians kept 6 months medical records of their type 2 DM patients, without any interference to their routine practice. Scores of degree of adherence were calculated. This report depends on analysis of data of 885 patients included in prospective phase.

Within this population, 62% were women, mean age 55.3±10.4 yrs and DM duration 7.1±6.7 yrs. 82% had been under pharmacotherapy (46% on OAD, 11% on insulin and 25% on OAD+insulin).

Vast majority of patients (76.0%) were evaluated for presence of chronic complications at baseline visit. 47.3% had at least one complication (32.3% one, 12.3% two, 2.5% three, and 0.1% more). Neuropathy was the most frequent (27.0%), followed by retinopathy (23.4%), and cardiovascular (18.0%).

Only 19.5% of patients without any complication was at A1C target (≤6.5%), at baseline visit. This figure decreased gradually in those with complications (13.7%, 3.8% and 5.6% in patients with one, two or more, respectively; p<0.001).

General adherence score was inversely correlated with the levels of average and minimum A1C and FBG levels (all p<0.05).

Average and minimum FPG levels were lower in patients with higher compliance to guideline suggestions on medical history evaluation, physical examination and laboratory evaluation (all p values <0.05). That of A1C levels were lower in patients with higher compliance to laboratory evaluation (p<0.05).

Since data analyzed here have been collected from current real-life practice, findings represent physician's overall clinical practice pattern. It is suggested that, adherence to guidelines is associated with better glycemic control and a decrease in the number of chronic complications.

1190-P

Impact of Bariatric Surgery on Long-Term Remission and Relapse of Type 2 Diabetes Mellitus: Multi-Site Study

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Bariatric surgery (BS) often leads to remission of type 2 diabetes mellitus (T2DM), but long-term follow-up to determine the durability of T2DM remission and predictors of relapse is needed.

We conducted a retrospective cohort study of adults with uncontrolled or medication-controlled T2DM who underwent BS in three health care systems in the HMORN from 1995-2008. A second comparison cohort included all adults with severe obesity (BMI ≥35) and uncontrolled or medication-controlled T2DM from 2005-2008 (years in which BMI data were available from electronic medical records). Our main outcomes of interest were remission and relapse of T2DM, which were defined using pharmacy and laboratory data. We used multivariable-adjusted Cox proportional hazards models and propensity scores to investigate the impact of BS vs. usual care on diabetes remission.

We identified 4,353 adults with uncontrolled or medication-controlled T2DM who had BS from 1995-2008. Most procedures were Roux-en-Y gastric bypass (RYGB; 53.6% open; 42.8% laparoscopic); 1.8% were gastric banding, and 1.8% were other procedures. Overall, 80.0% experienced an initial T2DM remission within five years after BS. Among those with initial T2DM remission, 36.7% relapsed to T2DM within five years. Median duration of T2DM remission was 7.5 years. Significant predictors of remission and relapse were procedure type, poor preoperative glycemic control, insulin use, and longer duration of T2DM. In multivariate analysis of 1,395 BS subjects and 62,167 non-surgical subjects in 2005-2008, BS significantly increased the likelihood of T2DM remission [Hazard Ratio:18.7; 95% Confidence Interval:17.1 to 20.4].

Compared to usual care, BS substantially increases likelihood of T2DM remission, but about one-third of those who achieve remission with BS relapse within 5 years. Caution should be advised in recommending BS as a "cure" for T2DM in severely obese patients.

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1191-P

Improvement in Glycemic Control in Diabetes Patients Adopting a Personal Health Record: EHealth2go

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Health information technology tools are playing an emerging role in assisting diabetes care. Optimal care for diabetes is provided by a multidisciplinary team with ongoing communication among all involved. Currently, patients gather blood glucose (BG) and related data at home and ideally, bring it for review at follow-up visits, typically 3 months apart.

Web-based Personal Health Records (PHR) allow patients to save, store, review, and share personal health information with providers. It has been suggested that PHRs may be used as tools to enable diabetes self-management and to aid communication across the spectrum of care. To-date, high risk minority patients are known to have less access to technology-facilitated healthcare opportunities.

We set forward to demonstrate that minority and vulnerable patients with diabetes can successfully adopt a patient-centric, web-based PHR called eHealth2go as a tool to enable engagement in self-care behaviors and improved outcomes. The eHealth2go PHR uses the Microsoft HealthVault platform. In this pilot project, health navigators assist patients, including those with low computer literacy, to set-up and maintain an eHealth2go PHR. Hgb A1C, BG, BP and LDL-Cholesterol (LDL-C) are performed at baseline and at 3 months. Patients are encouraged to enter and/or download BG data from meters into eHealth2go from home to share with providers. At program completion access to the PHR is still available.

Fifty patients have been enrolled and 29 (African American 86%, average age 62 years) have completed to-date. All, including those with low computer literacy and the elderly, have successfully established PHRs. Interim analysis reveals a trend for improvement in glycemic control, as shown below.

	A1C (%)	BG (mg/dL)	BP (mmHg)	LDL-C (mg/dL)
Pre-	9.3	180	131/76	83
Post-	7.7	151	129/74	83

*Average Values

Of completers, 86% report that they will continue using the PHR. Our experience suggests that the role of the health navigator is essential to assuring successful adoption of the PHR. Interim results suggest that a web-based PHR can be successfully adopted by minority and vulnerable persons with diabetes and used as a tool to enable glycemic control.

1192-P

Medical Home Adoption by Small Primary Care Practices Leads to Better Diabetes Outcomes

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The Patient Centered Medical Home (PCMH) holds significant promise to improve primary care outcomes for chronic illness such as diabetes. Most initiatives have involved practices in large health systems supported by a single payer, despite the fact that most primary care is provided in unconnected small and mid-size practices. Pennsylvania has a statewide multi-payer PCMH initiative focused initially on diabetes and involving state-led learning collaboratives supported by practice coaching and monthly registry-based outcome reporting in over 150 practices.

We report the results from Northeast PA (NEPA), where 29 small to mid-size practices (average of 2 provider FTEs per practice) are receiving payer

support from the region's two largest competing health plans to develop patient registries, redesign their practices guided by the Chronic Care Model, become NCQA-recognized PCMHs, and fund practice-based care management. At the end of each year, the practices will be eligible to share in any payer savings.

Registry generated practice data was examined by regression analysis for the percentage of patients at goal for key diabetes measures for a total population of 11,000 patients. Significant improvements in the percentage of patients at goal for 9 key diabetes measures were noted during the first year (Table 1).

Table 1

Measure	Abs. % Difference from Baseline
HbA1C >9%	-5.9%
HbA1C <7%	+5.3%
BP <130	+11.5%
BP <140	+6.7%
LDL <100	+10.6%
LDL <130	+11.5%
Yearly Foot Exam	+24.7%
Yearly Eye Exam	+18.2%
Yearly Diabetic Nephropathy Screening	+12.8%

Central to the success of the NEPA collaborative has been an early introduction of practice-based care managers, the learning collaborative, and planned care and proactive risk assessment at every patient visit to prevent exacerbations.

Improvements in diabetes care can be realized through adoption of PCMH in small practices. State government can play a critical role in spreading PCMH by convening multiple payer and provider groups to develop infrastructure support for PCMH implementation. This intervention looks promising to improve diabetes patient outcomes and rein in costs.

1193-P

Outcomes Following Insulin Therapy Disruption after Hospital Discharge in Type 2 Diabetes Patients

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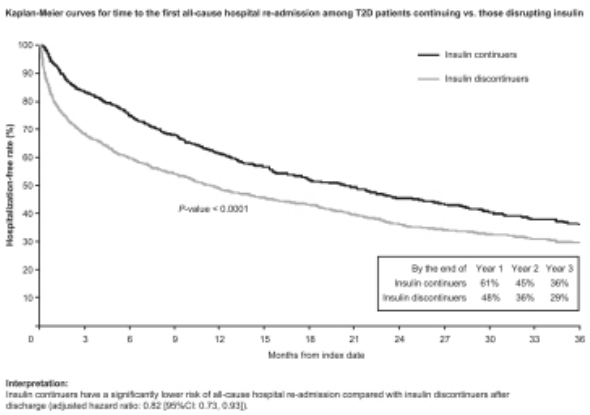
This study investigated clinical outcomes and urgent care use following disruption of insulin therapy (INS) after hospital discharge among T2D patients who had used INS before and during the hospital stay. 2,160 adult T2D patients were identified with INS use within 30 days before and during a hospital stay from electronic medical records in a coordinated health care system (01/2004-04/2010). Outcomes were compared between patients with vs. without INS continuation over the first 60 days post-discharge. Compared to patients with INS disruption, patients who continued INS were younger (63 vs. 65yr $P<0.01$), had more frequent baseline ophthalmic complications (36% vs. 29%, $P<0.01$), and higher blood glucose on admission (211 vs. 187mg/dl, $P<0.01$). Kaplan-Meier analysis showed that patients who continued INS had significantly lower risks of all-cause re-admission compared to patients with INS disruption, which was confirmed using Cox models (figure). INS continuation was associated with significantly lower risk of diabetes-related re-admissions (HR 0.88; 95%CI: 0.77, 0.99) and ER visits (HR 0.88; 95%CI: 0.78, 0.99). Patients who continued INS had greater A1C reduction within 1 year after discharge vs. those with INS disruption (0.51 vs. 0.17%; $P<0.01$). A similar trend was observed among patients with A1C ≥7% before discharge (0.75 vs. 0.42%; $P<0.01$) which consists of 71% of overall population. Multivariate regression analysis showed that patients with INS continuation had a significantly higher A1C reduction–both in the overall population (diff=0.31% $P<0.01$) and in those with A1C ≥7% (diff=0.29% $P<0.05$). T2D patients who continued INS after hospital discharge had greater A1C reduction and lower risk of urgent care visits vs. patients who disrupted INS.



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1194-P

Similar Effects on Essential Parameters Using Telemedical Diabetes Consultations Compared to Regular Outpatient Control: 6-Year Results from the Svendborg Telemedical Diabetes Project

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In order to improve diabetes control and adherence to consultations on the island of Aeroe (7500 inhabitants) a telemedical solution was set up in 2005. The present study´s objective was to examine the impact of this solution on various diabetes variables and patient satisfaction.

The telemedical diabetes consultation were carried out with the patient and nurse specialist placed in a consultation room on Aeroe in audiovisual communication with the physician placed at the hospital on the mainland. An adjustable video camera with zoom function can be directed by the physician. Electronic patient record and a web-based diabetes database were used, including automatic capture of retinal photos.

Patients living on Aeroe with known or recently discovered diabetes were referred to telemedical consultation. Inclusion criteria for the present study were at least 6 month´s of telemedical control, with a minimum of two visits and two HbA1C-values. Results were compared with data from the Danish national diabetes registry, NIP which comprises more than 31.000 diabetic subjects.

In total 24 T1DM, mean age 66,2 yr (range 48-84), diabetes duration 23,5 yr (SD=6,4), BMI 26,5 kg/m^2 (SD=3,8) and 47 T2DM patients, 64,5 yr (range 44-84), 13,3 yr (SD=8,1), 31,6 kg/m^2 (SD=5,7) were included. HbA1C before/after telemedicine, mean (SD), was in T1DM 8,6 (0,6) vs 8,2 (0,5) and in T2DM 8,2 (17) vs 7,2 % (1,2). NIP-values (median) for HbA1C were 8,0 and 7,6 % for T1 and T2DM resp. Systolic/diastolic blood pressure, mean (SD), after telemedical control was in T1 131 (9)/79 (8) and in T2DM 134 (12)/80 (8) mmHg. In T2DM the LDL cholesterol after control was 2,1 mmol/l (SD=0,7). Patient satisfaction was high and mostly related to a reduced transportation time of 5-6 hours.

In conclusion, telemedical consultations for remote outpatient diabetes control is feasible and the interdisciplinary interventions secured a high quality in essential diabetic parameters. Also highly cost-effective due to reduced costs of transportation and less use of specialist working hours related to the diabetes consultations.

1195-P

Skin Autofluorescence: A Tool for Identification of Prediabetes (preDM) and Diabetes (DM)

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While 24 million Americans have DM, 57 million others have preDM. They are at increased risk of developing DM, and thus are candidates for intensive prevention efforts. Laboratory testing is inconvenient, expensive, and not available to many. A non-invasive test would make widespread screening for preDM and DM far more feasible. The advanced glycation endproducts (AGE) reader may offer such a test.

The reader detects accumulated AGEs in tissue, by measuring skin autofluorescence (AF) when the volar forearm is illuminated by ultraviolet light. Skin AF is elevated in DM patients compared to controls, and it is particularly elevated in those with complications, including coronary heart disease, and microvascular complications. Thus, measuring AGE levels may allow early detection of DM, DM complications, and preDM.

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

Our goal was to determine whether elevated levels of AGEs, as measured by skin AF, would identify individuals with preDM, and thus be a useful non-invasive screening method. Subjects were adults receiving care at an outpatient clinic. Those with skin phototype V or VI were excluded, as little reflectance could be measured.

During 2009-2010, 143 patients were tested using a Diagnoptics reader. 44 of these had no chart evidence of glucose measurement, and were excluded. The remaining 99 patients were analyzed. Subjects were age 18-85, 20% were male. 55 patients had normal glucose. The remaining 45 had either known DM or preDM, or had abnormal fasting or random glucose or gestational DM. To account for normal increasing AF with age, skin AF was adjusted for age according to the controls previously reported. AF was considered elevated if above the following levels of arbitrary units (AU) for each age category:

≤ 49 years: 1.84 AU
50-59: 2.12 AU
60-69: 2.50 AU
70-79: 2.76 AU
≥80: 2.89 AU

Of 45 subjects with DM or preDM, 34 were identified by elevated AF levels. As a means of detecting either DM or preDM, AF had sensitivity of 76%, specificity of 46%, positive predictive value of 54%, and negative predictive value of 69%. Although it lacks specificity, AF testing is a sensitive test for predm, and is useful for widespread screening.

1196-P

Team-Based Care: Barriers and Facilitators to Its Adoption in the Patient Centered Medical Home

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Team-based patient care is widely accepted as a way to improve the quality of care for patients with chronic conditions, such as diabetes, and is an essential element of both the Patient Centered Medical Home (PCMH) and the Chronic Care Model (CCM). Twenty-five primary care practices in Southeast Pennsylvania that started implementing the CCM in May 2008 and became NCQA-recognized PCMHs were studied to understand their adoption of team-based care. The practices were in the first of 7 regional rollouts of the Pennsylvania Chronic Care Initiative that now includes 152 practices. The practices participated in a multi-year learning collaborative and received financial incentives to transform from six of the region's health insurers. The primary focus of the initiative was on improving diabetes care.

Domains investigated were (1) knowledge and motivation of the team, (2) relationships within the team, (3) characteristics of a successful team, (4) satisfaction of team members, (5) leadership of the team, and (6) communication. Providers and non-providers on the improvement teams at each of the 25 practices were surveyed (n=98), and interviews and focus groups were completed at 10 practices. Survey responses were analyzed for internal consistency using Cronbach's Alpha and for differences in paired groups using the Wilcoxin test with each domain and demographic characteristic. Qualitative transcripts were coded and analyzed using Nvivo. No significant differences were noted between providers and non-providers.

Key findings that contributed to team-based care include the importance of regularly scheduled meetings, standing orders to empower team members, an overall redistribution of workload, recognition and rewards, facilitative leadership, an electronic medical record system to facilitate communications, and collaborative learning and sharing with other practices. Some practices more fully adopted team-based care than others, but overall participants were appreciative of the opportunity and had a positive experience.

1197-P

Underestimated Impact of Non-Severe Nocturnal Hypoglycemic Events (NHEs) on Patients' Functioning and Well Being: Approximately 30% of Events Result in Work Absenteeism and Productivity Loss

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Non-severe nocturnal hypoglycemic events are experienced by both children and adults, occurring approx. during 8.5% of nights. Despite the fact that these events are not uncommon, there is little in the published literature about NHEs and their impacts. Three data sources were used to assess the impact of non-severe NHEs: 1) a systematic literature review using multiple databases of English articles from 1995–2010; 2) qualitative data from 70 patients in focus groups in 3 countries; 3) a 4-country survey, which was quantitatively analyzed for subjects who had experienced a non-severe NHE in the past month. The literature search identified 32 relevant articles out of 746. These suggested that NHEs impact patients' sleep quality as well as affecting them the following day, causing increased fatigue levels and decreased cognitive ability resulting in work absenteeism, missed appointments and lost work productivity. Major themes identified in the focus groups, regardless of country, were sleep quality issues, negative impacts on patients functioning the next day, and fear and worry about health and diabetes status. Out of 2,600 survey responders, 1,844 subjects had experienced a non-severe NHE in the last month. 54% of these subjects worked; of these, 22.7% reported they showed up late or missed a full day of work the following day and 31.8% reported that they missed a meeting or work appointment or did not finish a work task on time. For respondents reporting missed work, an average of 14.7 (SD: 11.6) working hours were lost (absenteeism). On average, 20% of subjects who experienced a non-severe NHE contacted a healthcare professional and 20% reduced their insulin dose over subsequent days as a result of the event. In conclusion, approx. 30% of non-severe NHEs result in lost work productivity and absenteeism. Thus, the impact of non-severe NHEs is not inconsequential and has been both underestimated and underrepresented in the published literature. These results highlight the need for more attention clinically and in research in order to improve life for those affected by NHEs.

PEDIATRICS—OBESITY

[***See also: Presidents Poster 420-PP, page A116.***]

1198-P

Abdominal Adiposity as a Predictor of Metabolic and Cardiovascular Risk Factors in Youth

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BMI screening in children is limited due to the variation in body shape, maturation patterns, and muscle mass. Moreover, BMI does not provide information about abdominal fat, which conveys substantial health risk. In youth, waist circumference (WC) and waist-hip ratio (WHR) are independent predictors of insulin resistance (IR) and cardiovascular (CVD) risk factors and may be superior to BMI. There are minimal data evaluating abdominal height (AH) as a predictor of metabolic and cardiovascular risk factors in youth. The purpose of this study was to evaluate WC, WHR and AH as predictors of IR and CVD risk factors, independent of BMI. Sixty-five youth (26 M, 44 AA, mean±SD=14.4±1.6 yr) who were referred to rule out diabetes were evaluated. Anthropometry and laboratory studies (HbA1C, glucose, insulin, c-peptide, lipid levels, IGFBP1) were obtained. Pearson partial correlations (pr) were obtained between WC/WHR/AH and the CVD and IR outcomes independent of BMI. Logarithmic transformations of triglycerides, insulin, and HOMA IR were used in order to normalize their skewed distributions. WC and WHR were significantly correlated with triglycerides, insulin, c-peptide and HOMA IR, independent of BMI. AH was correlated with c-peptide, independent of BMI.

	WC		WHR		AH	
	pr	*p-value*	*pr*	*p-value*	*pr*	*p-value*
LN (Triglycerides)	0.378	0.002	0.428	<0.0005	0.156	0.23
LN (Insulin)	0.394	0.001	0.351	0.005	0.142	0.27
C-peptide	0.399	0.001	0.456	<0.0005	0.336	0.008
LN (HOMA IR)	0.328	0.008	0.343	0.006	0.171	0.18

Conversely, while BMI had statistically significant bivariate correlations with triglycerides, insulin, and c-peptide (and marginally with HOMA IR), these correlation coefficients were reduced and became statistically non-significant after adjusting for either WC or WHR (for triglycerides, insulin, c-peptide, and HOMA IR) or AH (for c-peptide). The bivariate and partial correlation analyses suggest that WC and WHR provide important information about CVD risk and HOMA IR, independent of BMI, among youth being evaluated for diabetes. AH did not perform as well as an independent predictor, except as a stronger predictor of c-peptide than BMI.

1199-P

Association of Lipid Concentrations with Puberty and Fat Mass in Argentina's School Children

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Abnormal lipid levels often emerge during childhood. The aim of this: to determine the association between lipid concentrations and puberty, and fat mass; b) to compare the prevalence of dyslipidemia as defined by the NCEP (the National Cholesterol Education Program standards) & AHA (American Heart Association) criteria with our percentiles.

Data were collected cross-sectionally from 1264 children (604 M) aged 5-15 y in 8 schools in April and September 2007-2009. Anthropometric measurements, blood pressure, Tanner, glucose and lipids were measured.

The prevalence of obesity was 15.4% (195) and of overweight 16.6% (210) per CDC. Median values of triglycerides (74 vs 64 mg/dL, p<0.01) were higher whereas values of LDL-C (87 vs 93 mg/dL,p<0.01) were lower in pubertal than in pre-pubertal children. The effect of sexual maturation on LDL-C was larger in boys, whereas its effect on triglycerides was larger in girls. A comparison of rates calculated using our percentiles or those proposed by the NCEP & AHA, showed significant differences for high triglycerides and low HDL-C in pre-pubertal children, and for high triglycerides and high LDL-C in pubertal girls.

		Pre-pubertal		Pubertal	
Lipids		NCEP %	McNemar p values	NCEP %	McNemar p values
Low HDL-C	Boys	7.8	**<0.01***	9.4	0.02*
	Girls	7.6	0.03*	9.0	**<0.01***
High Triglycerides	Boys	3.6	0.02*	3.6	0.25
	Girls	1.2	**<0.01***	7.5	0.01*
High Total cholesterol	Boys	5.2	0.99	1.4	0.03*
	Girls	4.2	0.25	7.0	0.02*
High LDL-C(mg/dL)	Boys	4.1	0.25	2.2	0.13
	Girls	3.8	0.13	2.3	**<0.01***

Significant correlation was found for hypertriglyceridemia and [pubertal stage OR, 1.3; (95% CI 1.1-1.6), gender OR, 1.6; (95% CI 1.1-2.3) and obesity OR, 2.2; (95% CI 2.8-6.0)] and for low HDL-C and [pubertal stage OR, 1.3; (95% CI 1.1-1.5), and obesity OR, 1.8; (95% CI 1.6-3.1)], adjusted for age.

This research suggests that the usual levels of blood lipids are significantly dependent on pubertal development, BMI and waist circumference in children.

1200-P

Childhood Obesity: Risk Factor to Precocious Cardiometabolic Disease

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The natural history of atherogenesis begins early in life and may be anticipated and accelerated by some risk factors such as childhood obesity. We aimed to evaluate the association between excessive weight and metabolic syndrome [MS] and endothelial dysfunction in 124 Brazilian youth (1.88±0.83 BMIzs; 63[49.2%] girls, 14.6±2.7y). Measurements: body mass index (BMI), waist circumference (WC), blood pressure (BP), Homeostasis model assessment of insulin resistance (HOMA-IR), laboratory tests (glucose, insulin, glycated hemoglobin, leptin, interleukin-6, cholesterol, high-density lipoprotein cholesterol [HDL-C], apolipoprotein A1 and B, free fatty acid, triglycerides [TG], uric acid, C-reactive protein, alanine and aspartate aminotransferases [ALT/AST]) and imaging tests (carotid intima-media thickness [C-IMT], endothelium-dependent brachial artery flow-mediated dilatation (FMD) at rest and during reactive hyperemia). By anthropometry 66 (51.6%) and 51 (39.8%) had excessive and normal weight respectively and by International Diabetes Federation criteria 9 (7.0%) had MS. The rate of high BP and TG, low HDL-C and glucose disturbance was respectively 17.2%, 10.9%, 14.8% and 0.8%. It was found a significant correlation between C-IMT and age (r=0.346, p<0.001), systolic BP (r=0.393, p<0.001), WC (r=0.310, p=0.002), uric acid (r=0.386, p=0.001), insulin (r=0.271, p=0.026), glucose (r=0.265, p=0.026), HOMA-IR (r=0.334, p=0.005), ALT (r=0.341, p=0.004), AST (r=0.332, p=0.005) and Apolipoprotein A1 (r=-0.284, p=0.018). Also with FMD at rest and with reactive hyperemia and age (r=0.356, p<0.001; r=0.398, p<0.001), BMIzs (r=0.266, p=0.008; r=0.260, p=0.011), WC (r=0.453, p<0.001; r=0.471, p<0.001), systolic BP (r=0.392, p<0.001; r=0.460, p<0.001), uric acid (r=0.439, p<0.001; r=0.497, p<0.00), HbA1c (r=0.284, p=0.022; r=0.309, p=0.012), ALT (r=0.565, p<0.001; r=0.54, p<0.001), AST (r=0.635, p<0.001; r=0.584, p<0.001), glucose (r=0.403, p=0.001; r=0.264, p=0.031) and HOMA-IR (r=0.315, p=0.009; r=0.293, p=0.017). These observations suggest that vascular health is affected in early stages of life in population with traditional cardiometabolic risk factors such as obesity, systolic hypertension, insulin resistance and atherogenic profile.

Supported by: State University of Feira de Santana, FAPESB, Alvaro Laboratory

1201-P

Community-Based Diet and Exercise Program for Overweight and Insulin-Resistant Youth

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Objectives: Children and adolescents in working and lower income communities are more affected by obesity than children from affluent backgrounds, but resources for management and prevention are limited. We sought to evaluate the feasiblity and effectiveness of an intervention that utilized the resources of community progams, as a model for action in the community setting.

Study Design: A community health center data base was used to identify children (ages 9-13), with BMI>85% for age. The intervention was provided at local youth center in Lowell. After informed consent was obtained, 24 children were enrolled in a 5-month after-school program, once/week, and met for 1 hour with a nutritionist and 1 hour of high-activity exercise. Meetings with families were held at midpoint and completion. At baseline and completion, we collected a fasting fingerstick blood sample, and evaluated weight, height, and answers to a behavioral survey. The study was approved by the University of Massachusetts IRB.

Results: The intervention was completed by 15 children. The fingerstick blood sample method was acceptable to all participants who remained in the study. The 100 μL serum volume was sufficent to measure insulin (ELISA, CV, 10%), glucose (hexokinase, CV, 5%), and several other indicators that are planned. A diagnosis of metabolic syndrome was suggested in 11 subjects (baseline fasting insulin>15 μU/ml). No subject with diabetes (fasting glucose>120 mg/dL) was observed. The subjects showed a trend toward continued weight gain (average, 2.5 kg) and increased fasting insulin (both ns). Subjects did not show improved attitudes toward diet and exercise, as determined by behavioral survey.

Conclusions: The study demonstrated that overweight children could be enrolled in an intervention, that was based on community programs that are part of their customary after-school activities. The objectives of improvement in metabolic syndrome indicators and behavioral attitudes were not achieved, but we hypothesize that a 1-y intervention will be needed. Our findings support the feasibility of community-based programs to provide intervention for overweight youth in lower income and working class communities.

1202-P

Determinants of Weight Loss among Obese Children Enrolled in a Multidisciplinary Weight Management Program

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Individual responses to lifestyle treatment for obesity vary, especially for adolescents who experience dramatic physical growth and development. Therefore, we investigated determinants of weight and BMI loss among 162 obese children (BMI ≥95th percentile, 11-18 yrs, 34% boys, and 75% African American) enrolled in a multidisciplinary weight management program. Subjects completed a 6 month intervention, including nutrition education, physical activity, and behavioral modification. During this period, children attended biweekly nutrition education sessions with their parents and were expected to exercise for a >1 hour, 3 days/week, including ≥ one supervised session/week. A 48-hour dietary recall and 7 day physical activity recall were conducted by a registered dietician and trainer at baseline and 6 months. Pubertal development was measured by Tanner stage by a physician. At 6 month, BMI had lowered significantly to 36.7±6.9 from 37.6±6.9 kg/m^2 (mean ± SD, P<0.001). Specifically, we considered age, sex, race, Tanner stage, family history of obesity, reduction of energy intake (REI), increase of energy expenditure (IEE) of daily activities, and baseline weight or BMI for the prediction of changes in body weight and BMI. Surprisingly, neither IEE (P>0.80) nor Tanner Stage (<0.30) was significantly associated with weight change in univariate linear regression models. The non-significance of IEE may be due to its relative small change (11.9±43.8Met-h/week). We forced age, sex, and race, and included REI in linear regression models to predict weight and BMI loss at 6 months. Age was positively associated with

For author disclosure information, see page 785.

weight loss (1.68kg/yr, p=0.001) and BMI reduction (0.31kg/m^2/y, p=0.034). REI of 100 kcal /day was significantly associated with weight loss 0.30 kg (p=0.004) and BMI reduction 0.1Kg/m^2 (P=0.006). Sex and race were not associated with weight change and BMI reduction. In conclusion, age and change in REI were important predictors of adolescent obesity reduction resulting from lifestyle modification. Obese adolescents may still maintain their obesity status with small IEE only.

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1203-P

Effects of a Community-Based Diabetes Prevention Program for Overweight Latino Youth

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Obesity and insulin resistance disproportionately impact Latino youth who experience one of the highest lifetime risks for developing type 2 diabetes (T2D). Few diabetes prevention programs have addressed "upstream" factors related to T2D, nor the specific culturally relevant lifestyle needs of overweight Latino youth. The purpose of this study was to test the efficacy of a culturally informed, community-based diabetes prevention program for overweight Latino adolescents on insulin sensitivity and glucose tolerance. Overweight Latino adolescents (n=18, BMI%=96.2±4.1, age 15.2±1.0 yrs) were invited to participate in a 12-week lifestyle education program developed through a partnership between a community health clinic, an academic institution, and a local YMCA. Weekly group nutrition and lifestyle education classes were delivered to families by bilingual/bicultural *promotoras* and three, 1-hr moderate to vigorous exercise sessions per week were held for youth. The program was designed to improve health by empowering youth and their families to make healthy lifestyle choices as well as empower community agencies to collaboratively facilitate these choices. A multi-sample 2-hour oral glucose tolerance test with 30 minute sampling for insulin and glucose was used to assess T2D risk before and after the program. Fifteen youth (7 boys / 8 girls) completed the program and attended 91% of the education and physical activity sessions where mean heart rate was 146 ± 21 BPM. Compared to baseline, insulin sensitivity (Matsuda Index) increased by 33.1% from 2.4 ± 1.3 to 3.1 ± 1.4; p=0.01, 2-hour post-challenge glucose decreased by 9.2% from 117.2 ± 4.8 to 104.5 ± 2.7 mg/dl; p<0.01, and 2-hr post-challenge insulin decreased by 37.6% from 161.2 ± 21.3 to 88.8 ± 16.7 µIU/ml; p=0.001. No significant changes were noted for fasting glucose or insulin. The improvements in insulin sensitivity and 2-hr glucose measures following the lifestyle intervention indicate a potential reduction in T2D risk among this high-risk population. Community-based efforts are needed to close the diabetes-related health disparities gap and collaborative partnerships may prove most effective for reaching high-risk youth.

1204-P

Effects of a Lifestyle Intervention on Cardiometabolic Risk Factors in Overweight/Obese Latino Adolescents

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Overweight youth are at high risk for developing cardiovascular disease and type 2 diabetes. Lifestyle intervention is the cornerstone for preventing long-term obesity-related chronic health conditions but few successful risk-reduction programs for overweight youth have been described in the literature. The purpose of this study was to test the efficacy of a combined nutrition education and physical activity program on cardiometabolic risk factors in a vulnerable population of high-risk youth. Fifteen (7 Male; 8 Female) overweight and obese (BMI percentile = 96.4 ± 4.5) Latino adolescents (15.0 ± 1.0 years old) completed a 12-week lifestyle intervention that included weekly group nutrition education classes and 180 minutes of moderate to vigorous exercise per week (3 X 60 minute sessions). Participants were assessed at baseline and follow-up for BMI percentile, waist circumference, blood pressure, and fasting cardiometabolic risk factors (total, HDL, and LDL cholesterol and triglycerides). As a result of the intervention, BMI percentile decreased 1.3% (96.3 ± 1.2 to 95.0 ± 1.4, p=0.02), waist circumference decreased 3.7% (107.0 ± 4.3 to 103.1 ± 5.0 cm, p=0.02), systolic blood pressure decreased 3.8% (122 ± 3 to 118 ± 2 mmHg, p=0.03), total cholesterol decreased 13.3% (153.7 ± 7.0 to 133.2 ± 7.9 mg/dL, p<0.01), LDL-cholesterol decreased 16.1% (90.1 ± 6.1 to 75.7 ± 6.5 mg/dL, p<0.001), and triglycerides decreased 30.5% (141.2 ± 14.3 to 98.2 ± 9.8 mg/dL, p<0.01), while no changes were noted for HDL-cholesterol (40.0 ± 1.8 to 39.2 ± 1.1 mg/dL) or diastolic blood pressure (71 ± 2.4 to 68 ± 2.4 mmHg). Significant reductions in cardiometabolic risk factors among high risk youth were observed in response to the lifestyle intervention. Moreover, improvements were noted in the absence of weight loss (90.7 ± 6.8 to 89.9 ± 7.2 kg). These findings suggest that lifestyle modification can improve cardiometabolic health independent of weight loss among overweight and obese adolescents.

1205-P

The Prevalence of Insulin Resistance and Obesity and Their Correlation in School-Age Children Undergoing Population Based Health Check-Up Programs

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Little information is available regarding the prevalence of insulin resistance and obesity and their correlation in school-age children.

With a population of some 12,000, Tsunan town is counted among the leading "longevity towns" in Niigata prefecture, Japan.

Of the junior school 3rd graders (14 to 15 years old) participating in the health check-up program (participation rate: 100%) sponsored by the town in 2009-10, 157 (86 males and 71 females) were included in this study. Presence of insulin resistance was defined as a HOMA-IR of 2.5 or greater, and presence of obesity defined by BMI (22.96 or greater for males and 23.66 or greater for females). The percentages of those who met either definition were compared by using Mann-Whitney test. The relationship between the HOMA-IR and the BMI were examined by using Spearman's correlation coefficients.

The median fasting glucose and insulin levels, HOMA-IR, and BMI (25%–75% values) were 89(85-93) mg/dL, 6.9 (5.8-8.3) µIU/mL, 1.2 (1.8-1.7), and 19.3(18.2-20.9) for the males, and 87(83-90) mg/dL, 6.1(5.8-6.6) µIU/mL, 1.4(1.2-2.0), and 20.4(19.0-22.1) for the females. Comparisons between the males and females showed that, of all the variables examined, the insulin level, HOMA-IR and BMI were significantly higher (p=0.006, P<0.001, P=0.007) among the males than in the females. Nine males (10.6%) versus 12 females (16.9%) were diagnosed as insulin-resistant, while 8 males (9.4%) versus 7 females (9.9%) were diagnosed as obese, with 3 each (3.5% versus 4.2%) diagnosed as both insulin-resistant and obese in either sex. The correlation coefficients between the HOMA-IR and the obesity index demonstrated no significant correlation (r = 0.214; P = 0.073) among the females, but a significant correlation (r = 0.272; P = 0.012) among the males.

In a survey involving virtually all the junior high school 3rd graders in a local town, the frequency of individuals diagnosed as insulin-resistant or obese was about 10% among the children of each sex. However, the diagnoses of insulin resistance and obesity were found not necessarily consistent in both males and females.

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1206-P

Wrist Circumference Could Be a Clinical Marker of Insulin Resistance in Overweight/Obese Children and Adolescents: A Hypothesis

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Excess fat is one of the main determinants of insulin-resistance also in young subjects, representing the metabolic basis for developing future cardiovascular disease (CVD). The aim of the study was to correlate wrist circumference (an easy to detect bone anthropometric marker) with insulin resistance parameters in order to open new perspectives in the prediction of cardiovascular risk.

Four-hundred and seventy-seven overweight/obese children and adolescents (mean age 10.31±2.80) were consecutively enrolled. Standard deviation score Body Mass Index (SDS-BMI), fasting biochemical parameters, Homeostasis Model Assessment of Insulin-Resistance (HOMA-IR) were evaluated. Statistical differences were investigated using multiple linear regression analysis.

Manual measure of wrist circumference was evaluated in all children and adolescents. Fifty one randomly selected subjects, underwent a Nuclear Magnetic Resonance (NMR) of the wrist to evaluate transversal wrist area at Lister's tubercle level. A significant association was found between manual measure of wrist circumference and insulin levels or HOMA-IR (β=0.34 and 0.35 respectively, p<10^{-5} for both comparisons). These associations were

more significant than those between SDS- BMI and insulin levels or HOMA-IR (β=0.12 and 0.10 respectively, p<0.02 for both comparisons).

NMR imaging acquisition clarified that the association between wrist circumference and insulin levels or HOMA-IR reflected the association with bone tissue related areas (p<0.01 for both), but not with the adipose tissue ones (p>0.05), explaining 20% and 17% of the variances of the two parameters.

Our findings suggest a close relation between wrist circumference, its bone component and insulin resistance in overweight/obese children and adolescents opening new perspectives in the prediction of cardiovascular risk.

PEDIATRICS—TYPE 1 DIABETES

[***See also: Presidents Posters 421-PP to 422-PP, page A117.***]

Guided Audio Tour: Pediatrics—Type 1 Diabetes—Autoimmunity, Complications, and Beyond *(Posters 1207-P to 1214-P), see page 15.*

1207-P

A1c Variability Predicts the Risk of Microalbuminuria among Children with Type 1 Diabetes Mellitus (T1DM)

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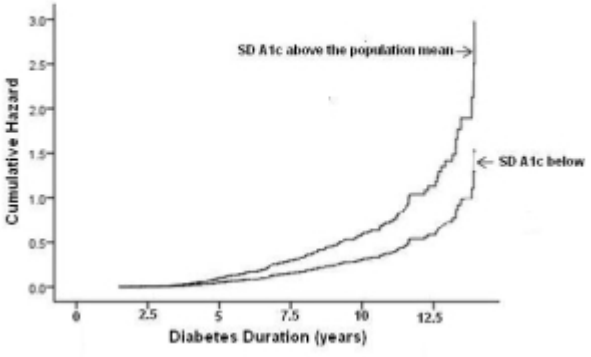
Glycemic variability has been a focus of attention as a possible risk factor for T1DM related complications, including development of microalbuminuria (MAU). Whether hemoglobin A1c (HbA1c) variability is associated with MAU in pediatric T1DM populations is unknown.

We studied the relationship between HbA1c variability and development of MAU in 893 pediatric patients with T1DM treated at a single large tertiary care referral center from 1993-2009. MAU was defined as albumin excretion rate ≥ 20 mcg/min or microalbumin:creatinine ratio ≥ 30 mg/gm Cr.

The mean level (Mean) and variability of HbA1c, defined as the standard deviation (SD) of HbA1c, were both analyzed separately and simultaneously in relation to the development of microalbuminuria with Cox regressions.

Patients in the cohort (mean age at diagnosis 8.17 (± 3.73) years, 53.1% female) were followed for an average of 7.00 (± 2.85) years, with a maximum duration of 14 years. During follow-up, 188 patients (21%) developed MAU. The mean HbA1c level was 9.2% (±1.55) in patients with vs. 8.7% (± 1.31) in those without MAU (p-value on tests of equality = 0.000 and 0.003 respectively). After adjusting for age, sex, and race, the mean HbA1c remained associated with MAU (HR 1.275, 95% CI 1.14-1.43, per 1 unit HbA1c increase). In similar analysis, the SD was associated with MAU (HR 2.16, 95% CI 1.67 - 2.79).

Cumulative Hazard for Microalbuminuria in Patients with SD A1c Above and Below the Population Mean SD A1c



However, when both the Mean and SD were included in a model, the SD continued to be significantly associated with MAU (HR 1.91, 95% CI 1.37-2.66), while the Mean was no longer significant (HR of 1.07, p=0.37).

HbA1c variability is associated with the development of microalbuminuria in children with T1DM after controlling for mean HbA1C and traditional risk factors. Whether reducing HbA1c variability is feasible, and whether it can lower the risk of MAU remains to be determined.

1208-P

Continued Reduction in the Prevalence of Retinopathy in Adolescents with Type 1 Diabetes: Role of Insulin Therapy and Glycaemic Control

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The management of type 1 diabetes in young people has changed over the last decade, with increasing use of insulin pumps (CSII) and multiple daily injection (MDI) regimens. Our aim was to examine trends in microvascular complications in adolescents with type 1 diabetes between 1990-2009 in Sydney, Australia. Design: cross-sectional analysis of complications (n=1605, 54% female, age 12-20 years, median diabetes duration 8.6 years), stratified by time periods: T1 (1990-1994), T2 (1995-1999), T3 (2000-2004), and T4 (2005-2009). Early retinopathy was detected using 7-field fundal photography; albumin excretion rate (AER) using timed overnight urine collections or albumin to creatinine ratio (ACR); and peripheral nerve function by thermal and vibration threshold. Over the 20 years, retinopathy declined (50%, 35%, 27%, 14%, P<0.01), as did borderline elevation of AER/ACR (45%, 30%, 26%, 30%, P<0.01) and microalbuminuria (8%, 4%, 3%, 3%, P=0.006). MDI/CSII use increased (17%, 54%, 74%, 69%, p<0.001), median HbA1c decreased (9.3%, 8.9%, 8.5%, 8.5%, p<0.001) and severe hypoglycemia was unchanged (6%, 8%, 10%, 7%, P=0.272). In multivariate logistic regression, time period was associated with all complications except microalbuminuria. Retinopathy was also associated with duration (OR 1.15, 95% CI 1.11-1.19), HbA1c (1.16, 1.08-1.25), systolic BP SDS (1.32, 1.18-1.48), socioeconomic disadvantage (1.41, 1.04-1.90) and 1-2 injections/day (vs MDI/CSII) (1.36, 1.06-1.74); borderline AER/ACR with male gender (1.31, 1.02-1.67), age (1.13, 1.06-1.21), HbA1c (1.17, 1.08-1.27), weight SDS (1.25, 1.07-1.47), insulin dose/kg (1.59, 1.09-2.32), 1-2 injections/day (1.41, 1.08-1.83) and socioeconomic disadvantage (1.63, 1.20-2.22); microalbuminuria with diastolic BP SDS (1.75, 1.27-2.41), cholesterol (1.31, 1.04-1.65) and 1-2 injections/day (1.85, 1.09-3.11). In conclusion, MDI/CSII use in adolescents with type 1 diabetes is associated with lower HbA1c and declining retinopathy rates, while microalbuminuria has reached a plateau. Our findings provide some reassurance for lower glycemic targets and intensive management in young people with type 1 diabetes.

1209-P

Vitamin D Deficiency Is Associated with Retinopathy in Children and Adolescents with Type 1 Diabetes

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Vitamin D has recognised immunomodulatory properties and vitamin D deficiency (VDD) has been implicated in the development of microvascular disease, including proliferative retinopathy, in adults with type 2 diabetes. We sought to examine the association between VDD and microvascular complications in young people with type 1 diabetes, without renal impairment. This was a two year cross-sectional study of 517 patients (52% male) with type 1 diabetes, aged 8-20 years, from Sydney, Australia. Retinopathy was assessed by 7-field stereoscopic retinal photography, peripheral neuropathy by thermal and vibration threshold testing and microalbuminuria by albumin excretion rate (AER) or albumin to creatinine ratio (ACR). Serum 25-hydroxyvitamin D (25-OHD) was measured using the LIAISON® analyser (DiaSorin Inc, MN, USA) and VDD was defined as 25-OHD ≤ 50 nmol/L. Logistic regression analysis was used to examine factors associated with complications outcomes; explanatory variables examined were 25-OHD, HbA_{1c}, C reactive protein, lipids, ethnicity, coeliac disease, socioeconomic status, BMI and blood pressure. Mean age at assessment was 14.9 years, mean diabetes duration 7.2 years and 71% were of Caucasian ethnicity. Mean HbA1c was 8.6%. Patients with VDD had a higher prevalence of retinopathy compared to their sufficient counterparts (18 vs. 9%, p=0.02); in contrast VDD was not associated with microalbuminuria or peripheral nerve abnormalities. In logistic regression, retinopathy was associated with VDD (OR 2.25, 95% CI 1.09 – 4.65) and diabetes duration (1.12, 1.03 – 1.22). Abnormal peripheral nerve function was associated with male gender (1.60, 1.06 – 2.41), BMI SDS (1.46, 1.11 – 1.92) and age (1.13, 1.04 – 1.24). Elevated AER or ACR was associated with systolic blood pressure SDS (1.34, 1.03 – 1.74) and non-Caucasian ethnicity (0.59, 0.37 – 0.94). In conclusion, VDD is associated with a higher prevalence of retinopathy in young people with type 1 diabetes. Whilst the inflammatory and angiogenic effects of VDD may contribute to early retinal vascular damage, the underlying mechanisms for this novel association warrant further investigation.

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

1210-P

Reduced Heart Rate Variability in Youth with Type 1 Diabetes: The SEARCH CVD Study

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Reduced heart rate variability (HRV) is the earliest sign of cardiac autonomic neuropathy (CAN), a major diabetes complication. We examined differences in HRV markers reflecting early (parasympathetic loss with sympathetic override) or more advanced (sympathetic and parasympathetic loss) subclinical CAN in multi-ethnic youth, mean age 19 +/- 3 years, with type 1 diabetes (T1D) (n=237; mean duration 10+/-4 years) and without T1D (n= 125). Resting HRV measures were obtained using the SphygmoCor Vx (AtCor Medical, Lisle, IL). Body mass index (BMI), blood pressure (BP), fasting lipids and A1c were measured. General linear models were used to assess case/control HRV differences, after adjustment for covariates. Compared with controls, T1D youth had lower HRV parameters in both time [standard deviation of normal RR intervals (SDNN), root mean square successive difference (RMSSD), percent o fnormal RR intervals less than 50 msec (pNN50)] and frequency domains [low and high frequency power (LF,HF)], even after adjustment for age, sex, race, BMI, BP and lipid levels(Table 1). On further adjustment for A1c, all differences became non-significant. A pattern of combined parasympathetic and sympathetic loss (reduced pNN50, RMSDD, HF with higher LF: HF ratio) reflecting a more advanced CAN stage was evident in T1D youth. These findings advocate for CAN screening in youth with T1D and suggest the need for improved glycemic control to prevent the development and progression of CAN.

Adjusted HRV parameters among T1D and controls*

HRV parameters	T1D	Controls	p-value
SDNN (msec)	63.3	76.3	0.002
RMSSD (msec)	59.2	75.2	0.002
pNN50 (%)	41.5	47.1	0.03
HF_power (Hz)	56.4	61.3	0.04
LF: HF ratio	1.11	0.82	0.055

* Adjusted for age, sex, race, BP and lipid levels

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1211-P

Are Overweight Children with Type 1 Diabetes Mellitus (T1DM) at Increased Risk of Cardiovascular Disease (CVD)?

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Rates of overweight have increased in children with T1DM mirroring the escalating rates in US youth. This may compound their diabetes-related macrovascular disease risk due to obesity-related CVD co-morbidity. Therefore, this investigation aimed to test the hypothesis that overweight children with T1DM will have evidence of early abnormalities in markers of CVD compared with normal weight peers with T1DM and non diabetic overweight peers. Children with T1DM and overweight controls (BMI≥85th %), age 12 to 20 years, underwent evaluation of carotid intima media thickness (IMT), fasting lipid profile, HbA1c, DEXA for % body fat, and abdominal CT scan for visceral adipose tissue (VAT).

Characteristics of the 37 Caucasian participants are depicted in the table (mean ± s.d.). There were no differences in sex distribution, systolic (119±14 vs 118±9 vs 117±11, p=0.87) and diastolic blood pressure (DBP) (65±3 vs 64±6 vs 65±8, p=0.78) between the three groups. Normal weight vs. overweight T1DM did not differ in diabetes duration (6.4±2.3 vs 8.3±3.7 years, p=0.18) or mean HbA1c of the last 5 clinic visits (7.6±0.6 vs 7.7±0.7%, p=0.67).

	T1DM Normal Weight (n=9)	T1DM Overweight (n=13)	Control Overweight (n=15)	p-value (ANOVA)
Age (years)	15.4±1.8	15.7±1.5	15.9±2.8	0.85
BMI (kg/m2)	20.5±2.6	26.8±2.3*	34.3±7.7	0.0005
% body fat	21.4±8.6	31.4±8.8*	42.1±8.5	0.0005
VAT (cm2)	27.3±10.9	46.9±19.9*	86.9±39.2	0.0005
Triglycerides (mg/dl)	67±20	80±23	115±59	0.02
HDL-cholesterol (mg/dl)	60±15	50±9**	40±9	0.001
LDL-cholesterol (mg/dl)	77±19	98±24*	94±31	0.16
TG/HDL	1.15±0.35	1.66±0.60*	3.08±2.17	0.006
IMT (mm)	0.489±0.023	0.494±0.040	0.484±0.033	0.76

* p<0.05 normal vs. overweight T1DM ** p=0.06 normal vs. overweight T1DM BMI, % body fat and VAT correlated with triglycerides (r=0.534, r=0.431 and r=0.346, p<0.05) and HDL-cholesterol (r=-0.504, r=-0.414 and r=-0.482, p<0.005). Additionally, VAT correlated with DBP (r=0.334, p=0.04). In conclusion, overweight youth with T1DM compared with their normal weight peers have higher LDL and lower HDL enhancing their risk of CVD. These observations underscore the importance of obesity prevention and/or intervention in youth with T1DM.

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ADA-Funded Research

1212-P

Infant Infections and the Risk of Islet Autoimmunity: The Diabetes Autoimmunity Study in the Young (DAISY)

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The incidence of type 1 diabetes (T1D) has been doubling every 20 years. Improved hygiene and reduced childhood infections are possible causes. Alternatively, childhood infections may trigger islet autoimmunity (IA). The link between reported infant infections and later development of IA was examined prospectively in the Diabetes Autoimmunity Study in the Young (DAISY).

Complete illness interviews through 9 months of age were collected for 1729 children, 1174 without and 555 with a first degree relative with T1D. IA was defined as positive autoantibodies to insulin, GAD65, or IA-2 on at least two consecutive study visits. Illnesses were grouped as upper respiratory (UR) symptoms (cough, cold, runny /stuffy nose, sinus or ear infection), gastrointestinal (GI) illness (vomiting or diarrhea), any episode of fever >100 F, and respiratory illness (croup, pneumonia or bronchitis). Cox proportional hazards models were used to examine whether the number of reported symptoms or illnesses during the first 9 months of life predicted the development of IA.

IA developed in 109 children during an average 6 years of follow-up; 39 have already developed T1D. A greater number of GI illnesses predicted IA, but only among children first exposed to gluten (wheat, barley) <4 or ≥ 7 months of age (*P* for interaction=0.02). There was no association of IA with other types of infections.

The effect of reported infant infections on the risk of IA: hazards ratios (HR) and the 95% confidence intervals (CI)§

	HR	95% CI	p-value
UR symptoms	0.99	0.97-1.01	0.447
Fevers	0.94	0.84-1.05	0.281
Respiratory illnesses	0.98	0.65-1.52	0.977
GI illnesses among infants exposed to gluten at:			
0-3 months	1.38	0.13-1.67	0.002
4-6 months	0.92	0.74-1.13	0.440
7+ months	1.10	1.03-1.18	0.003

§ Adjusted for HLA group (DR3/4 vs. other genotype), family history of T1D, breastfeeding, daycare, birth order, and transglutaminase antibodies.

Early childhood exposure to enteropathogens such as enteroviruses or rotavirus may increase the risk of IA. The temporal relationship between infant diet, infections, and IA require further investigation in higher resolution datasets, e.g., TEDDY.

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ADA-Funded Research

1213-P

Children with Islet Autoantibodies and Enterovirus Infection Demonstrate a Predominantly Pro-Inflammatory Cytokine Response

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Enterovirus (EV) infection is a putative initiator of islet autoimmunity in type 1 diabetes (T1D), while cytokines/chemokines are important mediators of insulitis and beta-cell death. However, there are limited clinical data examining the relationship between EV infection, islet autoimmunity and cytokines. We therefore examined cytokine profiles and EV infection in a prospective cohort study of children at risk of T1D (affected 1st degree relative). We included 67 children - 27 were positive for islet autoantibodies (Ab+) and 40 age-matched autooantibody-negative controls (Ab-). Half of the children had EV RNA detected in plasma and/or stool at the time of sampling or in the previous six months (EV+) and the remainder were negative for EV and other viruses (EV-). Plasma concentrations of 65 cytokines and

chemokines were measured and results analysed by autoantibody status and EV PCR positivity. A total of 16 cytokines and chemokines were elevated ($p<0.01$) in Ab+ children (IFNα2, TNFα, IL-2, IL-7, IL-12(p70), IL-13, IL-17, IL-20, IL-28A, GM-CSF, EGF, CX3CL1, CCL1, CCL13, CCL26, CXCL5), the majority of which have predominant pro-inflammatory effects. Only one cytokine (IL-10) was significantly elevated in children with an EV infection (EV+). Comparing groups by autoantibody and/or enterovirus infection status (Ab+EV+, Ab+EV-, Ab-EV+, Ab-EV-), 11 cytokines were significantly different across four groups (IFNα2, TNFα, IL-12(p70), IL-20, IL-21, IL-28A, GM-CSF, EGF, CX3CL1, CCL1, CCL26). However cytokine levels were not different between Ab+EV+ and Ab+EV- children. Healthy controls (Ab-EV-) had the lowest cytokine concentrations, with 16 cytokines undetectable in over 50% of the samples. In conclusion, children with islet autoimmunity have significantly higher levels of cytokines and chemokines with predominant pro-inflammatory cytokine profiles, compared with autoantibody-negative controls. This is consistent with an active inflammatory process in the pre-diabetic state, which is unrelated to co-incident EV infection. Apart from increased levels of IL-10, EV infection does not appear to be associated with a specific cytokine profile.

1214-P

The OGTT Index as an Indicator of the Pre-Diabetic State of Type 1 Diabetes in Children

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Metabolic abnormalities tend to occur several years before type 1 diabetes (T1D) is diagnosed using ADA/WHO glucose criteria. We have assessed whether T1D can be detected earlier by an alternative metabolic measure, the oral glucose tolerance test (OGTT) Index, than by standard criteria (fasting glucose≥126 mg/dl and/or 2-hr glucose≥200 mg/dl). Data from Diabetes Prevention Trial-Type 1 participants less than 15 years of age (n=512; 9.3±3.1 years) were analyzed. The participants were all islet cell autoantibody positive relatives of patients with T1D who underwent 2-hr OGTTs at 6-month intervals. The OGTT Index is based on estimates from a proportional hazards model which includes 3 variables: log fasting C-peptide, and sums of C-peptide and glucose (30, 60, 90 and 120 minutes) during an OGTT. We studied children who had an OGTT Index<4.50 at baseline and who then exceeded that threshold during follow-up. The risk for T1D after first exceeding the 4.50 threshold was very high (3-year risk=0.97; n=86). For comparison, we studied children who had normal glucose tolerance at baseline and then subsequently met criteria for dysglycemia (impaired fasting glucose, impaired glucose tolerance, and/or a glucose value ≥200 mg/dl at 30, 60 or 90 minutes) during follow-up (n=227). The 3-year risk after the first dysglycemic OGTT was only 0.54. Even when the 2-hr glucose was restricted to ≥160 mg/dl (instead of ≥140 mg/dl) among those dysglycemic, the 3-year risk was also lower (0.74; n=60) than the risk after exceeding the 4.50 threshold. Among those who developed T1D, the 4.50 threshold was first exceeded 1.05±0.81 years before a diagnosis by ADA/WHO criteria ($p<0.001$). Peak C-peptide values were substantially higher at the time the 4.50 threshold was exceeded than at diagnosis (4.32±1.29 ng/ml vs. 3.04±1.36 ng/ml; $p<0.001$). In conclusion, among autoantibody positive children who undergo periodic OGTT surveillance, the OGTT Index identifies those who have a very high likelihood of being diagnosed within 3 years. Thus, the OGTT Index could potentially be used as a surrogate endpoint for T1D in prevention trials, and as an indicator of the pre-diabetic state of T1D in children.

Guided Audio Tour: Pediatrics—Type 1 Diabetes—Treatments and Glycemic Control *(Posters 1215-P to 1222-P), see page 15.*

1215-P

Center Differences in Metabolic Control in 1133 Children with T1DM below 11 Years: Insulin Regimen or Centers Recipe?

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The Hvidoere Study Group (HSG) has demonstrated persisting center differences in metabolic control in adolescents in 4 continents.These differences appear to be not attributable to specific insulin regimens but seem to be influenced by centers effectiveness in implementing treatment regimens. To evaluate this in prepubertal children, HSG performed a cross sectional study in children <11 years with T1DM.

All children, <11 y with a diabetes duration ≥1 y, were invited to participate. CRF's included information on clinical characteristics, treatment, DKA (hospital admission needed), hypoglycaemia (loss of consciousness/ seizures), language difficulties and co morbidities. A1c was measured centrally by ^{R}Tosoh liquid chromatography (DCCT aligned, range 4.4-6.3%).

In total 1133 children from 18 centers participated (♀: 47.7 %; mean age 8.0 ± 2.1 y; mean diabetes duration 3.8 ± 2.1 y).The grand mean A1c was 8.0±1.0 % without significant impact of diabetes duration, age or gender. Language difficulties had an adverse effect ($p=0.036$) on A1c. Significant ($p<.000$) center differences were demonstrated with mean A1c varying between **7.3±0.8 and 9.0 ±1.1%**. Different insulin regimen were used (*CSII* :32.8%, *Basal bolus* 16.9%; *Conventional* : free mix :36.5%; premix :6.3 %; freemix+ (mainly 1 center :extra insulin for snacks/meals), 7.5%). Significantly lower A1c was observed in freemix+ (7.3 ±0.8 %) and higher in the premix group (8.5 ± 1.7%). Significant center differences ($p<.000$) in blood glucose measurement (BGM) frequency were reported (2.5 to 8.3x /day) with a higher frequency in CSII treated and younger children. A significant ($r=-.170$, $p<.000$) inverse correlation was seen with A1c and BGM frequency.

In summary, center differences in metabolic outcome are already present in children <11 years, unrelated to diabetes duration, age, or gender, and despite generally lower A1c values. BGM frequencies differ between centers and do have a weak effect on the A1c level. Although treatment regimen has some effect, the centers effectiveness (recipe) using a specific treatment strategy remains the key factor for the outcome, confirming previous observations.

1216-P

New Insights to an Old Disease: Major Clinical Outcomes within First Year of Diagnosis for Youth with Type 1 Diabetes (T1D) from Pediatric Diabetes Consortium (PDC) Cohort

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We analyzed the PDC database of pediatric patients (age <19 yrs) with new-onset T1D to investigate clinical outcomes of youth with T1D during the 1st year after diagnosis. Data from the 393 out of 886 enrolled subjects who had been diagnosed for at least one year as of 12/9/10 with varying follow up data were included in the analysis. Most were between 5-15 yrs of age (mean 9.4 yrs), 49% were female, with considerable racial/ethnic diversity (63% white, 24% Hispanic, 7% African American, 3% Asian). Clinical characteristics at diagnosis and 3, 6, 9 and 12 mos after diagnosis are depicted in the Table. Two had cataracts and 6 had psychiatric co-morbidities at diagnosis. A1c was in target range (<7.5%) in 63% at 6 mos and 55% at 12 mos. By 12 mos, 33% of pts were using pump therapy. Percent of patients in partial remission, defined by dose adjusted A1c (IDDA1c= A1c+ 4x insulin dose unit/kg/day) ≤9, peaked at 51% at 6 mos and fell to 35% by 12 mos. Of 13 severe hypoglycemia events, 12 occurred during the first 6 mos; whereas all 6 DKA events occurred during the second 6 mos.

The PDC clinical outcomes study provides important insights regarding the efficacy of current treatment of youth with new-onset T1D in pediatric diabetes treatment centers in the US, as well as up to date data regarding rates of clinically important adverse events. Such data can serve as a basis of comparison and help inform the design of future clinical trials evaluating the efficacy and safety of β-cell preservation and other new therapies of T1D in children and adolescents at the onset of the disease.

Months	Diagnosis	3	6	9	12
Median A1c% (quartiles)	10.9 (9.4,13.0)	7.1 (6.4,8.0)	7.0 (6.3,8.0)	7.4 (6.6,8.1)	7.2 (6.6,8.1)
Median insulin dose (u/kg/day) (quartiles)	0.8 (0.5,1.0)	0.5 (0.3,0.7)	0.5 (0.3,0.7)	0.6 (0.4,0.7)	0.6 (0.4,0.8)
Insulin Regimen					
MDI	74%	74%	73%	67%	53%
Fixed dose	26%	21%	17%	13%	14%
Pump therapy	0	5%	10%	20%	33%
Partial remission (IDAA1c≤9)	-	49%	51%	34%	35%
Cumulative # of Events					
Severe hypogylcemic events	-	8	12	12	13
DKA events	-	0	0	3	6
Hospital admissions (for any reason)	-	4	6	7	9
BMI >85% for age and gender	23%	32%	28%	26%	31%

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

1217-P

Residual β-Cell Function in Youth with T1D: Achievement of Target A1c Levels with Negligible Hypoglycemia and Lower Glucose Variability

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To examine the effects of residual b-cell function on hyper- and hypoglycemia in youth with T1D during the first year of treatment, blinded, 3-7 day continuous glucose monitoring (CGM) profiles were compared in: 1) *Short-term T1D* 16 patients (8-18 yrs, duration T1D 6-52 wks) with peak c-peptide levels >0.40nmol/L during mixed meal tolerance test (mean±SD: 0.96±0.42); 2) *Well Controlled Longer-term T1D* 34 patients, T1D >5 yrs, matched for age and A1c with the short-term T1D group; and 3) 26 age-matched *Non-diabetic* (ND) controls. Despite matching for A1c, and therefore mean CGM glucose in the T1D groups, short-term T1D subjects had a greater % of CGM readings in the target range due to a reduction in both hyper and hypoglycemic levels. Overall glucose variability (assessed by the coefficient of variation of CGM glucose levels) and variability of pre-breakfast glucose values were also reduced in short-term vs longer-term T1D subjects. Target A1c levels were achieved in the longer-term group at the expense of frequent biochemical hypoglycemia; whereas, hypoglycemia exposure in the short-term group did not differ from that in the ND group. Thus, the metabolic benefits of residual b-cell function during the honeymoon phase of T1D extend beyond lowering A1c levels and include reductions in glucose variability and exposure to recurrent biochemical hypoglycemia.

	Non-diabetic N=26(A)	Short Term T1D N=16(B)	Longer Term N=34(C)	P-value for A vs. B	P-value for B vs. C
DCA HbA1c (%) Mean±SD [range]	5.3±0.2 [4.9 to 5.7]	6.8±0.7 [5.5 to 7.8]	6.8±0.6 [5.6 to 7.8]	<0.001	0.57
Overall Mean Glucose (mg/dL) Mean±SD	102±10	148±37	156±28	<0.001	0.58
% Within 71-180 mg/dL Median (quartiles)	98 (95, 100)	77 (67, 86)	60 (54, 71)	<0.001	0.003
%>180 mg/dL	0 (0, 0)	17 (8, 28)	32 (21, 41)	<0.001	0.04
%≤70 mg/dL	1.7 (0.0, 3.8)	0.4 (0.0, 2.3)	7.6 (1.6, 11.6)	0.79	<0.001
%≤60 mg/dL	0.2 (0.0, 1.9)	0.0 (0.0, 1.0)	3.3 (0.4, 6.5)	0.48	<0.001
%≤50 mg/dL	0.0 (0.0, 0.3)	0.0 (0.0, 0.3)	0.6 (0.0, 3.1)	0.82	0.004
CV Overall (%)	16 (12, 19)	27 (24, 32)	42 (37, 49)	<0.001	<0.001
CV Prebreakfast (%)	8 (6, 10)	30 (21, 32)	45 (31, 54)	0.002	0.001

1218-P

Effectiveness and Safety Study of the Prototype 4th Generation Dexcom Seven Day Continuous Glucose Monitoring System in Youths with Type 1 Diabetes Mellitus

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72 youths at 3 US centers were studied to test the performance of the prototype 4th generation Dexcom CGM system in children and adolescents. Subjects were scheduled for three consecutive 7-day wear periods (new sensor for each period, one blinded and two display periods). The OneTouch® Ultra2® meter was used for CGM system calibrations and diabetes management, and subjects were asked to confirm high and low CGM System glucose alerts/alarms by taking a meter reading immediately after receiving an alert/alarm. Subjects were instructed to use the CGM System information as an adjunct to their meter readings.

70 subjects (97%) completed all visits. 37 subjects (51.4%) enrolled were male; 98.6% were White. The mean ± SD age of the enrollment population studied was 12.6 ± 2.8 (6.1 to 17.6) yrs. The mean ± SD duration of diabetes was 6.3 ± 3.7 yrs. 59 subjects (81.9%) used CSII for insulin therapy; 13 subjects (18.1%) were on MDI therapy. The mean ± SD baseline HbA1C was 8.26±1.49%.

Over three 7-day wearing periods, there were no serious adverse events, sensor fractures, or infection complications. Except for infrequent mild (12.0%) or moderate (1.2%) skin irritations at the sensor insertion and adhesive sites, no other device related adverse events were obtained. A total of 6466 paired CGM sensor and meter glucose values were obtained. CGM sensor measurements were within 20% (or 20mg/dL for SMBG value ≤ 80mg/dL) of the reference value 74.5% (95% CIs: 73.5%-75.6%) of the time. The overall mean and median Absolute Relative Differences (ARD) vs. SMBG were 16.3% and 12.0%, respectively. During display wear, the true alert rates were 88.3% at the high alert level of 200 mg/dL and 67.0% at the low alert level of 80 mg/dL. The duration of diabetes, age, sex and BMI showed no significant impacts on the System performance and there were no significant System performance differences between study centers or with blinded vs. display wear.

The accuracy, alert rates, and sensor life of the Dexcom CGM in youth were similar to that of adult patients and compared favorably to the CGM system currently approved for pediatric use.

1219-P

Feasibility of Continuous Glucose Monitoring in Infants and Toddlers with Type 1 Diabetes

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Tight glycemic control in young children with diabetes is often limited by the fear of hypoglycemia, actual hypoglycemia and hyperglycemia, the latter two of which possibly contribute to risk for cognitive impairment. Continuous glucose monitoring (CGM) in very young children has not been studied and several challenges exist including small body surface area and possibly skin reactions. We studied the feasibility of CGM use in 23 children with type 1 diabetes (T1D) less than 4 years of age, 15 males and 8 females, whose families expressed an interest in using CGM. Mean (±SD) age was 3.0±0.8 years and HbA1c 8.0±0.8% at baseline. Ten children were using an insulin pump and 13 were using multiple daily injections (MDI). Each participant was provided with a CGM device (FreeStyle Navigator® or Paradigm®). Safety and use were monitored over 6 months.

Three children dropped out of the study before the end of 6 months. Among the 20 children who completed 6 months of follow-up, CGM in month 6 was being used ≥6 days/week in 9, 3-5 days/week in 4 and <3 days/week in 7. Skin reactions were minimal. HbA1c did not change (7.9±0.8%) at the end of 6 months. Over the 6-month period, CGM documented that hyperglycemia was present during more than half of the day and biochemical hypoglycemia was infrequent (Table).

CGM Glucose Range	Median Percent of Sensor Data in Range over 6 Months (25th, 75th Percentiles)
≤60 mg/dL	0.2% (0.1%, 0.6%)
≤70 mg/dL	0.8% (0.5%, 1.8%)
71-180 mg/dL	43% (39%, 55%)
>180 mg/dL	56% (43%, 60%)
>250 mg/dL	25% (15%, 28%)

In summary, more than 40% of these very young children were using CGM on a daily or near-daily basis after 6 months. This is similar to the use reported in an older cohort taking part in a RCT using CGM, where 30% of 14-24 year olds and 50% of 8-14 year olds were wearing the CGM sensor at least 6 days a week at 6 months (NEJM2008). CGM provided the ability to document glycemic control over a 6-month period in this young age group without frequent hypoglycemia. Hyperglycemia was present for the majority of the day.

1220-P

The Addition of Glargine to Continuous Subcutaneous Insulin Infusion Therapy Worsens Glucose Variability

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Blood glucose variability is increasingly recognized as an important component of type 1 diabetes management. Some patients report that adding a once daily injection of insulin glargine as substitution for a portion of their basal continuous subcutaneous insulin infusion improves glucose variability but this has never been formally studied.

The primary objective of this study was to measure the effect of the addition of once daily insulin glargine to continuous subcutaneous insulin infusion therapy on glucose variability by using a new statistical measure based on self monitored blood glucose measurement, the average daily risk range (ADRR).

In a pilot study using a repeated measures design, we monitored 12 children, ages 8-18 years, with type 1 diabetes mellitus on standard

continuous subcutaneous insulin infusion therapy for 3 months. After this run-in period, basal infusion settings were reduced by 50% and a daily injection of insulin glargine at a dose equivalent to the basal infusion reduction was given for another 3 months. The ADRR was calculated during both the run-in and experimental treatment periods. Hemoglobin A1c levels, frequency of blood glucose level < 40 mg/dl and > 400 mg/dl, frequency of ketonuria, frequency and duration of device disconnection, total daily bolus insulin dose, number of urgent medical visits, and diabetes specific quality of life assessments were also performed.

In a paired analysis comparing the individuals' pre-glargine ADRR with the post-glargine ADRR, glucose variability worsened after the addition of insulin glargine (pre-glargine mean ADRR 44.77 ± 7.41 vs. post-glargine mean ADRR 47.00 ± 10.18, p-value 0.04). Other secondary measurements did not differ significantly between therapies.

The method of adding a once daily injection of insulin glargine as a substitute for a portion of basal continuous subcutaneous insulin infusion may worsen glucose variability as measured with the ADRR and should therefore be used with caution in children with type 1 diabetes mellitus.

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1221-P

Volume of Intravenous Fluid Administration and Time to Resolution of Pediatric Diabetic Ketoacidosis

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Background: The rate, volume and composition of the initial intravenous fluid replacement in diabetic ketoacidosis (DKA) have been linked to the risk of life-threatening cerebral edema and remain a subject of controversy.

Objectives: The study objective was to determine if the volume of fluid administration affects the rate of normalization of serum bicarbonate, beta-hydroxybutyrate (B-OHB), pH as well as the length of treatment (LOT).

Methods: Fifty children with DKA (mean age 9.3± 4.7, 60 % F) were randomized to receive fluids at either slow rate (10 ml/kg bolus of normal saline (NS) followed by 1.25 x maintenance rate) or fast rate (20 ml/kg bolus NS followed by 1.5 x maintenance rate) (n=25 in each). All patients received the NS bolus and ¾ NS with potassium supplement maintenance fluids. The primary outcomes were time to bicarbonate normalization and LOT. LOT was defined as the time of hospital stay after start of fluid infusion. Kaplan-Meier survival analysis and the log-rank statistic were used to evaluate time to metabolic normalization and LOT.

Results: Participants' pre-treatment characteristics were similar in the two treatment groups except for higher baseline bicarbonate levels in the group of patients treated with slower rate of fluid infusion: 10 ± 3 vs. 8 ±4 mmol/L in the fast infusion rate group (p=0.04). After adjusting for the initial differences in bicarbonate levels, the time to normalization of bicarbonate did not differ between the slow 5.9 h; (95%CI 5.3-8.4) and fast 7.9 h; (5.3-8.4) fluid infusion rate groups (p=0.63). Time to normalization of pH also did not differ 4.7 h; (3.8-9.3) vs. 6.9 h; (4.3-8.7, p=0.42). The slow fluid infusion rate group had a nearly significant shorter LOT: 20.5 h; (16.9-23.2) vs. 24.5 h; (18.5-35.0) in the fast fluid infusion group (p = 0.07). The slopes of bicarbonate, B-BOH, and pH normalization were not different by treatment groups. No patient developed cerebral edema.

Conclusions: Slower initial fluid infusion rate in treatment of DKA does not slow down metabolic normalization time or increase the length of treatment. Further investigation in a larger sample of differing fluid infusion rates is warranted.

1222-P

Intensive Subcutaneous Insulin Therapy and Intravenous Insulin Infusion at Onset of T1DM Preserve Beta-Cell Function Equally Well in Children

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Swedish children with newly diagnosed diabetes type 1 (T1DM) have since 20 years been treated with intravenous (IV) insulin infusion for the first 48-72 hours. One reason for this has been to achieve immediate good metabolic control to prolong the residual beta cell function. Our aim was to see if IV insulin therapy at diagnosis preserves beta-cell function better than MDI. At diabetes diagnosis, 54 children, aged 9.9±3.5 years (range 2.8-14.9), without ketoacidosis, were included in a 2 year, multicentre study, randomized (factoring for puberty and centre) to treatment with multiple daily injections (MDI) from start or 48-72 hours iv-insulin (IV) initially, with the ambition of achieving normoglycemia in both groups. 33 (61%) were boys. 22 (41%) were in puberty. 48 subjects completed a 12 month follow-up and 42 completed 24 months. HbA1c at diagnosis was 10.6% DCCT, 92 mmol/mol for IV, 11.0%, 96 mmol/mol for MDI (ns). During the first two full days of insulin therapy, mean plasma glucose was 8.2 mmol/l for IV, 9.5 for MDI (p=0.025) and mean insulin dose 1.5 U/Kg/day for IV vs. 1.0 for MDI (p=0.001). After the initial therapy, both groups received MDI, but 16 (7 in IV, 9 in MDI group) started with pumps during the follow-up. 1, 6, 12 and 24 months after diabetes onset, HbA1c, fasting serum C-peptide and insulin doses/kg/24h were registered. At 24 months a mixed-meal tolerance test (MMTT) was performed. There were no differences in HbA1c, C-peptide or the insulin-dose/kg/24h between the groups at the 1, 6 and 12 month follow-up. At 24 months, HbA1c (7.5% DCCT, 58 mmol/mol, for IV, 7.2%, 55 mmol/mol, for MDI; ns) and insulin doses (0.79 U/kg/day for IV vs. 0.88 for MDI; ns) did not differ. Fasting C-peptide (0.08 pmol/l for IV vs. 0.12 for MDI), maximal MMTT response (0.19 pmol/l for IV vs. 0.25 for MDI), and AUC (18.2 pmol/l*min for IV vs. 24.0 for MDI) also did not differ significantly. In conclusion, in spite of higher insulin doses and lower plasma glucose during initial IV therapy, we found no difference in 24 month's preservation of beta-cell function when using IV insulin vs. MDI at diabetes diagnosis in children.

1223-P

Mutational Analysis of K_{ATP} Channel in Patients with Transient Neonatal Diabetes and Assessment of Minimal Incidence of Neonatal Diabetes in Italy

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Neonatal/Infancy onset diabetes mellitus (NDM) is a genetic form of diabetes with onset within 6 months from birth. Two distinct types of NDM are recognized: permanent (PNDM) and transient (TNDM). In TNDM remission of hyperglycemia usually occurs within 6 months from diagnosis. TNDM is frequently caused by paternal isodisomy of chromosome 6 and PNDM by mutations of insulin gene, but both condition can be associated with gain-of-function mutations in genes encoding the subunits of the K_{ATP} channel, *KCNJ11* and *ABCC8*. Incidence of PNDM in Italy is 1:210.000. *ABCC8* and *KCNJ11* genes were screened in 14 patients with TNDM. Minimal incidence of NDM was calculated counting patients with PNDM and TNDM born in Italy between 2005 and 2009 and referred to our laboratory for genetic screening by members of the Italian study group on diabetes of ISPED. We identified mutations in 10 patients with TNDM: three heterozygous mutations of *KCNJ11* (R50Q [x2], E229K, E179K) in 4 subjects and 7 heterozygous mutations of *ABCC8* (H105Y, S459R, T540I, R826W, R1380C, R1380H, V1523M) in 6 patients (1 compound het. for H105 and T540I). In these 10 patients, duration of insulin therapy ranged between 17 day and 8 months. No difference in mode of presentation of diabetes was found between patients with TNDM or PNDM (29 subjects) due to mutations of K_{ATP} channel identified in our laboratory. Mild hyperglycemia (<400 mg/dl) was distinctive of patients of both groups who received diagnosis of diabetes in the first 2 weeks from birth. However, mutations found in patients with TNDM were all different from those detected in PNDM. Minimal incidence of NDM was calculated at 1:117.000. We conclude that before remission of diabetes, no specific clinical feature allows us to distinguish TNDM from PNDM due to K_{ATP} channel mutations. With the inclusion of data on chromosome 6 defects we are collecting through a questionnaire, we estimate that global incidence of NDM in Italy could range between 1:90.000 and 1:80.000 live births.

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

1224-P

The Washington University Wolfram Syndrome (WS) Clinic: Initial Results

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WS (OMIM 222300) or DIDMOAD (diabetes insipidus [DI], diabetes mellitus [DM], optic atrophy [OA], deafness [D]) is an autosomal recessive disorder resulting from mutations in the *WFS1* gene at chromosome position 4p16.1. *WFS1* encodes an endoplasmic reticulum (ER) protein (Wolframin) involved in regulation of ER stress and calcium homeostasis. In addition to the commonly-recognized manifestations (DIDMOAD), WS is a progressive neurodegenerative disease with survival rarely beyond the 3rd decade of life.

To define the natural history of WS, 10 patients from 7 families identified through the Washington University WS Registry [https://wolframsyndrome.dom.wustl.edu/] participated in our first annual WS Clinic. All had DM with onset at 5.8±2.7 years (mean±SD; median 6; range: 2.3-10.9). 9 had been diagnosed with OA (at mean age 8.2±2.8 years; median 9; range 6.0-12.6), 7 with DI (at mean age 10.4±4.1 years; median 10; range 6.0-17.0) and 3 with deafness. 9 out of 10 (all with OA) were color blind and 7 out of 10 had microsmia or anosmia. Neurologic (impaired vibratory sensation in 4 of 10; gait disturbance in 7 of 10) and MRI (enhanced T2 signal in the pons in 4 of 8) abnormalities were nearly universal by 13-14 years old. All were using basal:bolus insulin therapy and 4 CSII. Glycemic control was generally good (HbA1c: 7.7±1.5; range 6.0-11.5; only 2 were ≥8.0). Fasting C-peptide was low (≤0.2 ng/mL) in 7 (mean 0.33±0.35; range <0.1-1.0), and 2-hour Boost-stimulated C-peptide was low (≤0.5) in 6 (out of 7 studied; mean 0.53±0.57; range 0.2-1.8). HbA1c did not significantly correlate with fasting, 2-hour or ΔC-peptide, DM duration or disease severity (as assessed by a newly-developed Wolfram Syndrome Unified Rating Scale [WURS], adapted from the Unified Battan Disease Rating Scale).

WS is a progressive, neurodegenerative disease with onset of DM, DI and OA typically in the 1st decade and neurologic and neuroimaging abnormalities byt the 2nd decades of life. Continued standardized longitudinal follow-up of this and other cohorts is important to thoroughly understand the natural history of WS and enable testing of possible interventions to slow or halt disease progression.

1225-P

Structural Neuroimaging in Wolfram Syndrome: Preliminary Findings of Early Regional Vulnerability

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Wolfram syndrome (WS; OMIM #222300) is a rare autosomal recessive disease with clinical signs early in childhood of diabetes mellitus, optic atrophy, hearing loss, diabetes insipidus and neurodegeneration, resulting in death by middle adulthood. Little is known about the course of neurodegeneration in WS, particularly in the early stages of the disease. We recruited 10 relatively young WS patients through the Washington University WS Registry. Structural magnetic resonance imaging was performed on 7 patients (mean age=12.7, SD=5.3); images were quantitatively analyzed for brain volume and microstructural white matter integrity (Diffusion Tensor Imaging; DTI). WS cases were compared to convenience samples of healthy controls over a similar age range. General volume measures of brain development (cortical and subcortical gray matter, cortical white matter volume) showed differences between groups in developmental trajectories (age x group interactions, p<.05). Controls (n=26) showed the expected pattern of decreasing cortical gray and increasing white matter over age and slight increases in subcortical gray matter volume. However, WS cases showed greater decreases in gray matter and no increase in white matter over the same age range. Thus, as age (and disease) progresses, WS cases diverged from the normal neurodevelopmental trajectory, particularly for cortical white matter and subcortical gray matter. In addition, DTI measures detected significant abnormalities in the WS group in the cerebellum, cerebellar peduncle, splenium, central semiovale, and prefrontal cortex (all p<. 05) compared to 10 controls. Even the youngest, least affected WS cases had reduced white matter integrity in the cerebellum compared to age comparable controls, suggesting sensitivity to early neurodegeneration in WS. These preliminary results demonstrate the feasibility of our multidisciplinary research clinic approach to collecting quantitative, sensitive neuroimaging data and indicate that certain neuroimaging variables have promise as potential biomarkers of neurodegeneration in early WS.

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1226-P

Age Influences Cystatin C in Adolescents with and without Type 1 Diabetes

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Despite improvements in care, diabetic kidney disease continues to cause early morbidity and mortality in type 1 diabetes (T1D). Current clinical markers of renal function include serum creatinine and urinary albumin excretion. Serum cystatin C has been proposed to be a superior biomarker of renal function but no data exist in adolescents with T1D. Our objectives were to compare cystatin C levels in adolescents with and without T1D and to determine what factors affect cystatin C levels in T1D and non-diabetic (non-DM) subjects.

Fasting labs were collected from youth, age 12-19 years with (n=259, T1D duration 8.8±3 years, A1c=8.9±1.6%) and without T1D (n=78). Cystatin C was measured in the *University* of Colorado Hospital clinical lab using the Dade-Behring assay. Data were compared by T1D status and linear regression was used to determine factors affecting cystatin C.

Subjects were similar for age and sex but T1D subjects had higher BMI, A1c, and CRP than non-DM subjects (p<0.05). Serum creatinine was higher in non-DM than T1D subjects (0.71±0.15 v. 0.65±0.14 mg/dl, p=0.003), but cystatin C (0.698±0.083 v. 0.688±0.126 mg/L, p=0.43) was similar. In univariate analyses, cystatin C was associated with sex and serum creatinine in non-DM subjects and with age, sex, serum creatinine, A1c, BMI, and CRP in T1D subjects (p<0.05). In multiple linear regression (backward selection) stratified by T1D, cystatin C was associated with age, and serum creatinine in non-DM subjects (R^2=0.2527) and sex, age, and serum creatinine in T1D subjects (R^2=0.2380) (Table).

Multiple Linear Regression

	Non-DM		T1D	
	β-coefficient	p-value	β-coefficient	p-value
Age	-0.20	0.003	-0.021	<0.0001
Sex, (male=reference)			-0.039	0.01
Serum Creatinine	0.339	<0.0001	0.390	<0.0001

Cystatin C levels are similar in adolescents with and without T1D. As previously reported in NHANES data, age, sex, and serum creatinine are all associated with cystatin C levels in adolescents. Understanding age-related changes in cystatin C in adolescents is a first step in determining the potential role of cystatin C in management of early renal disease in adolescents with T1D.

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1227-P

Risk Factors for Diabetic Nephropathy (DN) According to Age at Diagnosis (Dx) and Attained Age in Type 1 Diabetes (T1D)

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Predicting DN is crucial for effective prevention. Microalbuminuria (MA) and hyperfiltration have been considered antecedents of DN in T1D. However, estimated GFR (eGFR) can be challenging in patients with early or no kidney disease. We investigated risk factors for DN in patients with T1D of >7 yrs duration according to attained age and age at T1D Dx. In 118 patients (54% male, 21.5±4.5 yrs) with T1D of 15.2±4.0 yrs and 77 age-matched controls (36% male, 20.8±5.3 yrs), we assessed cystatin C-(cysC) and Cr-based eGFR and compared renal outcomes in the 2nd and 3rd decades of life (Table). Cr-eGFR used the Schwartz equation (age<20yrs) or MDRD equation (age≥20yrs); CysC-eGFR used the Stevens equation. Hyperfiltration was defined as eGFR>140 ml/min/1.73m^2; MA as urine alb/cr >20µg/mg x2. Cr-eGFR was lower than cysC-eGFR, although both were correlated (r=.93, p<.0001). Hyperfiltration was more common in T1D patients vs age-matched controls, independent of age (p<.0003). Neither age at Dx nor T1D duration were related to hyperfiltration, although elevated eGFR was more common in the 3rd decade of life (p=.04). MA was also more common in the 3rd decade, but only in those with T1D diagnosed in early childhood. T1D patients with MA had significantly higher A1c than those without MA (p=.03). A1c was correlated with cysC-eGFR (r=.33, p<.0002) and with Cr-eGFR (r=.28, p=.01). There appears to be an interaction of age at Dx and attained age for risk of DN, with highest risk among young adults diagnosed with T1D early in life.

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	10-19yrs T1D n=39	10-19yrs Controls n=36	20-29yrs T1D Dx≥5yrs old n=37	20-29yrs T1D Dx<5yrs old n=42	20-29yrs Controls n=41
Age(yrs)	16.1±2.7	16.0±2.7	24.5±2.4	23.8±2.6	25.0±2.9
Age at Dx(yrs) T1D Duration(yrs)	3.3±1.5 12.8±1.9		11.8±2.0 12.7±1.9	4.3±2.2 19.6±2.9	
A1c(%)	8.5±1.2	5.3±0.4	8.2±2.0	8.7±1.7	5.1±0.4
Cr(mg/dL)	0.8±0.2	0.8±0.2	0.9±0.1	0.9±0.2	0.9±0.2
CysC(mg/L)	0.7±0.1	0.7±0.1	0.7±0.1	0.7±0.1	0.8±0.1
Cr-eGFR(ml/min/1.73m^2)	90±16	94±22	112±22	113±25	106±17
CysC-eGFR(ml/min/1.73m^2)	126±20	123±18	125±21	132±22	113±14
%Hyperfiltration Cr/CysC	0%/15%	3%/11%	11%/32%	10%/33%	0%/2%
%MA	13%	14%	8%	19%	5%

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Clinical Diabetes/ Therapeutics **POSTERS**

1228-P

Impact of Co-Morbid Conditions on Health-Related Quality of Life (HRQOL) in Youth with Type 1 Diabetes

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Current management of pediatric type 1 diabetes (T1D) places substantial demands on families and may be detrimental to youth HRQOL. Other chronic conditions have also been associated with reduced youth HRQOL. We assessed the relationship between number of co-morbid conditions and HRQOL in youth with T1D. Youth (n=278, 48% female) had a mean age of 13.4±2.9 years, T1D duration of 6.4±3.4 years, and A1c of 8.6±1.4%. Data were collected as part of a cross-sectional study of pediatric T1D management, excluding youth with chronic GI disease. Youth and parents completed the PedsQL, a measure of youth HRQOL. Parents reported their child's co-morbid conditions.

The most prevalent co-morbid conditions were asthma (n=30, 11%), mental health conditions (n=26, 9%), hypothyroidism (n=23, 8%), and seasonal allergies (n=21, 8%). One-third of youth (n=91) had ≥1 co-morbid condition (table). Neither youth age nor A1c differed by number of co-morbid conditions. Youth self-report and parent report of youth HRQOL were lower for youth with ≥2 co-morbid conditions than for youth with 0 or 1 co-morbid condition. In addition, a significantly higher proportion of youth with ≥2 co-morbid conditions were hospitalized in the previous 6 months vs. those with no co-morbid conditions.

In this sample, HRQOL was similar for youth with T1D and 0 or 1 co-morbid condition. However, youth with T1D and ≥2 co-morbid conditions had significantly poorer HRQOL; these youth warrant additional support in order to preserve HRQOL.

Sample characteristics and HRQOL by number of co-morbid conditions	**0 (n=187)**	**1 (n=51)**	**≥2 (n=40)**	**P**
Age (years)	13.2±2.8	13.5±2.9	13.9±3.0	
A1c (%)	8.5±1.4	8.7±1.3	8.7±1.6	
Hospitalized in previous 6 mos (%)	4%	6%	18%	0 vs ≥2: p<.01
Youth report of HRQOL - Total	84±13	84±11	78±14	0 vs ≥2: p=.02 1 vs ≥2: p=.03
. . Psychosocial scale	82±14	83±12	77±15	0 vs ≥2: p=.05 1 vs ≥2: p=.05
. . Physical scale	87±13	87±11	82±16	0 vs ≥2: p=.01 1 vs ≥2: p=.04
Sample characteristics and HRQOL by number of co-morbid conditions	**0 (n=187)**	**1 (n=51)**	**≥2 (n=40)**	**P**
Parent report of youth HRQOL - Total	80±12	78±13	72±14	0 vs ≥2: p<.0001 1 vs ≥2: p=.01
. . Psychosocial scale	79±13	77±14	69±15	0 vs ≥2: p<.0001 1 vs ≥2: p<.01
. . Physical scale	84±13	82±15	78±17	0 vs ≥2: p=.02

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1229-P

Evaluating Eating Disorder Risk (EDR) in T1D Youth Transitioning to Insulin Pump (CSII) Therapy (Rx)

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Weight gain may accompany improved glycemic control and could contribute to eating disorder risk. CSII Rx is known to reduce weight gain while improving glycemic control and could therefore attract teens with weight concerns and EDR. To assess whether teens seeking CSII Rx may be a vulnerable group for EDR, we examined factors associated with EDR (Eating Disorder Inventory, EDI-3) and *diabetes-specific eating disorder risk (DEPS)*: age, sex, weight (BMI%tile), glycemic control (A1c), body size satisfaction (BSS, Collins Silhouettes) prior weight control behavior (Youth Risk Behavior Survey, YRBS), depression (CDI) and anger (Pediatric Anger Expression Scale) - suppression (AS), out (AO), control (AC) and expression (AX) in 42 teens (53% male) mean age = 12.9yrs; mean BMI%tile = 69±26; mean (most recent) A1c% = 8.3±1.3 before initiating CSII use. Mean EDR%tile (EDI-3) was 24±23 and mean DEPS total score = 20±10, *indicating low level risk when using general criteria, but increased risk when using a measure containing diabetes-specific eating disorder questions*. In a model of EDR (EDI-3, R^2= 76%, p<.001), BMI%tile (t=3.0, p<.006), BSS (t=2.8, p<.008), CDI (t=6.9, p<.001), exercising to keep from gaining weight (YRBS, t = -2.34, p<.03) and AS (t= -2.65, p<.01) each made independent contributions. In a model of *diabetes specific eating disorder risk (DEPS*, R^2= 69%, p<.001) BMI%tile (t=2.27, p<.03), most recent A1c (t=2.13, P<.04), CDI (t=4.57, p<.001) and AS (t= -1.84, p<.08) made significant independent contributions. Although general eating disorder risk in youth transitioning to CSII Rx was not elevated, factors known to be associated with EDR were confirmed. However, using *diabetes-specific criteria (DEPS),* elevations in risk were found, known factors were confirmed, and in addition, elevated A1c was associated with elevated risk. These data suggest that teens seeking CSII Rx may be vulnerable to diabetes-specific EDR. Thus it appears important to use diabetes-specific criteria and measures when evaluating EDR in teens with T1D as disease specific outcomes, such as glycemic control (A1c), may place pressure on teens to adopt disordered eating behaviors. **ADA-Funded Research**

1230-P

Sex Differences in Pulse Wave Velocity in Adolescents with and without Type 1 Diabetes

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Adolescents with type 1 diabetes (T1D) are at increased risk for premature cardiovascular disease (CVD). Improved risk stratification is needed to focus preventive efforts. Arterial stiffness, assessed by aortic pulse wave velocity (PWV), predicts CVD in adults with and without diabetes. We hypothesized that PWV would be higher in adolescents with T1D compared to non-diabetic (non-DM) controls and that traditional CVD risk factors (A1C, blood pressure, lipids) would predict increased PWV. We assessed PWV in the carotid-femoral segment in 278 adolescents with T1D (age 15.4±2.1 yrs, 49% male, T1D duration 8.8±3.0 yrs) and 94 non-DM controls (age 15.3±2.0 yrs, 48% male). Measurement of PWV was obtained using arterial tonometery with the Sphygmocor Vx (AtCor Medical, Lisle, IL). Demographics, anthropometrics and fasting labs were also obtained. T1D subjects were similar to non-DM controls in age, gender distribution, BMI, HDL and triglycerides (TG) but had higher systolic (SBP) and diastolic blood pressure (DBP), total cholesterol (TC) and LDL (Table). PWV was not significantly different in T1D adolescents compared to non-DM controls (T1D: 5.3±0.7 vs non-DM: 5.2±0.6 m/sec, p=0.15). When stratified by gender, T1D males had significantly higher PWV compared to non-DM males (5.4±0.7 vs 5.2±0.7 m/sec, p=0.04) but T1D females had similar PWV compared to non-DM females (5.2±0.7 vs 5.2±0.5 m/sec, p=0.84). In multiple linear regression, age, male sex and DBP were associated with higher PWV. In non-DM subjects, lower HDL and higher TG were associated with higher PWV and in T1D subjects, higher LDL but not A1C was associated with higher PWV.

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	Non-DM	T1D	P-value
BMI, kg/m^2	22.0±4.4	22.7±3.7	0.10
A1C, %	5.3±0.3	8.9±1.6	<0.0001
TC, mg/dl	147±28	157±35	0.005
LDL, mg/dl	82±23	89±27	0.03
HDL, mg/dl	48±9	51±11	0.008
TG, md/dl, median (IQR)	77 (59-96)	71 (57-98)	0.84
SBP, mmHg	109±9	113±9	0.002
DBP, mmHg	64±6	68±7	<0.0001

In conclusion, aortic PWV is higher in T1D adolescent males compared to their non-DM peers; however, no difference in PWV was seen in females. Higher PWV in T1D males may reflect a worse CVD risk factor profile in adolescent T1D males.

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1231-P

Validated Measure of Diabetes-Related Burden in Parents of Youth with Type 1 Diabetes (T1D)

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In pediatric patients, perceived parental burden may impact efforts at effective T1D management. We aimed to re-examine and revise the Problem Areas in Diabetes–Parent Version survey (PAID-P), a measure of perceived parental burden associated with caring for a child with T1D in the current era of intensive insulin therapy. A geographically diverse population of youth (N=376) with T1D and their parents (80% mothers) included patients from the Joslin Clinic and participants in the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring study. Data were collected on demographics, T1D management, diabetes-specific family conflict, youth quality of life (QOL), and perceived parental burden. Youth were 12.9±2.7 years old with T1D duration of 6.3±3.5 years. Youth were checking blood glucose (BG) 5.2±2.3 times/day and 58% were receiving insulin pump therapy. Mean A1C was 8.0±1.2%. Factor analysis yielded 2 factors, 'Immediate Burden' and 'Theoretical Burden', and eliminated 2 survey items. The revised, 18-item PAID-PR demonstrated excellent internal consistency (Cronbach's α=0.87). Greater parental burden was associated with more frequent BG monitoring, higher A1C, more diabetes-specific family conflict, and lower youth QOL (see tables). Test-retest analysis was acceptable (r=0.62). This brief measure may have both clinical and research utility in the management of youth with T1D.

Tables: Correlations with PAID-PR

	PAID-PR	Factor 1: Immediate Burden	Factor 2: Theoretical Burden
	r	r	r
BG monitoring frequency (times/day)	0.17*	0.07	0.23*
A1C (%)	0.09	0.16*	0.001
Parent report surveys			
Diabetes-specific family conflict	0.47*	0.39*	0.42*
Youth Psychosocial QOL	-0.48*	-0.43*	-0.42*
Youth Physical QOL	-0.37*	-0.31*	-0.35*
Youth Diabetes-specific QOL	-0.52*	-0.50*	-0.44

*p<0.05

	PAID-PR	Factor 1: Immediate Burden	Factor 2: Theoretical Burden
	r	r	r
Youth report surveys			
Diabetes-specific family conflict	0.17*	0.22*	-0.07
Psychosocial QOL	-0.10*	-0.10	-0.08
Physical QOL	0.01	-0.04	0.05
Diabetes-specific QOL	-0.19*	-0.22*	-0.13

p<0.05

1232-P

Minimal Impact of a Double Diagnosis: Quality of Life in Pediatric Patients with Diabetes and Celiac Disease

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Despite the advent of sensitive testing to detect celiac disease (CD), screening in high-risk populations such as type 1 diabetes (T1D) remains controversial, especially in asymptomatic patients. Many diabetes clinics remain apprehensive about the prospect of introducing a second illness requiring intensive lifestyle changes in patients and families already managing a chronic condition.

The goal of this study was to determine the impact of managing CD+T1D on general and health-related quality of life in families, with attention to the effect of adherence with a gluten-free diet (GFD) and metabolic control.

This cross-sectional assessment was conducted in the diabetes clinic at the Hospital for Sick Children. Quality of life was evaluated using the Peds QL Inventory Generic Core Scale & Diabetes Module. There were no significant differences in baseline characteristics between the 2 groups; Mean age in years was 13.55$\pm$ 2.97 in the CD+T1D (n=28) group and 14.58 $\pm$ 1.94 in the T1D (n=40) group. On average, participants in both groups had been diagnosed with T1D for about 7 years and subjects in the CD+T1D group had been diagnosed with CD for 3 years (range 0.57 – 8.64 years). Mean HbA1c was 8.4 % in the CD+T1D group and 8.8% in the T1D group (p=0.32).

No significant differences were observed in quality of life domains between subjects with CD+T1D and subjects with T1D alone. Parents of children with CD+T1D reported lower social functioning scores than parents of children with T1D (p=0.03). In the CD+T1D group no differences in quality of life were observed in regards to age at CD diagnosis or CD duration. No differences in quality of life were observed on the basis of adherence with the GFD, although there was a trend for compliant patients to have higher emotional (p=0.09) and psychosocial (p=0.09) functioning.

These results suggest that the double diagnosis of CD+T1D has a limited impact on quality of life in patients; however, parents do describe worse social functioning for their children.

1233-P

Can a Computer Game Improve Adherence to Treatment in Children with Type 1 Diabetes?

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Interventions to improve compliance in Type 1 Diabetes are limited. The aim of this research was to adapt a computer game, developed initially for patients with Inflammatory Bowel Disease (IBD), to patients with Type 1 Diabetes Mellitus (T1DM) and to determine whether this interactive application would have an effect on behavior intention and adherence to treatment in this population. Two game frameworks were created, the active intervention (E_H) which contains an embedded self –care framework which adapts to the patient's behaviour to motivate the patient and a second game framework (E_0) which does not adapt to patient behaviour. The study implemented a longitudinal cross-over design. Patients aged 7-14 were eligible. Patients were randomized to either G_1 (played E_H for 3 weeks, followed by E_0 for 3 weeks) or G_2 (played E_0 followed by E_H). The total study duration was 6 weeks. The study used a modified version of the Theory of Planned Behavior (TPB) questionnaire which was converted to behaviour intention score (BIS). Compliance with blood glucose testing and insulin administration was reported daily by a parent. Adherence rate was calculated and presented to participants daily as health points in E_H. 42 T1DM patients participated (25/42 males) with a mean age of 10.7 years. 21 were assigned to G_1 (11/21 males) and 21 were assigned to G_2 (14/21 males). A significant difference was seen in adherence between E_H and E_0 in the first half of the study (12.86%, p=0.002) and in the second half of the study (6.71%, p=0.024). There was no effect of A1C seen on BIS in either group. This study showed that, over a short period of time, a game framework which provided positive reinforcement to recommended treatment behaviors lead to improved adherence to treatment in children with T1DM. This effect was lost or not present when the game framework did not provide positive feedback. These results are promising and provide support to the use of interactive media to promote healthy behaviors in children and adolescents with T1DM.

1234-P

Frequency of Self-Monitoring of Blood Glucose (SMBG) Is Associated with Hemoglobin A1c (HbA1c) Levels in Youth with Type 1 Diabetes (T1D) Enrolled in the T1D Exchange Clinic Registry

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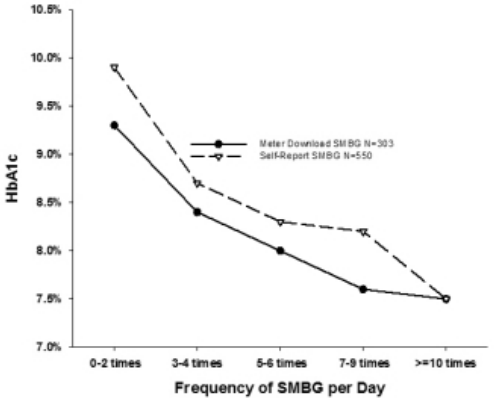
Recently, state insurance companies have questioned whether or not sufficient evidence is available to justify SMBG coverage for children with T1D. The purpose of this study is to examine the relationship between the number of times SMBG is performed per day and HbA1c among participants < 18 years of age enrolled through December 31, 2010 in the T1D Exchange clinic registry. The registry, which will include over 60 centers in the U.S., commenced enrollment of up to 45,000 adults and children with T1D in September 2010, with longitudinal participant data collected through medical records and participant questionnaires.

The analysis included 556 participants with T1D; (mean age 11.9 years, 50% female, 83% non-Hispanic white, mean diabetes duration 4.9 years, and mean HbA1c 8.3%). SMBG was collected from home glucose meter (HGM) downloads and self-report. The mean± standard deviation (SD) number of SMBG per day from the 303 participants with an available download and the 550 participants with a self-reported number was 5±3 and 6±3 respectively. A strong association (P<0.001) was present between SMBG and HbA1c, with increasing daily SMBG being associated with lower HbA1c for both the HGM downloads and self-reported number [Figure 1].

This study provides strong evidence of a linear trend between number of SMBG measurements per day and HbA1c levels.

Figure 1.



	Meter Download SMBG		Self-Report SMBG	
Frequency of SMBG	N	Mean±SD	N	Mean±SD
A) 0-2 times per day	27	9.3 ± 2.2	11	9.9 ± 2.1
B) 3-4 times per day	112	8.4 ± 1.5	145	8.7 ± 1.9
C) 5-6 times per day	95	8.0 ± 1.2	188	8.3 ± 1.4
D) 7-9 times per day	41	7.6 ± 1.0	135	8.2 ± 1.4
E) >=10 times per day	28	7.5 ± 0.9	71	7.5 ± 1.1

1235-P

Obesity and DKA Are Common in Youth at T1D Onset: Findings of the Pediatric Diabetes Consortium (PDC)

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To define initial presentation and clinical care of youth with new onset T1D, the 7 diabetes centers making up the PDC obtained data from 838 children (52% male) <19 years of age (mean 9.3 yrs) who were recently diagnosed with T1D. While the majority of patients were non-Hispanic Caucasians (63%), 22% were Hispanic and 8% African American (AA).

At diagnosis, 23% required ICU care and 16% were treated only as outpatients. When all 3 diabetes auto-antibodies were measured (62% of cohort), 93% were positive for ≥1 and 33% for all 3. Mean BMI percentile was 52% for age and gender but 23% were overweight or obese with AA children the most severely affected (39% overweight or obese). 35% of patients presented in DKA (range 24-42% by site). The risk of DKA was greater for younger children (p=0.02), AA children (p=0.006) and those without private insurance (p=0.02). Cerebral edema (CE) occurred in 2% of those with DKA.

For author disclosure information, see page 785.

Our data demonstrate that at diagnosis, children with T1D: 1) are often overweight, 2) have a high prevalence of DKA and 3) continue to be at risk of CE. Increased public awareness of T1D symptoms in children should be a priority to lower the risk of this major source of morbidity and mortality in youth with T1D.

	<5 years N=153	5-11 years N=450	12-18 years N=235	Complete Cohort N=838
% Female	38%	53%	43%	48%
Mean HbA1c (%) at diagnosis	10.3	11.3	11.8	11.3
Mean BMI %	42%	53%	56%	52%
% subjects overweight	16%	22%	28%	23%
% subjects obese	6%	11%	16%	11%
Autoimmunity * (%)	94%	93%	83%	90%
Inpatient Management				
Subjects presenting with DKA	55%	41%	43%	44%
Subjects presenting without DKA	45%	59%	57%	56%
Insulin Regimen				
Injection (fixed dose)	31%	36%	38%	35%
Injection (MDI)	69%	64%	62%	65%

Available data varied for A1c (n=762), BMI (n=650), autoimmunity (n=653), inpatient DKA status (n=528), and insulin regimen (n=701). *Testing positive for at least one antibody.

1236-P

Case Management (CM) with Psychoeducation Benefits Youth with Suboptimal Glycemic Control

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Studies demonstrate that case management (CM) or psychoeducational support can improve glycemic control (A1c) in youth with type 1 diabetes (T1D), reversing the natural tendency for A1c to increase with age during childhood. We sought to determine if a low-cost, clinic-based intervention of family-focused psychoeducation combined with CM was more effective than CM alone in maintaining glycemic control.

In a 2 year randomized clinical trial, 153 youth (44% male), aged 8-16 years with T1D for (X±SD) 6.3±3.5 years, were assigned to 1 of 3 groups: routine quarterly diabetes visits with CM by a lay case manager (Care Ambassador [CA], n=51); routine CM plus monthly CM outreach (CA+, n=50); and routine CM with both monthly CM outreach and quarterly family-focused diabetes psychoeducation (e.g., family teamwork, avoidance of diabetes-specific family conflict [DFC]) (CA+Ultra, n=52). Chart review provided medical data; youth and parents completed validated surveys on diabetes family responsibility sharing (DFR) and DFC.

The CA and CA+ groups were similar at baseline and after 2 years, supporting their combination into one group (CA/CA+). At baseline, CA/CA+ youth had an A1c of 8.5±1.5% and received 1.0±0.3 U/kg/day, with 23% pump treated. At baseline, CA+Ultra youth had an A1c of 8.4±1.4% and received 1.0±0.2 U/kg/day, with 22% pump treated. After 2 years, A1c increased similarly in CA/CA+ and CA+Ultra youth, 0.3±1.1% and 0.3±1.0%, respectively. Overall, 37% of CA/CA+ youth improved or maintained their A1c compared with 49% of CA+Ultra youth (p=0.2). To assess the impact of the interventions on youth with suboptimal control, we compared the 55 CA/CA+ youth with baseline A1c≥8% to the 25 CA+Ultra youth with baseline A1c≥8%. In this subgroup analysis, 49% of CA/CA+ youth improved or maintained their A1c compared with 76% of CA+Ultra youth (p=0.02). In addition, DFR was improved or maintained in 3 times more CA+Ultra youth than CA/CA+ youth (36% vs 11%, p=0.008) while DFC did not significantly increase.

CM with psychoeducation improved or maintained A1c in youth with suboptimal glycemic control, likely by increasing family involvement without increasing diabetes-specific family conflict.

1237-P

Do Parent Goals for A1c and Blood Glucose (BG) Impact Glycemic Control in Youth with Type 1 Diabetes (T1D)?

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Previous studies suggest that A1c may vary according to healthcare providers' recommended goals. To evaluate the impact of goal-setting on A1c in youth with T1D, we assessed parent glycemic goals and parent perceptions of providers' goals. Parents (20% fathers) of 153 youth (44% male), age 12.9±2.3 years with T1D for 6.3±3.5 years, completed surveys

Guided Audio Tour poster ADA-Funded Research

regarding their goals and their perceptions of providers' goals for their child's BG and A1c levels. Youth had a mean A1c of 8.4±1.4% and checked BG levels 3.8±1.2 times/day; 23% received pump Rx.

Youth A1c did not vary according to parent BG goals except at the highest target: 22% of parents reported BG goals of 100(80-120) mg/dL, youth A1c 8.5±1.6%; 49% reported goals of 130(80-180) mg/dL, youth A1c 8.3±1.3%; 26% reported goals of 150(120-180) mg/dL, youth A1c 8.4±1.3%; 3% reported goals ≥180mg/dL, youth A1c 10.0±3.1% (p<.05 Vs others). Youth A1c did not vary according to parents' report of providers' BG goals, including the 9% of parents who reported provider goals ≥180mg/dL or unawareness of providers' BG goals. Parent BG goals were tightly linked with parent perception of providers' BG goals (69% concordant, p<.0001).

For A1c goals, 4% of parents reported goals <6%; 75% reported 6-8%; 10% reported 8.1-10%; and 11% reported >10% or no A1c goal. Most parents' A1c goals (88%) matched their perceptions of providers' A1c goals (p<.0001); 75% reported provider goals of 6-8% and 17% reported provider goals >10% or unawareness of provider A1c goals. Youth A1c was significantly lower for parents reporting A1c goals ≤8% Vs >8% or unawareness of goals, 8.3±1.2 Vs 9.1±1.8% (p=.02). Youth age was significantly associated with parent A1c and BG goals: 88% of parents of youth aged <12 years reported A1c goals ≤8% Vs 73% of parents of youth aged ≥12 years (p=.02); 62% of parents of youth aged <12 years endorsed a wider range for BG goals (80-180 mg/dL) Vs 41% of parents of youth aged ≥12 years (p=.03).

Parents appear to set glycemic goals based upon their perceptions of provider goals. There may be opportunities to improve glycemic control in youth with T1D by concerted goal-setting between families and providers.

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1238-P

How Irish Children Less Than 7 Present with Type 1 Diabetes Mellitus from 2004-10

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Patients with Type 1 Diabetes Mellitus (T1DM) generally present with classical symptoms. Late presentation is associated with metabolic decompensation and diabetic ketoacidosis (DKA). DKA is a more common presenting feature in the younger child who is unable to articulate their thirst and is wearing nappies, as health care professionals may not identify the classical symptoms. This cohort are at increased risk of cerebral edema. The aim of this study was to review the clinical presentation of children ≤ 7 years with newly diagnosed T1DM at our centre.

A retrospective chart review of all patients attending Children's University Hospital, Temple Street diagnosed with T1DM at age ≤ 7 years between 2004-2010 was undertaken. 80 (41 male) children were identified. The mean age at presentation was 4.1 years (range 0.75-7.5 years). Thirty percent of children presented in DKA and of these 37% required ICU admission. The severity of illness varied with 55% in mild DKA, 27% in moderate DKA and16% in severe DKA. The mean HbA1c at presentation was 10.1% (range 6.1-16.9). Of the 18 children in this cohort aged less than 2 years, 58 % presented in DKA and 55% of them required ICU admission. Two children developed cerebral edema (aged 1.8 and 7.3 years respectively). In this cohort of children ≤ 7 years at presentation, 8 children presented in 2005 compared with 14 in 2010. Children < 3 years accounted for 25% of these in 2005 compared and 57% in 2010. All 80 children are developmentally normal at follow up and 36 of these patients (45%) are being managed on pumps. We found that the incidence of T1DM in young children is rising and the age at presentation is falling at our centre. Pre school children are more likely to have DKA at presentation, are more likely to require ICU admission and require more support from the diabetes service at follow up.

1239-P

Metabolic Control in Emerging Adults with Type 1 Diabetes

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Older adolescents and emerging adults with type 1 diabetes (T1D) are at risk for worsening metabolic control and increased diabetes related complications. Due to changing demands, the transition from high school to college may disrupt self-care, potentially setting the stage for enduring negative health outcomes. This retrospective study explores metabolic control (A1c) and clinic attendance in a sample of emerging adults and examines data from their last year in high school to their first year of college. Medical data were extracted from clinic records of 78 college-bound adolescents who maintained primary care at a pediatric diabetes clinic at least one year post-high school (53% male; 63% Caucasian; *M* age at baseline=17.45 yrs, *SD*=.44; *M* disease duration=10.59 yrs, *SD*=4.04). 73% of adolescents used a basal/bolus regimen (51% MDI; 22% pump) and 27% were on a conventional insulin regimen. Use of a basal/bolus regimen was associated with significant lower A1cs than a conventional regimen at both time points (p<.05). Using paired sample t-tests, mean A1c did not significantly change from high school (*M*= 8.39%) to the first year of college (*M*=8.32%; p=.49). 44 adolescents (56%) had mean A1cs higher than the ADA-recommended target (A1c<7.5%) in high school and college, and A1c values of 8 (10%) more adolescents declined to out-of-range in college. Adolescents attended significantly more clinic visits in the last year of high school (*M*=3.23 visits) than the first year of college (*M*=2.16 visits; p<.01). Metabolic control in emerging adults can be improved, and A1cs for more than half of the sample consistently fell out of the ADA-recommended range. Decreased clinic visit frequency may contribute to persistent negative health outcomes in adulthood and highlights a gap in clinical care for adolescents transitioning to adult medical care. Development of preventative interventions and transition planning for late adolescents with T1D is needed. Future research with this sample will evaluate multiple indicators of adherence, including BG monitoring frequency, BG range, and acute complications.

1240-P

Body Mass Index and Waist Circumference Are Associated with C-Reactive Protein and Heart Rate Variability in Adolescents with Type 1 Diabetes

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Type 1 diabetes (T1D) predisposes youth to cardiovascular risks. The SEARCH Case-Control study group, part of the SEARCH for Diabetes in Youth investigation recently reported elevated inflammatory markers in adolescents with T1D. Additionally, the Coronary Artery Risk Development in Young Adults (CARDIA) study noted that elevated inflammatory markers are associated with decreased heart rate variability (HRV). The CARDIA findings support earlier evidence in animal studies that implicates a cholinergic anti-inflammatory pathway for inhibiting cytokine release. Although lower HRV occurs in adolescents with T1D, factors associated with a decline in HRV have not been studied. The purpose of this study was to explore the influence of body mass index (BMI), waist circumference (WC), body composition [i.e. %fat free mass (FFM)] and glucose control on HRV and inflammatory markers (i.e. CRP and TNF-alpha). We also examined the possible associations between HRV and inflammatory markers. A sample of 23 adolescents with T1D participated (11 females; 12 males). There were 11 Hispanics and 12 non-Hispanic whites. Mean age was 14.2 ± 1.5 years; mean duration of diabetes was 5.4 ± 2.9 years. Mean A1C was 9.0 ± 1.8%; mean BMI was 23.5 ± 4.0. Waist circumference was measured using a Gulick II tape measure and 24-hour HRV recordings were analyzed using the Vision Premier Holter Analysis System Software Version 3.41. Body composition was measured with the Quantum X™. A1C was obtained with the DCA 2000® and blood samples for CRP and TNF-alpha were analyzed using the quantitative sandwich enzyme immunoassay technique. HRV measures were negatively associated with A1C, BMI and WC (r = -.44 to -.58, p < .05) and positively associated with FFM (r = .43 to .59, p < .05). Although no associations between inflammatory markers and HRV were found, BMI and WC were positively associated with CRP, r values .44 and .53 respectively (p < .05). Our findings provide support for closer scrutiny of not only glucose control but also adiposity, particularly central adiposity, for identifying those at greater risk for heart disease.

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1241-P

Glycated Albumin Is a Useful Indicator of Glycemic Control in Patients with Neonatal Diabetes Mellitus

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Since high fetal hemoglobin levels lead to apparently low A1C levels, it is difficult to use A1C as an indicator of glycemic control in patients with neonatal diabetes mellitus (NDM). Glycated albumin (GA), which is not affected by hemoglobin metabolism, is another indicator of glycemic control. The present study established the reference range of GA levels in healthy infants and evaluated GA as an indicator of glycemic control in

patients with NDM. We enrolled 19 healthy infants and 5 patients with NDM. The age of healthy infants ranged from 30 to 234 days (94 ± 75 days). Their randomly measured plasma glucose (PG) and GA were measured. Age at diagnosis and referral of patients with NDM were 38 ± 20 (14–58) days and 58 ± 11 (53–75) days, respectively. Insulin therapy was started to all patients after diagnosis. For patients with NDM, GA was measured monthly for 6 months. Based on the results of self-monitoring of blood glucose, mean PG (MPG) levels for 1-month period were calculated. We confirmed the genetic etiology for 4 patients [the KCNJ11 gene mutation in 3, paternal uniparental disomy of chromosome 6 (pUPD6) in 1]. The other patient had pancreatic hypoplasia of unknown etiology. The patient with pUPD6 discontinued insulin therapy at 5 months of age, showing transient NDM. The other patients exhibited permanent NDM. PG and GA levels of healthy infants were 86.4 ± 10.8 mg/dl and 10.1 ± 1.2%, respectively. GA was positively correlated with PG (R = 0.537, P = 0.018) as well as age (R = 0.717, P = 0.001). However, PG was not correlated with age (R = 0.262, P = 0.279), suggesting that albumin metabolism may facilitate in early infancy. PG (535 ± 24 mg/dl) and GA (33.3 ± 6.9%) at diagnosis of patients with NDM were both elevated. With treatment for diabetes mellitus, MPG (R = -0.565, P = 0.002) and GA (R = -0.552, P = 0.003) decreased in parallel with increasing age. GA was positively correlated with MPG (R = 0.784, P < 0.0001). GA was also positively correlated with the data of both PG in healthy infants and MPG in NDM put together (R = 0.911, P < 0.0001). In conclusion, we firstly reported that GA is a useful indicator of glycemic control in patients with NDM.

1242-P

Risk Factors for Poor Glycaemic Control in Children, Adolescents and Young Adults with Type 1 Diabetes: The Role of Demographic Factors, Socioeconomic Status, Family Structure, Physical Activity, and Media Use

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Aim of the study was to evaluate the relationship between glycaemic control and sociodemographic factors, family structure, physical activity, and media use in children, adolescents and young adults with type 1 diabetes.

The cross-sectional study included children, adolescents and young adults with type 1 diabetes up to the age of 22 years. Self-report questionnaires were used to assess psychosocial variables. Clinical data and HbA1c levels were collected during outpatient clinic visits. Risk factors were analysed by linear regression.

A total of 296 children, adolescents and young adults with type 1 diabetes (age 13.7+/-4.1 years, HbA1c 8.7+/-1.6%, diabetes duration 6.1+/-3.3 years) participated in the study. Better glycaemic control was significantly associated with shorter diabetes duration (r=0.24; p<0.001). High socioeconomic status was significantly associated with better glycaemic control (mean HbA1c 8.0+/-1.0%) whereas middle and low socioeconomic status were associated with worse glycaemic control (HbA1c 8.5+/-1.4% and 8.9+/-1.7%; p=0.023 and p=0.001). Glycaemic control was better in two-parent families compared to single-parent families (HbA1c 8.2+/-1.3% vs 9.2+/-1.7%; p<0.001). HbA1c levels were not different in subjects who were physically active compared to those who were physically inactive (p=0.63). Subjects with type 1 diabetes who watched television and used the computer more than 3 hours per day had a mean HbA1c of 9.1+/-1.7% which was 0.6% higher compared to subjects who spent less than one hour watching television (8.5+/-1.5%; p<0.001). HbA1c was significantly increasing with daily time spent watching television and using computers (r=0.23; p<0.001). Linear regression analysis identified diabetes duration, socioeconomic status, family status, and daily time spent watching television and using computers as risk factors for glycaemic control.

Longer diabetes duration, lower socioeconomic status, single-parent status, and increased daily time spent watching television and using computers are significant risk factors for poor glycaemic control.

1243-P

An Evidence Based Practice Approach to Screening for Celiac Disease in Children with Type 1 Diabetes—The Experience of the Diabetes Center for Children at the Children's Hospital of Philadelphia

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Children with Type 1 diabetes (T1DM) are at-risk for the development of other autoimmune problems including celiac disease (CD). Screening for CD is important to prevent the negative impact on nutritional status and diabetes control, as well as the long-term problems associated with untreated celiac disease. The Diabetes Center for Children (DCC) developed clinical practice guidelines for screening children with T1DM. This presentation will describe our clinical algorithms and summarize the clinical data on children with positive celiac antibodies.

Between January 2005 and December 2007, 207 children had abnormal screens. Sixty-six children (31.8%) were diagnosed with celiac disease. Sixty six children (31.8%) had an inconclusive screens due to low (n=26) or intermediate IgA levels (higher than 20 mg/dl but below age specific norms) (n=40). Of the remaining 75 children (36.2%), one third was eventually found to be normal converting to a negative celiac screen, before or after a negative biopsy (n=26). 14 had persistent positive antibodies despite a negative biopsy (18.65%). The rest had an incomplete evaluation due to poor follow-up: 4 had a negative biopsy with no further follow-up (5.3%), 3 had an inconclusive biopsy without further follow-up (4%) and 28 were lost to follow-up prior to biopsy (37.3%).

The implementation of these guidelines allowed for a detailed description of how positive celiac screening results cluster into 3 groups: (1) Confirmed celiac disease, 2) Inconclusive due to IGA deficiency and 3) Antibody positive without confirmed CD**.** The diagnosis of CD can be a challenging process because children are usually asymptomatic and parents are already dealing with the burden of one chronic condition making some reluctant to follow through with further testing. The number of children with positive antibody status who were not biopsied in this study highlights the challenges to clinicians in presenting screening results to families so that parents follow through with biopsy for disease confirmation.

1244-P

Determinants of Diabetic Control in Adolescents

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Prospective memory (PRoM) is the memory needed to carry out intended actions and is essential in completing the daily activities required in the self management of type 1 diabetes mellitus (T1DM). Self-efficacy for diabetes (SED), the belief that one can perform behaviors related to diabetic care, also plays a fundamental role in T1DM. The relationships between PRoM, SED, and glycemic control (hemoglobin A1C (HbA1C)) have not been studied in adolescents.

Our primary study aim was to determine the relationship between PRoM, parent and/or child's ratings of SED, insulin regimen, and HbA1C in patients ages 6-18 years old with T1DM. In this sub-analysis we explore these relationships exclusively within the adolescent population.

53 of the 100 study participants were adolescents (12 years and older). Each subject had HbA1C and blood glucose measured and completed a PRoM screen and a SED scale. Higher scores implied better PRoM and a greater perception of SED respectively. Parents answered questionnaires regarding their child's diabetic, medical, and academic history.

A stepwise multiple regression analysis was conducted using SPSS 18 to identify the influence of sex, socioeconomic status, age, IQ, age at diagnosis, duration since diagnosis, frequency of diabetic ketoacidosis (DKA) and severe hypoglycemia, use of an insulin pump, PRoM, and SED on HbA1C in the adolescent subjects. Data from 2 subjects were excluded for medical co-morbidities or an underlying learning disorder. As HbA1C, frequency of DKA, and frequency of severe hypoglycemia were skewed, log transformations were performed prior to entrance into the regression analysis. HbA1C was found to be associated with SED (β= -0.348, p <0.01), duration of T1DM (β= 0.431 p <0.01), use of an insulin pump (β= -0.320, p <0.01), and PRoM (β= -0.362, p <.01) (R^2 = .42 Sig F= 0.009).

These findings suggest that higher levels of SED and PRoM as well as the use of an insulin pump help to decrease HbA1C in adolescents with T1DM. Conversely, the longer the duration of diabetes, a variable which cannot be controlled, the higher the HbA1C. Further studies need to be conducted to assess ways to increase SED and PRoM in adolescents as a means to improve glycemic control.

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1245-P

Associations of Youth and Parent Weight Status and Reported Intake vs. Predicted Daily Energy Intake in Families of Youth with T1D

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Youth with type 1 diabetes (T1D) are at risk for childhood overweight/obesity, likely from genetic and environmental factors. In 246 youth (52% male, 13±3 yrs) and their parents (16% male, 45±6 yrs), we assessed body mass index (zBMI and BMI, respectively), prevalence of overweight and obesity,

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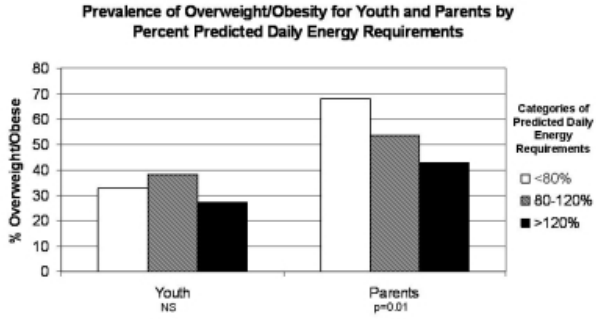
and compared reported intake vs. predicted daily energy requirements (DER). Youth had T1D duration of 6.3±3.4 yrs and A1c of 8.5±1.3%; 69% used insulin pump Rx. Daily calorie intakes were assessed using 3-day food record (youth) and food frequency questionnaire (parents). Predicted DER was estimated by the Schofield equation for youth (incorporating physical activity) and Mifflin-St. Jeor formula for parents (with constant activity factor). Overweight and obesity affected 23% and 11% of youth and 30% and 24% of parents, respectively. Youth and parent zBMI/BMI (r=0.38, p<0.001) and weight status (overweight/obese) (p<0.001) were significantly associated. A1c was not related to youth zBMI or weight status, but was associated with parent BMI (r=0.17, p=0.008) and weight status (p<0.001). 25% and 28% of youth reported daily calorie intakes <80% and >120% of predicted DER, respectively, while 31% and 32% of parents reported <80% and >120% of predicted DER, respectively. Percents of predicted DER for youth and parents were not associated, and percent of predicted DER was not related to weight status in youth (figure). For parents, there was a significant inverse association between % predicted DER and prevalence of overweight/obesity. There were nearly 60% more overweight/obese parents among those <80% DER vs. >120% DER. Overweight and obesity are prevalent in families of youth with T1D. Validated recall methods may under-represent calorie intake or overestimate daily expenditures.



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1246-P

Glycemic Control, Diabetes Management, Diabetes Self-Efficacy, and Weight Control Behaviors of Youth with Type 1 Diabetes Transitioning from High School

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The transition to adulthood is a critical time for youth with type 1 diabetes (T1D). Because little is known about adolescents with T1D after high school (HS) graduation, we examined differences in key variables in relation to glycemic control and gender among adolescents with T1D approximately 9 months post HS.

Adolescents completed web-based surveys on diabetes management (DSMP, Harris et al 2000), diabetes self-efficacy (DSE, Littlefield et al 1992) and weight control behaviors (WCB, Neumark-Sztainer et al 2002). A1cs for 2008 and 2009 graduation cohorts were obtained from charts every 3 months. Mean DSMP, DSE, and WCB were compared between groupings based on A1c Slope (positive / negative), A1c Mean (> / < 8%) and Gender.

Data were obtained from 73 youth (38% M; 97% white). At ~9 months after graduation (range 8-14 months), mean age was 19.2±0.4 yr and mean T1D duration was 9.6 yr (range 1.8-17.7) with 59% using pumps (mean pump use 6.1 yr, range 1.3-11.4), 90% in college, and 53% not living with parents. Only 34 youth had A1c data available at the 9 month study assessment (mean A1c = 8.3±1.2%,range 5.9-10.6%); Of the 66 that had at least 1 A1c value available during the 9 months after graduation, only 9 had a mean A1c < ADA guideline of 7.5%.

Youth with mean A1c values > 8% over the study period had lower DSE scores (t=2.29, p=0.02). Those with increases in A1c over the study period reported more unhealthy WCB (t= -2.02, p=0.048). Females had better DSMP scores for hypoglycemia management than males (t=3.75, p=0.0004), and exhibited both more healthy (t=3.92, p=0.0002) and unhealthy(t=2.38, p=0.02) WCB. There were no other significant differences observed by A1c measures or gender.

In the larger longitudinal study, we will explore changes over time in key factors as well as factor relationships during this transition. Given the poor overall control of our cohort, identifying key times and influential factors is critical for future interventions to improve glycemic control for youth transitioning to adulthood.

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1247-P

Children and Adolescents with Type 1 Diabetes Mellitus and Metabolic Syndrome/Obesity Have Higher YKL-40 Levels

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YKL-40 is involved in endothelial dysfunction, plaque rupture, and increased cardiovascular risk in adult patients with and without diabetes. The aim of our study was to investigate if presence of metabolic syndrome (MetS) influences YKL-40 in children and adolescents with Type 1 diabetes mellitus (T1DM).

Levels of YKL-40 and CRP were analyzed in 143 children and adolescents (7-19 years of age, 73 female, 70 male) with T1DM cross-sectionally. Metabolic syndrome (MetS) was assumed, if 2 or more of the following parameters were present: High triglycerides (TG), low HDL-cholesterol, arterial hypertension and overweight. Students T-Test, ANOVA, Correlation, and Linear Regression were applied as appropriate. A p-value < 0.05 was considered statistically significant. Results are given in mean±STD or median (25;75 percentile).

Patients with MetS exhibited higher levels of YKL-40 compared to those without: YKL-40: 43.7 (27.6;86.1) vs. 30.5 (21.6;39.0) ng/ml (p=0.013). YKL-40 was significantly higher in the overweight/obese patients compared to lean: YKL-40: 33.6 (23.3;57.7) vs. 30.0 (20.8;38.7) ng/ml, p=0.019. CRP was higher in MetS as well: 0.48 (0.23;1.01) vs. 0.17 (0.06;0.42) mg/dl (p<0.001). The multivariate regression models for explanation of YKL-40 withstood adjustment for MetS. In contrast, CRP was attenuated by MetS. The final multivariate regression revealed, that YKL-40 was predicted by age, diastolic blood pressure, triglycerides, total insulin dose and gamma-glutamyl-transferase.

We are first to show that YKL-40 is elevated in children and adolescents with T1DM and associated augmented BMI and/or MetS. Thus, higher levels of YKL-40 are not restricted to adults with type 1 and 2 diabetes. In multivariate models, CRP but not YKL-40 was attenuated by MetS. Thus, YKL-40 in T1DM children might confer an underlying cardiovascular risk independent from MetS.

1248-P

Impact of Insulin Regimen and Adherence on Glycemic Control in Youth with Type 1 Diabetes (T1D)

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Continuous subcutaneous insulin infusion (CSII) may provide improved glycemic control when compared to basal-bolus injection (B-B) therapy in youth with T1D. Studies show decreased glycemic control (A1C) over time with CSII suggesting that improved adherence when starting a new therapy may contribute to the reported benefit of CSII.

We studied whether CSII was associated with better glycemic control than B-B after adjusting for adherence level, measured by parent and youth survey and adherence with endocrinology physician visits (MD visits).

In this cross sectional study, subjects were recruited from a pediatric diabetes center via US mail (response rate 44%). Youth were 6-17 years, had T1D >1 year and were on B-B or CSII for at least 6 months before the study. Parents and youth completed the Diabetes Behavioral Rating Scale for CSII or B-B, a validated adherence survey. Clinical data were obtained from medical records.

53 youth participated, 12 on B-B and 41 on CSII. Youth on B-B had a median(IQR) age of 11.4(4.7) years, diabetes duration of 3.3(1.7) years, and A1C of 8.5(1.0) vs. a median age of 12.7(5.2) years, diabetes duration of 5.4(4.4) years, and A1C of 8.2(0.9) on CSII. B-B youth were 83% male and 73% white vs. 56% male and 87% white on CSII. Mean(SD) parent reported adherence was 71(12) for B-B and 69(9) for CSII (p=0.5). Median(IQR) averaged patient and parent adherence was 72(12) for B-B and 69(15) for CSII (p=0.3). In the B-B group, 50% had <4 MD visits in the past year vs. 44% on CSII (p=0.6).

CSII was associated with lower A1C (bivariate analysis, p=0.04). Diabetes duration, reported and MD visit adherence, race, age and sex were not associated with A1C. After adjusting for age, MD visits, and either parent-reported adherence (P) or averaged youth- and parent-reported adherence(YP), CSII was associated with A1C values that were 0.9% lower than in B-B (P: p=0.006), (YP: p=0.01).

CSII was associated with better glycemic control vs. B-B after adjusting for reported and MD visit adherence. CSII seems to improve glycemic control for youth regardless of degree of adherence.

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page 785.

PEDIATRICS—TYPE 2 DIABETES

[*See also: Presidents Poster 423-PP, page A117.*]

Guided Audio Tour: Factors Associated with Childhood Obesity and Type 2 Diabetes *(Posters 1249-P to 1256-P), see page 15.*

1249-P

Rapid Deterioration of Insulin Secretion in Obese Adolescents Who Develop Type 2 Diabetes

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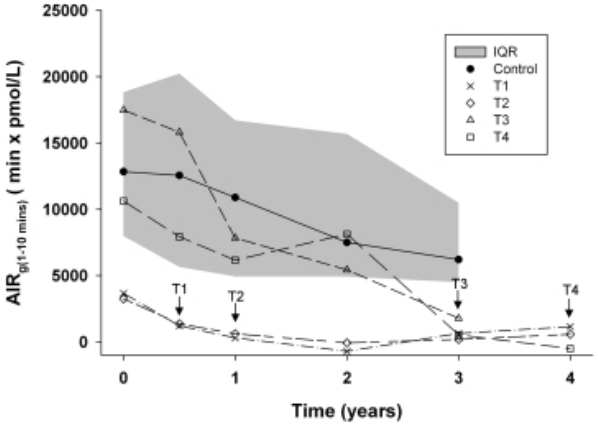
Islet β-cell dysfunction is central to Type 2 Diabetes (T2DM) in adults, with a progressive decline starting years before diagnosis. In young people with T2DM the pre-morbid state is necessarily shorter and β-cell dysfunction at disease onset is not well characterized. We detail parameters of insulin secretion and sensitivity in four obese adolescents during their progression to diabetes. Forty-one nondiabetic obese adolescents had serial evaluation of the acute insulin response to IV glucose (AIRg) at baseline, 6 months, 1, 2, 3 and 4 years. Insulin (I) and proinsulin (PI) concentrations were measured before and after the glucose bolus. Four adolescents developed type 2 diabetes over the follow up period of 2-4 years, while 37 remained nondiabetic. Prior to diagnosis, the fasting glucose was < 6.0 mmol/l in 3 of the 4 subjects who developed diabetes, which overlapped glucose values in the highest 25% ile of the controls. Compared to the subjects that maintained normal fasting glucose levels, the diabetic subjects had lower AIRg at the baseline visit (n=2), or had a sharp decline in AIRg in the 6-12 months before the diagnosis of diabetes (n=2).



The subjects that developed diabetes also had higher fasting and stimulated PI/I ratio than the controls prior to and at the diagnosis of diabetes. Markers of insulin resistance (BMI and HOMA-IR) did not predict the acute change in AIRg over the four year time period. These findings demonstrate that in adolescents developing type 2 diabetes, a decline in beta-cell function is rapid and seems to be independent of changes in insulin sensitivity. Fasting glucose and PI levels may predict transition to diabetes in some individuals. These results support the central role of beta-cell dysfunction in the pathogenesis of T2DM in adolescents.

1250-P

Oral Glucose Tolerance Test or Mixed Meal Test To Evaluate β-Cell Function in Obese Youth with Dysglycemia?

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Indices of insulin secretion derived from the oral glucose tolerance test (OGTT) or mixed meal test (Boost) are used extensively in epidemiologic and clinical studies. This study aimed to compare indices of insulin secretion derived from the OGTT to those derived from the Boost test in evaluating β-cell function in obese children with impaired glucose regulation (IGR) and type 2 diabetes (T2DM). We hypothesized that Boost will induce greater insulin secretion than OGTT in these youth.

19 obese youth with IGR and 17 with T2DM (on lifestyle and/or metformin therapy) of similar age, BMI: 36.6±6.2 and 38.1±5.7 kg/m^2, % body fat (by DEXA): 44.0 ±5.8% and 44.9 ±4.6% and VAT (by CT scan at L4-L5): 84.9±39.2 and 95.3±44.7 cm^2 respectively underwent OGTT and Boost tests within 2-3 weeks in random order. The ratio of the incremental insulin/glucose at 15 and 30 min ($\Delta I_{15}/\Delta G_{15}$, $\Delta I_{30}/\Delta G_{30}$), and the ratio of the early to total area under the curve (AUC) of insulin: $AUC_{0\text{-}30}/AUC_{0\text{-}120}$ of the OGTT and Boost were compared. Similar indices were calculated using C-peptide (C). Results are mean±SD.

	IGR (9F/10M, 14.5±1.7yrs)		T2DM (11F/6M, 15.4±1.8yrs)	
	OGTT	BOOST	OGTT	BOOST
$\Delta I_{15}/\Delta G_{15}$ (μu/ml per mg/dl)	3.2±2.0	7.7±8.5	1.7±1.8	2.6±1.9
$\Delta I_{30}/\Delta G_{30}$ (μu/ml per mg/dl)	2.8±1.2	8.3±10.0*	1.8±2.7	3.4±3.1*
$\Delta C_{15}/\Delta G_{15}$ (ng/ml per mg/dl)	0.13±0.06	0.3±0.3*	0.06±0.08	0.12±0.06
$\Delta C_{30}/\Delta G_{30}$ (ng/ml per mg/dl)	0.12±0.04	0.3±0.3*	0.06±0.05	0.14±0.09*
Insulin $AUC_{0\text{-}30}/AUC_{0\text{-}120}$	0.14±0.05	0.22±0.06*	0.16±0.04	0.21±0.09*
C-peptide $AUC_{0\text{-}30}/AUC_{0\text{-}120}$	0.16±0.04	0.21±0.04*	0.18±0.02	0.20±0.04*

(* p<0.05 for paired t-test comparisons between OGTT and Boost derived indices within each group).

Insulin $AUC_{0\text{-}30}$ and C-peptide $AUC_{0\text{-}30}$ were significantly higher during the Boost test (~20% of total $AUC_{0\text{-}120}$) than during the OGTT (~15%, p<0.001 to 17% of total $AUC_{0\text{-}120}$, p<0.001) in IGR and T2DM, respectively.

Insulin secretion indices are in general twice higher during a mixed meal than an OGTT. Thus, a mixed meal may be a better stimulus than only glucose in evaluating failing β-cell function in obese youth.

1251-P

Impaired Glucose Tolerance: A Condition Associated with Greater CV Risk Than Impaired Fasting Glucose?

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Although individuals with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are classified as having prediabetes, studies in adults suggest there are differences in risk profiles between the two groups, which may lead to differential long-term health outcomes. For example, some studies have shown that individuals with IGT have greater adverse cardiovascular risk factors. Therefore, our objective was to evaluate for differences in clinical characteristics and cardiovascular risk factors among children with IFG vs. IGT. Our study population consisted of children 12-18 years of age who had both fasting plasma glucose (FPG) and a 2 hour glucose tolerance test, using data from the National Health and Nutrition Examination Surveys (2006-2008). We first compared individuals with IFG only (FPG>=100 & <126), those with IGT (2-hr glucose>=140 & <200) only, and those with IFG plus IGT. We also performed additional analyses comparing all individuals with IGT (IGT only or both IFG and IGT) with those with IFG. Significance was defined as a p value <0.05. Of a sample of 1013 individuals, there was a high percentage of prediabetes. In this population, 21.7% (n=214) had IFG only, 3.4% (n=31) had IGT only and 2.2% (n=19) had both IFG and IGT. We found no differences in waist circumference, levels of triglycerides, high density lipoprotein, and systolic and diastolic blood pressure between the 3 groups (IFG, IGT, or both) or between the 2 groups (IFG, any IGT). Unlike in adults, we did not see differences in clinical or cardiovascular risk factors for IGT vs. IFG. Further studies are needed to understand whether there are differential long-term risks of childhood IGT vs. childhood IFG.

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1252-P

Sex Hormone Binding Globulin and Diabetes Risk in Overweight/ Obese Adolescents

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A number of studies suggest that sex hormone binding globulin (SHBG) is a predictor and possible mediator of incident diabetes in adults, as low SHBG levels represent an androgenic state, and sex hormones have been shown to influence insulin homeostasis. There are relatively fewer studies of SHBG and markers of diabetes risk particularly among US children. Our objective was to evaluate the relationship between SHBG, glucose tolerance status and insulin sensitivity among a population of overweight/ obese children. Children were 10-17 years of age with measures of body mass index percentile, insulin and glucose from a 2-hr oral glucose tolerance test, SHBG levels, and self-reported Tanner stages. For our independent variable, we created tertiles of SHBG for the population. Our dependent variables included: prediabetes/diabetes(fasting glucose ≥ 100 mg/dl or 2-hour post glucose ≥ 140 mg/dl); insulin resistance as measured by HOMA-IR and whole body insulin sensitivity index (WBISI). We performed

For author disclosure information, see page 785.

logistic and linear regression analyses, stratified by sex, which included demographic covariates (age, race) as well as BMI percentile and Tanner stage. Of the 165 children eligible for the analysis, 50.3% were female, 59.8% were white and 30.5% were black. Mean BMI percentile was 96.3% for girls and 96.8% for boys. There were 61 (37.0%) cases of prediabetes or diabetes. We found no association of SHBG tertiles with prediabetes/diabetes for either sex. Compared with the highest tertile, the lowest SHBG tertile was associated with a higher HOMA-IR (p=0.01 for girls; p=0.009 for boys) and lower WBISI (greater insulin resistance) (p<0.001 for girls; p=0.004 for boys). These relationships persisted even after adjustment for BMI percentile and Tanner stage. Because low SHBG levels are associated with higher levels of insulin resistance, a critical risk factor for development of diabetes, further studies are needed to determine whether SHBG levels may be a useful marker of long-term diabetes risk for pediatric populations. Additional analyses will also explore the relation between sex hormones and diabetes risk independent of SHBG.

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1253-P

Testosterone Concentration in Obese Young Males

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AIM: Obesity in adult males is associated with hypogonadotropic hypogonadism. In children, body mass index (BMI) has known to affect the age of initiation of puberty in both males and females. The objective of our study was to look at the effect of obesity on plasma testosterone concentrations in post pubertal male children. RESEARCH DESIGN AND METHODS: This was a cross-sectional case control study performed at Women and Children's Hospital of Buffalo, Endocrine and Diabetes Center. Blood samples were obtained between 8 and 10 am from 19 obese (BMI ≥ 97% for age) and 11 lean (BMI < 85% for age) males between the ages 14-20 years with Tanner staging ≥ 4. Total testosterone (TT), sex hormone binding globulin (SHBG) and C-reactive protein (CRP) levels were measured. TT was measured by LC-MS/MS, SHBG by an immunometric assay and CRP by ELISA. Free testosterone (cFT) was calculated from TT, SHBG and serum albumin. RESULTS: Obese males had a significantly lower TT, cFT and SHBG concentrations when compared to lean males: TT: 296±131 ng/dl vs 536±146 ng/dl, p<0.001; cFT: 7.5±3 vs 10.6±3.9 ng/dl; p=0.04; and SHBG 22±13 vs 46±25 nmol/l; p=0.01. After controlling for age and Tanner staging, the concentrations for total and free testosterone continued to be significantly lower in the obese males compared to the lean males. The CRP concentrations were higher in obese males when compared to the lean (2.2±1.9 vs 1.0±2.3 mg/l; p=0.001). TT (r=-0.67; p<0.001), cFT (r=-0.40; p=0.04) and SHBG (r=-0.56; p=0.002) were inversely related to BMI. CRP concentrations were inversely related to TT(r=-0.39; p=0.04) and SHBG(r=-0.40, p=0.04) and positively to BMI(r=0.65; p<0.001). Thus young obese post pubertal males have significantly lower TT, cFT and SHBG concentrations than those with normal BMI. The inverse correlation of these indices with CRP also suggests that these patients with lower T concentrations may be at a greater cardiovascular risk. Obese young men need to be screened for hypogonadism, systemic inflammation and potential cardiovascular risk.

1254-P

Monocyte Expression of Tumor Necrosis Factor-α Gene Correlates with Central Obesity and Dyslipidemia in Adolescents

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Metabolic syndrome (MetSyn) is a cluster of risk factors for cardiovascular disease and diabetes that affects 1 in 3 obese children. Inflammatory cytokines, including tumor necrosis factor (TNF)-α, are thought to be partly responsible for the metabolic abnormalities associated with MetSyn. While adipocytes and adipose tissue macrophages are known to secrete TNF-α, less is known about the role of the peripheral blood monocyte (macrophage precursor) in MetSyn. The objective of this study was to evaluate TNF-α gene expression in circulating monocytes from obese adolescents with MetSyn (obese-MetSyn), metabolically normal obese adolescents (obese-healthy) and lean adolescents. Clinical measurements (body weight, body mass index [BMI], percent body fat [via bioelectric impedance]), metabolic parameters (lipid profile assessment, fasting glucose, fasting insulin) and serum inflammatory marker (TNF-α) were performed. Gene expression of TNF-α was quantified by real-time quantitative PCR in monocytes from the same subjects. The primary outcome was differences in gene expression between the obese-MetSyn, obese-healthy and lean groups. The secondary outcomes included relationship of TNF-α expression to clinical and biochemical parameters. Twenty-two adolescents (five boys and seventeen girls) participated in the study. Six adolescents met the criteria for metabolic syndrome. There were no significant differences between the obese-MetSyn, obese-healthy and lean groups in age. In obese-MetSyn subjects, TNF-α expression in monocytes and TNF-α serum levels were increased compared to obese-healthy and lean control subjects. TNF-α expression in monocytes positively correlated with BMI (R=0.69, p< 0.001), body fat (R=0.5, p=0.05), waist circumference (R=0.75, p<0.001) and triglyceride level (R=0.57, p=0.005). TNF-α gene is expressed in monocytes, and expression correlates with BMI, body fat, waist circumference and triglyceride levels. The knowledge gained from this study will advance our understanding of the contribution of monocytes to the pathophysiology of MetSyn in a young population.

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1255-P

Relationships between Birth Size and Metabolic Status in Obese Adolescents

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Both small and large birth size for gestational age represent risk factors for insulin resistance, metabolic syndrome and type 2 diabetes in adulthood. We studied a cohort of obese adolescents for the relationship between body mass index (BMI), blood lipids, glycemia, insulin resistance, adipokines, blood pressure and endothelial function and birth weight. The REACH study (ClinicalTrials.gov number NCT00934570) will assess the effects of a structured lifestyle intervention and metformin (or placebo) on BMI and other risk factors for type 2 diabetes and cardiovascular disease in obese adolescents (age 10-16 years, BMI > 95th centile). Study entry data were analyzed prior to any lifestyle or pharmacologic interventions for 92 subjects (mean age 13.6 years, 49 F, 43 M; mean BMI 33.1) with a mean birth weight of 3525 gm (1899-4990 gm; gestational age 36-42 weeks). BMI z-score was positively correlated with birth weight (r^2=0.048, p=0.03), but not with waist circumference. Insulin resistance, as measured by HOMA (Homeostasis Model Assessment), was negatively correlated with birth weight (r^2=0.050, p=0.04), as was fasting plasma insulin (r^2=0.050, p=0.03), but not fasting glucose values. A positive correlation existed between birth weight and A1C (r^2=0.070, p=0.03). Adiponectin, but not leptin values were positively correlated with birth weight (r^2=0.042, p=0.02), although leptin was positively related to BMI z-score at study entry. Mean systolic and diastolic BP z-scores were 0.36 and 0.32 respectively. BP did not correlate with cardiovascular risk factors, including endothelial function as measured by endoPAT, or birth weight. Results show that BMI in obese adolescents is positively related to size at birth. However insulin resistance was worse in those who were relatively small at birth, despite the lower BMI. The difference in risk factors for obese adolescents associated with a birth weight of <2.5 kg vs >4.5 kg is approximately 0.2 BMI z-score, 0.2% A1C and a HOMA of 2.0. Consideration of birth size may be valuable in developing intervention strategies in obese youth at risk for metabolic syndrome and type 2 diabetes.

1256-P

Associations in Metabolic Parameters between Mother and Child after Pregnancy with Gestational Diabetes

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Prenatal exposure to maternal gestational diabetes (GDM) is suggested to impact the higher risk of obesity and diabetes in the offspring's later life. The aim of the study is to assess associations in metabolic parameters between early postnatal data of the mother and those of the child at a mean age of six years.

In a prospective study, 28 women affected by prior GDM received a detailed metabolic characterization (routine laboratory examinations, oral-glucose-tolerance-test (OGTT)) until 3 months after index pregnancy. The offspring of these mothers (28 children; f:14; m:14) were examined at an age of 4-9 years by anthropometric and laboratory measurements. Additonally, a 2h-OGTT was performed in all children and circulating levels of Adiponectin were measured.

A correlation analysis showed significant associations in the lipid profiles of GDM mothers and their offspring (Total-Cholesterol: r_s=0.53, p=0.006; LDL-Cholesterol: r_s=0.52, p=0.007; Non-HDL-Cholesterol: r_s=0.63, p=0.001; HDL-Cholesterol: r_s=0.41, p=0.043). With regard to liver enzymes, we observed similar results for AST and ALT (AST: r_s=0.53, p=0.008; ALT:

r_s=0.44, p=0.009) but not for γ-GT (r_s=0.27, p=0.202). Further, we found no associations in glycemic parameters between both groups (HbA1c, fasting insulin, fasting glucose, 2-hour glucose during OGTT). Most interestingly, the maternal 2-hour glucose level during OGTT was the best linear predictor for decreased Adiponectin in the child (β=-0.073, R^2=0.421, p<0.001), even after adjustment for sex and age.

Our data strengthens evidence for the effect of maternal lipid metabolism during pregnancy on fetal programming in women with gestational diabetes. Adiponectin as an early mediator of insulin resistance is highly associated with deterioration of maternal glucose tolerance.

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1257-P

NAFLD in Youth with Type 2 Diabetes: An Important but Under-Recognized Co-Morbidity

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Obese children have a high prevalence of non-alcoholic fatty liver disease (NAFLD). In adults, type 2 diabetes (T2DM) is an additional risk factor for NAFLD. Little is known about the prevalence or natural history of NAFLD in youth with T2DM. Biannual screening for NAFLD is recommended for all obese children (body mass index [BMI≥95%ile); however, the American Diabetes Association does not include screening for NAFLD in its T2DM screening guidelines. We hypothesized that NAFLD screening rates would be low in our pediatric T2DM population, but that the prevalence of elevated liver transaminases in those screened would be high.

All obese patients age 10-18 years seen for T2DM at Cincinnati Children's Hospital Medical Center between 2007-2009 were identified (N=59), and 2 years of clinical and laboratory data prior to that visit were abstracted from clinical charts. Appropriate screening was defined as having at least one ALT, AST or GGT, with the first ALT in the period as the primary measure. The degree of abnormality was classified as normal (<26 for males, <23 for females), mildly abnormal (26-52 for males, 23-46 for females) or abnormal (>2x normal), based on the 95th percentile for a healthy non-obese pediatric population (NHANES).

Patients were 76% female and 51% white, with a mean BMI=37.7 ± 9.2 and a mean HbA_1c=.8.3 ± 2.4. Liver enzymes were measured in only 63% (37 of 59), and a significantly greater percentage (86%) had lipids screened (p=0.003 by Fisher's exact test). The majority of those screened (54%) had a mildly abnormal ALT and only 30% had a normal ALT. Six (16%) patients had clearly abnormal ALTs, along with AST and GGT above the reference range, and most of these patients (83%) exhibited persistently elevated ALT on follow-up testing.

In conclusion, screening rates for NAFLD were suboptimal in youth with T2DM, despite a significant prevalence of elevated ALT in this population. Intention to screen based on obesity status is likely even lower, as transaminases were obtained for a variety of reasons. Pediatric diabetes providers need to be aware of the screening guidelines for NAFLD to ensure obese T2DM patients are screened and evaluated appropriately.

1258-P

Poor Literacy and Numeracy Skills in Caregivers Adversely Affects Glycemic Control in Children with Type 2 Diabetes

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Poor comprehension of nutrition labels because of inadequate literacy and/or numeracy skills in caregivers may pose an impediment to achieving optimal glycemic control in pediatric type 2 diabetes. We hypothesized that poorly controlled diabetes is associated with inadequate literacy/ numerical skills of caregivers in the pediatric type 2 diabetes population.

Primary caregivers were evaluated using the Newest Vital Sign (NVS) and a sociodemographic questionnaire. The NVS, a screening tool in English and Spanish, identifies persons at risk for low health literacy by measuring general literacy and numerical skills as applied to health information, yielding an overall estimate of health literacy.

Forty caregivers of type 2 diabetes children with mean HbA1C of 8.8 ± 3%, age of 14 ± 2.7 years, duration of disease of 3.1 ± 2.1 years, and BMI of 31.9 ± 5.4 Kg/ m^2 participated. Those with inadequate literacy were associated with significantly higher HbA1C at 11.2 ± 2.8% when compared with those of adequate literacy at 7.7 ± 2.3% (p<0.03). HbA1c was significantly lower in the children when caregivers answered 75 % of the arithmetic questions correctly (7.4 ± 2.4%) when compared with those who did not (9.8 ±3%), p< 0.009. Education and income of caregivers appear to have an insignificant effect on glycemic control.

Adequate literacy and numerical skills of primary caregivers was found to be associated with significantly better glycemic control in their children with type 2 diabetes. Targeting caregiver literacy may improve glycemic control.

1259-P

Shape of Plasma Glucose Curve during an Oral Glucose Challenge Is Associated with Diabetes Risk Factors in Youth

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The "shape" index derived from the glucose response to an Oral Glucose Tolerance Test (OGTT) prospectively and independently predicts type 2 diabetes (T2D) in adults. However, the association of the shape index and diabetes risk in younger populations has not been established. The purpose of this study was to compare diabetes risk factors in youth characterized by a monophasic or biphasic glucose response during an OGTT.

One hundred and twenty eight non-diabetic Latino youth (age 16.1 ± 2.8 yrs, BMI 26.3 ± 6.8 kg/m^2) participating in the Maricopa County Insulin Resistance Registry underwent a 2-hour OGTT and were characterized as having either a monophasic or biphasic glucose response. Monophasic response was characterized by a gradual rise and then a fall in glucose during the OGTT. In comparison, the biphasic response was defined by a gradual rise in glucose, followed by a ≥4.5 mg/dl drop, with a second rise of glucose of at least 4.5 mg/dl at a subsequent time point. Groups were compared for the following T2D risk factors: BMI, fasting and 2-hour glucose, HbA1c, and glucose area under curve (AUC).

Eighty six youths (67%) were categorized as monophasic and 42 (33%) were biphasic. No significant differences between groups were noted for gender, BMI, age, fasting or 2-hour glucose. However, participants characterized by a biphasic shape had significantly lower HbA1c (5.4 ± 0.3% vs. 5.5 ± 0.3%, p<0.05) and glucose AUC (14445 ± 2205 mg*dl^{-1}*h^{-1} vs. 16328 ± 2665 mg*dl^{-1}*h^{-1}, p<0.001) compared to youths in the monophasic group.

These data suggest that the shape of the glucose response during an OGTT may differentiate risk for T2D in youth. Our findings are similar to those reported for adults, in whom a monophasic response predicts greater risk for T2D compared to a biphasic response. Given that the prevalence of T2D is increasing in younger populations, early identification of phenotypes associated with greater risk for the development of T2D in youth is important. Our data suggest that the pattern of plasma glucose excursion in response to an oral glucose load may provide a useful predictor of risk of T2D.

1260-P

Vitamin D Status across the Spectrum of Glucose Tolerance in Obese Adolescents

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Low serum 25-hydroxyvitamin D (25[OH]D) is associated with increased risk of type 2 diabetes (T2DM) in adults and fasting hyperglycemia in children. Childhood obesity is a risk factor for hypovitaminosis D and impaired glucose metabolism, and adiposity may confound the relationship between vitamin D and glucose homeostasis. Therefore, this cross-sectional study aimed to (1) examine if plasma 25(OH)D levels vary across the spectrum of glucose tolerance in obese youth with similar degrees of adiposity, and (2) assess the relationship between 25(OH)D and oral glucose tolerance test (OGTT) glucose and insulin parameters. A total of 172 obese adolescents, 90 with normal glucose tolerance (NGT), 52 with impaired glucose tolerance (IGT), and 30 with T2DM were studied. The groups were comparable in age, BMI and percentage of body fat (assessed by DXA). Plasma 25(OH) D did not differ among the groups [NGT=17.4±0.9 ng/mL; IGT=15.7±0.9 ng/ mL; T2DM=17.7±1.0 ng/mL, p=NS]. Furthermore, the proportion of children who were vitamin D deficient (25[OH]D <20 ng/mL) did not differ across the groups (NGT=66%, IGT=81%, T2DM=60%, p=NS). Plasma 25(OH)D did not correlate with hemoglobin A_{1C}, fasting insulin or glucose, or OGTT area under the curve for glucose or insulin in all subjects, and in blacks and whites analyzed separately. In conclusion, the majority of obese adolescents with NGT, IGT and T2DM are vitamin D deficient, with no differences among the groups in 25(OH)D concentrations, and no relationship between 25(OH)D and glycemic parameters across the spectrum of glucose tolerance.

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

1261-P

Vitamin D Status and β-Cell Function in Black and White Youth: Is There a Relationship?

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Adult data suggest that vitamin D may influence insulin secretion. However, such data are limited in children. Therefore, we examined the relationship between plasma 25-hydroxyvitamin D [25(OH)D] and *in vivo* insulin secretion, assessed during a hyperglycemic (~225 mg/dl) clamp, in black (B) and white (W) youth (n= 280, 151 white, 139 male, 146 obese) aged 8 to <20 years. All underwent measurements of total body adiposity (DXA), and abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). In both whites and blacks, vitamin D deficient (25[OH]D <20 ng/mL) subjects had higher fasting insulin ± SEM (μU/ml) (W: 29.0±2.5 vs. 22.2±1.5, p=0.024; B: 28.5±2.0 vs. 21.1±2.2, p=0.022) and 1st phase insulin levels (μU/ml) (W: 157.3±12.7 vs. 127.4±11.1, p=0.013; B: 242.1±17.6 vs. 184.2±23.4, p=0.042) than non-deficient youth. Plasma 25(OH)D correlated with fasting insulin (W: r=-0.223, p=0.008; B: r=-0.230, p=0.010) and 1st phase insulin (W: r=-0.200. p=0.014, B: r=-0.173, p=0.05). However, the significance of these differences and correlations disappeared after adjustment for any adiposity measure (BMI or fat mass or VAT or SAT). Plasma 25(OH)D was not independently associated with 1st (partial r=0.019, p=0.76) or 2nd phase insulin levels (partial r=0.015, p=0.80) when adjusted for age, sex, race, Tanner stage, and BMI. In conclusion, this large data set demonstrate that the observed relationship between 25(OH) D concentrations and β-cell function in youth is mediated through adiposity which is inversely related to 25(OH)D and positively to insulin secretion.

PREGNANCY

[*See also: Presidents Posters 424-PP to 425-PP, page A118.*]

Guided Audio Tour: Gestational Diabetes and Post-Partum Follow-Up
(Posters 1262-P to 1265-P), see page 13.

1262-P

Prediabetes and Incident Diabetes One Year after GDM Pregnancy in the SWIFT Longitudinal Cohort

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Two prospective epidemiologic studies found that longer lactation reduced women's risk of incident type 2 diabetes in mid or late life based on self report of diabetes. In women with gestational diabetes mellitus (GDM) evidence is unavailable that lactation prevents type 2 diabetes years later. The study objective is to prospectively examine infant feeding method and incidence of diabetes and glucose intolerance (prediabetes) among women with recent GDM (63% Hispanic, Asian or Black) enrolled during 2008-2010 in the Study of Women, Infant Feeding and Type 2 Diabetes (SWIFT), an ongoing prospective observational cohort study of Kaiser Permanente Northern California members. SWIFT enrollees (n=603) met standard criteria for GDM diagnosis, delivered singleton, term, live births, were free of diabetes based on 2 hr 75 g OGTT screening, had no major medical disorders, and were predominantly breast or formula feeding at 6-8 wks postpartum (baseline). The analysis includes 203 SWIFT women (n=142 breast, n=61 formula) re-screened by 2 hr 75 g OGTT at 1 yr postpartum. We defined incident diabetes and prevalent prediabetes (IFG and/or IGT) cases based on fasting and 2 hr post load glucose values using ADA diagnostic criteria. Of 203, 13 developed incident diabetes, 6.4% (95%CI:3.5-10.7) and 83 had prediabetes, 40.9% (95%CI:34.1-48.0) at 1 yr postpartum. Predictors of incident diabetes, or prevalent prediabetes vs normoglycemia at 1 yr postpartum include obesity (69%, 53% vs 30%), being Asian or Hispanic (85%, 51% vs 63%) and higher mean fasting and 2 hr post-load glucose at 6-8 wks postpartum;all p<.01. Among formula compared to breast feeders, diabetes cumulative incidence was 8.2% (95%CI:2.7-18.1) and 5.6% (95%CI:2.5-10.8);p=.49, and prediabetes prevalence was 47.5% (95%CI:34.6-60.7) and 38.0% (95%CI:30.0-46.6);p=.21. Preliminary findings show a trend for 32% lower diabetes incidence and 20% lower prediabetes prevalence one year after GDM pregnancy in predominant breast versus formula feeders. Recruitment and follow-up screening are underway in SWIFT to attain sufficient power to assess these relationships long-term and elucidate mechanisms.

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1263-P

Weight Changes Related to Prediabetes and Incident Diabetes at One Year Postpartum in the SWIFT Longitudinal Cohort

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Weight gain following pregnancy is associated with new onset type 2 diabetes mellitus in women with a history of gestational diabetes mellitus (GDM). Yet, few studies have prospectively measured weight change during the first year postpartum in relation to glucose tolerance. This analysis examines % change in body weight measured at 6-8 weeks and again at 1 yr postpartum for participants enrolled during 2008-2010 in the Study of Women, Infant Feeding and Type 2 Diabetes (SWIFT), an ongoing prospective observational cohort study of Kaiser Permanente Northern California members. SWIFT enrollees (n=603; 29% Hispanic, 32% Asian or 8% Black) met standard criteria for GDM diagnosis, delivered singleton, term, live births, were free of diabetes via 2 hr 75 g OGTT using ADA diagnostic criteria, had no major medical conditions and were predominantly breast or formula feeding at 6-8 wks postpartum, and re-screened with the 2 hr 75 g OGTT at 1 year postpartum. Among 200 women re-screened and who had body weight measured at baseline and follow-up, 13 developed incident diabetes, 83 had prediabetes (IFG and /or IGT) and 104 were normoglycemic at 1 year postpartum. Among these 3 glucose tolerance groups, respectively, the median (IQR) for % weight change was 6.1 (8.2), 3.2 (9.1) and -2.5 (9.2); p<.001, and the % of women who lost any weight was 15%, 37%, and 62%; p<.01, at 1 year postpartum. Predominantly breastfeeding compared with predominantly formula feeding groups had lower % weight change; median (IQR) was - 0.3 (11.4) vs 1.9 (7.7); p=.12, and they were twice as likely to lose ≥5% body weight at 1 year postpartum; crude OR (95%CI): 2.1 (0.9, 4.7); p=.06. Weight gain during the first year postpartum is associated with glucose intolerance after GDM pregnancy. Lactation may promote greater weight loss in women with recent GDM. Follow-up is underway in the SWIFT cohort to examine the relationship between lactation and long-term glucose tolerance after GDM pregnancy, including the role of weight change.

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1264-P

Clinical and Genetic Differences between Women Who Progress to Diabetes Early Versus Late after Gestational Diabetes Mellitus

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Nearly half of women with gestational diabetes mellitus (GDM) progress to type 2 diabetes within 10 years after pregnancy. However, time to progression to diabetes after GDM pregnancy vary individually. The clinical and genetic differences between subjects who progress to diabetes early (2 months) versus late (more than 1 year) after parturition are mostly unknown.

In this study, we investigated the antepartum clinical, metabolic, and genetic differences between early converters and late converters after GDM pregnancy. The study enrolled 844 Korean women with GDM pregnancy. Oral glucose tolerance test (OGTT) was performed at 2 months postpartum and annually for median of 48 months. All the subjects were genotyped for 21 single nucleotide polymorphisms (SNPs) in *PPARG*, *IGF2BP2*, *CDKAL1*, *SLC30A8*, *CDKN2A/2B*, *HHEX*, *TCF7L2*, *KCNQ1*, *KCNJ11*, and *FTO*. Antepartum clinical, metabolic characteristics as well as allele frequencies were compared between women who progressed to diabetes early versus late after GDM pregnancy.

Among the 844 GDM women, 105 (12.0%) progressed to diabetes early postpartum. Among the 435 women who had normal glucose tolerance at early postpartum and had follow up visit for more than one year, 120 (27.6%) progressed to diabetes. Early converters had higher glucose and lower insulin concentration during diagnostic OGTT performed at pregnancy compared to late converters. The early converters had significantly decreased 1-hour insulinogenic index compared to late converters. Variations in *HHEX* (*P*=0.002) were significantly associated with early conversion to diabetes and variations in *CDKAL1* (*P*=0.000001) were significantly associated with late conversion to diabetes.

Women who progress to T2DM early post-partum have decreased insulin secretory capacity compared to late converters. These differences might be explained by difference in genetic predisposition.

1265-P

Evaluation of the Ability of Metabolic Parameters To Predict the Onset of Diabetes in Women with a History of Gestational Diabetes

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Gestational diabetes mellitus (GDM) is the specific type of diabetes that may develop during pregnancy. After delivery, women with previous GDM (pGDM) often normalize their glucose levels, but they are at increased risk of developing type 2 diabetes (T2DM), especially if they have other risk factors (i.e. obesity, hypertension, family history of T2DM). Aim of this study was to identify metabolic and anthropometric parameters in pGDM that, measured immediately after delivery, may be predictive of the possible onset of overt T2DM in the following years.

79 non diabetic pGDM were yearly evaluated for 3-6 years with a 75-g 3h oral glucose tolerance test with glucose, insulin and C-peptide measurements. Insulin sensitivity was assessed with the oral glucose sensitivity index (OGIS), while beta cell function through mathematical modelling of C-peptide, that yields beta cell sensitivity to glucose stimulus (BGS). pGDM were split into two groups based on the outcome of their last examination: 19 women progressed to diabetes and 60 remained non diabetic.

A logistic regression model with age, BMI, mean plasma glucose (MPG), BGS and OGIS as covariates, was fitted to quantify the predictive power of each covariate for the possible onset of T2DM. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated for 1 standard deviation (SD) increase of each parameter (see Table).

	OR per 1 SD increment (95% CI)	p
age	**2.24 (0.86 – 6.90)**	**0.120**
BMI	**4.41 (1.48 – 23.53)**	**0.028**
MPG	**4.02 (1.36 – 17.90)**	**0.026**
BGS	**0.18 (0.03 – 0.63)**	**0.019**
OGIS	**0.31 (0.08 – 0.87)**	**0.044**

These results, in confirming expected ones, show that 1 SD increment in BMI or MPG leads to a 4-fold increased risk of developing diabetes, while a higher BGS or OGIS decreases that risk.

BMI, MPG, BGS and OGIS have predictive capability in identifying, immediately after partum, those pGDM that will develop diabetes within 3-6 years. Early assessment of these metabolic parameters could prove useful to characterize those pGDM at highest risk, and could allow starting early prevention against the development of diabetes.

Guided Audio Tour: Pregnancy—Mothers and Fetus *(Posters 1266-P to 1271-P), see page 13.*

1266-P

AMP Kinase Mediates Effects of Oxidative Stress on Embryo Gene Expression in Diabetic Embryopathy

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Oxidative stress is central in causing abnormal gene expression and congenital malformations during diabetic embryopathy. Oxidative stress results from increased embryo glucose metabolism, which depletes availability of O_2 and the antioxidant, reduced glutathione (GSH), to the embryo. Oxidative stress inhibits expression of genes that are essential for embryonic development. In particular, expression of *Pax3*, a gene that is essential for neural tube closure, is inhibited, and this is associated with increased neural tube defects (NTD). How oxidative stress affects embryo gene expression is not understood. Here we tested the hypothesis that AMP-activated kinase (AMPK), which is stimulated by hypoxic and oxidative stress, mediates the adverse effects of maternal hyperglycemia on *Pax3* expression and NTD.

To test this, pregnant mice were made transiently hyperglycemic, or treated with antimycin A (AA) to induce oxidative stress, and AMPK activity in embryos was assayed. The effects of stimulating AMPK activity with 5-aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside (AICAR) on *Pax3* expression and NTD were determined. Mouse embryonic stem cells (mESC) were employed to investigate AMPK inhibition of *Pax3* expression *in vitro*. We found that maternal hyperglycemia stimulated AMPK activity, and stimulation of AMPK with AICAR inhibited *Pax3* expression (*in vivo* and *in vitro*) and increased NTD (*in vivo*). Stimulation of AMPK by hypoxia or AA was inhibited by the antioxidants, glutathione ethyl ester (GSH-EE) or vitamin E, indicating that hypoxia-induced oxidative stress mediates effects of hyperglycemia to stimulate AMPK. The AMPK inhibitor, Compound C, blocked the effects of hyperglycemia or AA on *Pax3* expression and NTD. These results indicate that stimulation of AMPK in embryos of diabetic mothers inhibits embryo gene expression in response to hyperglycemia-induced oxidative stress, thereby causing malformations.

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1267-P

Maternal Weight Gain during the Different Trimesters Seem To Influence Infant Body Composition Differently

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Maternal characteristics such as BMI, gestational weight gain (GWG), and glucose tolerance have been associated with early infancy body composition (EIBC) in their offspring. Here we extend these observations looking at the associations between gestational body composition (GBC) and GWG by trimester, in addition to gestational glucose tolerance and offspring EIBC.

Participants were 31 (16 female) singleton babies and their mothers (aged 25-35 yrs) in the eastern area of the county of Västerbotten in Sweden. Maternal weight was measured at gestational weeks 10-12 (beginning of second trimester), 28-32 (beginning of third trimester), and 37-41 (prenatal visit prior to delivery). GBC was assessed using isotope dilution and gestational glucose tolerance was assessed with a 2-hour, 75-gram oral glucose challenge at 28-32 weeks gestation. EIBC was assessed at 11-19 weeks of age using air displacement plethysmography. The relationships between maternal and infant variables were assessed with Spearman correlations. All infant variables were adjusted for age, sex, and length. All maternal variables were adjusted for the gestational week of measurement. GWG was additionally adjusted for first trimester BMI. Maternal fat mass was not significantly related to EIBC (infant fat mass: r=-0.02, p=0.90; infant fat-free mass: r=-0.11, p=0.54). Maternal fat-free mass was also not significantly related to EIBC (infant fat mass: r=-0.11, p=0.54; infant fat-free mass: r=0.03, p=0.89). Gestational glucose tolerance was not significantly related to any estimate of EIBC (infant fat mass: r=0.00, p=0.99; infant fat-free mass: r=0.05, p=0.80). Second trimester GWG was significantly positively related to early infancy fat mass (r=0.40, p=0.04) but not fat-free mass (r=0.33, p=0.08) whereas third trimester GWG was significantly positively related to early infancy fat-free mass (r=0.42, p=0.02) but not fat mass (r=-0.11, p=0.55). Previous research suggests that maternal glucose tolerance is associated with EIBC in the first few days of life, but diminishes over the first 3 months of life. Our findings regarding GBC and GWG by trimester and EIBC are novel.

1268-P

Lifestyle and Pregnancy (LiP) Study: The Clinical Effect of Lifestyle Intervention during Pregnancy in Obese Women

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Obesity in pregnancy is related to higher maternal and perinatal morbidity. The new Institute of Medicine (IOM) guidelines recommend gestational weight gain (GWG) of 5-9 kilos in obese women. Observational studies indicate that adverse pregnancy outcomes in obese women can be limited if GWG is restricted.

The aims are to study the effects of lifestyle intervention on GWG and obstetric outcomes.

The study is a randomized controlled trial in 360 obese women with body mass index (BMI) of 30-45 kg/m^2 allocated to either lifestyle intervention or routine obstetric care in early pregnancy. The intensive intervention program included recurrent dietary guidance, free membership in fitness centres, physical training and personal coaching in smaller groups. Women with chronically medical conditions were excluded together with women, who were tested positive for gestational diabetes (GDM) during 1st trimester.

A total of 360 obese pregnant women were included and 300 (83%) were followed until delivery. The intervention group had significantly lower GWG compared to the control group 7.3 (±4.4) kg vs. 8.7 (±4.6) kg (p=0.01). IOM recommendations were exceeded in 38% of the women in the intervention group vs. 50% in the control group (p<0.05). Overall, there was no significant difference in the obstetric outcomes in the intervention group vs. controls (%; p-value): Macrosomia (birth weight >= 4000 g) (32.0 vs. 24.8; p=0.17), emergency caesarean section (15.0 vs. 18.3; p=0.44), preeclampsia (6.8 vs. 5.9; p=0.74), GDM (6.1 vs. 5.2; p=0.74).

Intervention with diet and physical exercise in pregnancy resulted in limited GWG in obese pregnant women, but overall obstetric outcomes

For author disclosure information, see page 785.

Guided Audio Tour poster ADA-Funded Research

were similar in the two groups. Intensive lifestyle intervention resulted in a higher adherence to IOM recommendations. However, a significant number of women still exceeded the upper threshold.

1269-P

Osteocalcin- and CTX (Crosslaps)-Associated Hyperinsulinemia Rather Than Osteopontin-Mediated Insulin Resistance Play a Key Role in Gestational Diabetes Mellitus

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Reciprocal and regulatory interaction between bone and glucose metabolism might emerge early in the development of type 2 diabetes. Recently we reported that osteocalcin is higher in gestational diabetes and its serum concentrations parallel hyperinsulinemia. Other groups showed that osteocalcin can enhance insulin secretion and sensitivity. The C-terminal cross-linking telopeptide of Type-I collagen (CTX, crosslaps) and osteopontin, two hormones which were initially detected in bone tissue, have recently been associated with glucose metabolism and obesity-induced inflammation and insulin resistance. However a distinct role in gestational diabetes has not been studied yet.

Therefore we aimed to investigate serum concentrations of osteopontin and CTX as well as parameters of insulin sensitivity and secretion in 26 women with gestational diabetes (GDM) and 52 women with normal glucose tolerance (NGT), well matched for age and BMI, between 24th and 28th gestational week.

CTX was significantly higher in GDM compared to NGT(0.44±0.20vs. 0.28±0.12,p<.0001) and positively correlated with parameters of insulin secretion (Total InsulinSecretion, AUC of insulin and C-Peptide, Disposition- and Adaptation Index), while it showed an inverse correlation with hepatic insulin extraction and HDL-cholesterol. Furthermore, CTX was significantly inversely correlated with insulin sensitivity derived from OGTT (OGIS: R= -0.3,p=0.003). In contrast, osteopontin was significantly decreased in GDM compared to NGT (1.15±0.88vs.1.51±0.79;p<0.04), and did not show any relation to insulin secretion or sensitivity, but was significantly correlated with high-sensitive CRP (R=0.3,p<0.03).

Our findings support the idea of a tight regulation between bone and glucose metabolism, and suggest that osteocalcin- and CTX-associated hyperinsulinemia rather than osteopontin-mediated insulin resistance contribute to glucose intolerance in women with gestational diabetes, while osteopontin may play a role in inflammatory changes related to early disturbances of glucose metabolism.

1270-P

Intrauterine Growth Retardation Together with High Fat Diet in Rats Markedly Disturbs Islet Morphology without Loss of Beta-Cell Mass or Induction of Diabetes

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Pre- and post-natal factors such as intrauterine growth retardation (IUGR) and poor diet contribute to type 2 diabetes (T2D) development. Our aim was to determine if IUGR and high fat (HF) diets interact in T2D pathogenesis.

A previously described Sprague-Dawley rat model of IUGR (bil. uterine art. ligation) with sham (SH) controls, in which chow (CH)-fed IUGR rats develop diabetes, was used.[1] Male IUGR and SH pups (8-9/grp) were fed high fat (HF) or CH diets from weaning. Serial measures of body weight (wt.) and serum variables were made. Glucose tolerance (gluc. tol.) tests (ip) were done at 13 and 23 weeks of age. At 23 weeks, rat pancreases were harvested and submitted to blinded histological study including assessment of beta cell mass.

IUGR compared to SH pup wts. were approx. 25% lower. The CH-IUGR compared to CH-SH rats developed a minimally abnormal (abn.) metabolic phenotype with elevated fasted non-esterified fatty acids. Gluc. tol. and insulin secretion remained normal. HF-IUGR and HF-SH rats developed excess wt. gain, dyslipidemia, mild gluc. intolerance and hyperinsulinemia compared to CH-fed rats. HF-IUGR had higher fed triglyceride levels than HF-SH rats, but all other metabolic parameters were similar. IUGR rats had markedly abn. islet morphology, evident in 2 of 4 CH-IUGR rats and 4 of 5 HF-IUGR rats (chi-sq, IUGR vs SH, p=0.004). The islets were larger, irregularly shaped with fibrosis, peri-islet inflammation and hemosiderosis. Immunohistochemistry showed reduced beta-cell/islet area with increased numbers of Ki67+ cells. Despite the abn. morphology, overall beta-cell mass was not altered by IUGR with a trend for it to be mildly increased in both HF-fed groups.

In conclusion, the IUGR rats sustained normal islet beta-cell mass and compensatory insulin secretion to HF diet despite significant abnormalities in islet morphology. Islet beta-cell regenerative capacity seemed to be intact in this cohort of SD rats. Unknown genetic differences in islet susceptibility to failure could explain the variance in results between studies.[1]

[1]Simmons RA et al. Diabetes 2001; 50: 2279

Supported by: NHMRC Project Grant

1271-P

Circulating Endothelial Progenitor Cells and Abnormalities of Glucose Tolerance in Pregnancy

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EPCs contribute to vascular integrity. A role for EPCs has been claimed also in development of vasculature in pregnancy. Gestational diabetes (GDM) is associated with endothelial dysfunction, but only a few data about EPCs in pregnancies complicated by diabetes are available. We quantified EPCs in pregnant women with abnormalities of glucose tolerance undergoing a 3-hour, 100-g OGTT at 27±3.2 weeks of gestation. Insulin sensitivity and β-cell function were derived from fasting steady-state and OGTT. EPCs (CD34+KDR+CD133+ cells) were quantified by flow cytometry in 23 women with normal glucose tolerance (NGT), 18 with gestational impaired glucose tolerance (GIGT) - a single OGTT abnormal value - and 24 with GDM. GDM, GIGT and NGT were comparable for age, family history of diabetes, pre-pregnancy body weight (BW), BMI, incremental gestational BW, and blood pressure. AUCgluc (p<0.0001) and AUCins (p=0.06) increased from NGT to GIGT to GDM. Insulin sensitivity, ISIcomp and OGIS, reduced in NGT to GIGT and GDM (ISIcomp: 4.92±2.05, 4.43±2.68, and 3.35±1.87: p<0.05; OGIS 387±53, 357±70, and 316±79 mg/min/m2: p<0.005). The ISSI index was higher (p<0.0001) in NGT. Circulating CD34+ cells were similar in the three groups (NGT: 353.7±165.9; GIGT: 417.2±242.5; GDM: 423.3±220.0 cells/106 events), while EPCs (p=0.0172) were significantly higher in NGT (55.6±57.8) than in GIGT (26.5±19.6; p=0.018), and GDM (26.5±20.4 cells/106 events; p=0.011), with no differences between GIGT and GDM. EPCs were inversely correlated with age (r=-0.26, p=0.04), 1-h (r=-0.30, p<0.02) and 2-h post-load glucose (r=-0.36, p<0.005), and AUCgluc (r=-0.37, p<0.005), but not with insulin levels or AUCins. A weak positive correlation was observed between EPCs and ISSI (r=0.25, p<0.05). No associations have been shown between EPCs and fasting (HOMA%S: r=-0.13, p=0.32) or dynamic indexes of insulin sensitivity (ISIcomp: r=0.01, p=0.95; OGIS: r=0.15, p=0.24). In a multiple linear regression model, only age (p=0.021) and AUCgluc (p=0.027) remained significantly associated with EPCs. Alterations of glucose tolerance during pregnancy seem to act as the triggering factor for the EPCs depletion.

1272-P

Assessment of Hyperglycaemia in Pregnancies Complicated by Fetal Macrosomia Using Continous Glucose Monitoring System

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In order to achieve better glucose control and prevent poor neonatal outcome a tool to rate glucose fluctuations in pregnancies with gestational diabetes mellitus (GDM) or women with high-risk for GDM is the continuous glucose monitoring system.

Aim of the study was to detect the rate of hyperglycemic episodes using CGMS in pregnancies with fetal macrosomia in women with GDM and normal glucose tolerance (NGT) that are not able to be determined using common methods (oral glucose tolerance test (OGTT), euglycemic blood glucose profiles).

34 pregnant women with evident fetal macrosomia who underwent 75-g OGTT, based on the criteria of the Austrian Diabetes Association (fasting≥92mg/dl,1h≥180mg/dl,2h≥153mg/dl) were included (13 GDM/ 21 NGT). CGMS was inserted over 72 hours. To meet accuracy criteria patients were advised to calibrate the system at least 4 times a day.

No significant differences were found in total duration (170 and 172 minutes; p=0,845) and total number of hyperglycemic episodes (1.62±3.798 vs. 2.67±5.228; p=0.534) between both groups (GDM vs. NGT). Of a total of 21 women with NGT, 10 women had normal glucose profiles during the CGMS, whereas 11 women had high glucose levels (≥140mg/dl) during the CGMS (p=0.724). Statistically significant differences between NGT subgroups were found for systolic blood pressure (p=0.043) and FG, 1 hour and 2 hours after glucose loading in the OGTT (p=0.002, p=0.001, p=0.001). Interestingly, in

the NGT group with normal CGMS profile, total cholesterol, LDL-cholesterol levels and also birth weight percentile were significantly higher (p=0.037; p=0.027; p=0.027) compared to women with an abnormal CGMS profile.

Unproblematic use of CGMS is demonstrated in pregnant women. Women with NGT showed hyperglycemic episodes with the use of a CGMS which were not detected by the OGTT. Women with NGT and normal CGMS profile showed significant higher levels of cholesterol and LDL and a greater birth weight percentile that may be responsible for the disproportionate fetal growth. Continuous glucose monitoring and the surveillance of maternal blood lipids are recommended in pregnant women with macrosomic fetuses.

1273-P

Beneficial Impact of Promatoras on Compliance with Postpartum Glucose Tolerance Testing in Latina Women with Recent Gestational Diabetes Mellitus (GDM)

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This study was conducted among Latinas with GDM in a large urban safety-net institution to: (a) assess knowledge and risk perception of the relationship between GDM and future diabetes, and (b) determine if a community health worker (promotora) providing education, reminders and help accessing care could increase participation in diabetes screening after pregnancy. Postpartum, prior to hospital discharge, Spanish or English speaking women without overt diabetes who had telephone access and lived within 60 miles of the medical center were recruited. The Risk Perception Survey for Developing Diabetes, a questionnaire that assesses risk perception and modifiers of risk perception among women with histories of GDM, was administered. Subjects were randomized (stratified by age and BMI) to receive usual care alone (control) or usual care plus the *promotora* intervention. Those in the usual care group received an appointment for glucose tolerance testing and postpartum care. Those in the promotora arm also received a brief structured and tailored educational intervention and received visit reminders by telephone and help rescheduling appointments, if missed. Electronic medical records were reviewed at 12 weeks postpartum to assess compliance with postpartum visits for glucose testing and care. To date, 75 participants have reached 12 weeks postpartum (39 promotora and 36 control). Women in both groups recognize that GDM is a risk factor for future diabetes (90% vs. 86%, respectively; p=0.7) and that they have a moderate to high chance of developing diabetes (62% vs. 69%, p=0.5). Thirty-eight (97%) in the promotora group and 26 (72%) in the control group returned for the scheduled postpartum glucose testing and care visit (p=0.002). Nearly all Latina women with recent GDM understand that they are at increased risk for future diabetes. However, many fail to return for postpartum glucose testing with usual care. Bilingual, bicultural promotoras can significantly increase participation in postpartum glucose testing for Latina women with recent GDM.

Supported by: CDC

1274-P

Chinese Medicine Dwarf Lilyturf Tuber Reduces Hyperglycemia-Induced Developmental Anomalies in Mouse Embryos *In Vitro*

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Maternal hyperglycemia in early stage of pregnancy is associated with pregnant loss and congenital anomalies in offspring. Prevention of the developmental malformations by oral hypoglycemic and insulin therapy remains unsatisfactory. Chinese herbal medicines have being widely used on diabetes for thousands of years with potential therapeutic effects on control of glycemia and its complications. In this study, we investigated the efficacy of the most commonly used Chinese medicines, Dwarf Lilyturf Tuber (*Radix Ophiopogonis*), in reducing the hyperglycemia-induced developmental anomalies in mouse embryos *in vitro*.

Whole mouse embryo culture was employed to induce the diabetic embryopathies. Embryos from non-diabetic mice at late streak gastrulation stage (gestational day 7.5) were cultured in full rat serum, in which D-glucose with or without Dwarf Lilyturf Tuber extracts was supplemented for 48 hours (gestational day 9.5). Developmental morphology in the embryos was assessed and structural anomalies were analysed.

Results showed that 4mg/ml D-glucose significantly retarded the development and also induced open neural tube and other defects in mouse embryos, presenting with low mean total morphological score (TMS) 30.4±9.4 and high incidences of exencephaly (96.3%) and caudal regression (56.7%). Dwarf Lilyturf Tuber concentrations up to 0.11mg/ml (0.06 of oral clinical dose) did not deteriorate the normal development of control embryos (TMS: 67.7±0.9, exencephaly and caudal regression 0%). It significantly improved the development of D-glucose-treated embryos (TCM: 55.5±11.6, p<0.01) and reduced the hyperglycemia-induced exencephaly (25.1%, p<0.01) and caudal regression (12.8%, p<0.01). Bioassay-guided fractionation further confirmed hydrophilic sub-fraction of Dwarf Lilyturf Tuber extracts may contribute to the therapeutic effects.

The study indicated the efficacy of Dwarf Lilyturf Tuber in attenuating hyperglycemia-induced embryopathy *in vitro*.

1275-P

Circulating Adipokines and Gestational Hormones, and Nutrient Intakes Are Associated with the Development of Gestational Diabetes Mellitus in Korea

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Both type 2 diabetes and gestational diabetes mellitus (GDM) are increasing rapidly in Korea at relatively low BMI may be due to low insulin secretory capacity of Asians. We investigated the effects of circulating adipokines and gestational hormones and nutrient intakes on the development of GDM. At 24-28 week of pregnancy, 530 normal and 208 GDM women were recruited to investigate 1) anthropometric and biochemical measurements and 2) nutrient intake by 24 h recall. Age, BMI at prepregnancy and family history were used as adjusting factors in statistical analysis. Prepregnancy BMI was greater in GDM than non-GDM women, but there was no significant difference in weight gain up to 24-28 weeks of pregnancy. HOMA-IR, an index of insulin resistance, was higher and HOMA-B, an index of insulin secretion, was lower in GDM women. GDM women consumed 187 kcal/day more than non-GDM women (P<0.0001). GDM women consumed less plant fats and taurine than non-GDM women whereas sodium and saturated and monounsaturated fat consumption was higher in GDM than non-GDM. Serum adiponectin levels were significantly lower in GDM than non-GDM women, but GDM women had lower serum resistin levels. Serum leptin, adipsin, and visfatin levels were not affected by GDM but serum adipsin and leptin levels were positively correlated with prepregnancy BMI and with HOMA-IR. GDM women had increased serum progesterone levels but not serum prolactin levels and serum progesterone levels were negatively associated with HOMA-B but not HOMA-IR. HOMA-B was an important factor for GDM in Korean pregnant women that explained 65.5% of the variation in fasting serum insulin levels (β=74.6), HOMA-IR (β=-259.0), adiponectin (β=4.2), leptin (β=-23.3), saturated fat intake (β=-0.78), and animal protein (β=0.42). Therefore, GDM might be prevented by decreasing insulin resistance and increasing β-cell function by consuming less saturated fat but more animal protein in Korea. Serum adiponectin and progesterone levels can be used as biomarkers for Korean GDM. Further studies with different populations will be needed.

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1276-P

Does Pregnancy Increase Later Maternal Risk of Diabetes? A Prospective Population-Based Cohort Study (EPIC-Heidelberg)

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Pregnancy is characterized by transient insulin resistance and hyperinsulinemia and predisposes to elevated glucose levels but pregnant women with normal pancreatic function maintain these levels within the normal range. Pregnancy also increases caloric intake and adipose tissue deposition. Evidence that childbearing is associated with future development of diabetes in women remains conflicting and the role of pregnancy loss in this association has less been noticed. This population-based prospective cohort study was conducted to assess the contribution of pregnancy and pregnancy loss to the development of diabetes. All 13,612 women (aged 35–66) participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in Heidelberg, Germany (mean follow-up=10.7 years) were included in this study. Having more than four live births was associated with about three times higher risk of developing type 2 diabetes [age-adjusted hazard ratio (HR): 2.98, 95% CI: 1.48–6.00]. Having more than two miscarriages was associated with about two-fold higher risk of diabetes (age-adjusted HR: 1.91, 95% CI: 0.94–3.87). After considering total number of pregnancies, education, smoking, alcohol consumption, physical activity, BMI, waist/hip ratio, hypertension and hyperlipidemia, the significant association between high live births and diabetes disappeared (fully-adjusted HR: 1.55; 95% CI: 0.74-3.26), but the higher risk of diabetes in those who had history of more than two miscarriages did not change substantially (fully-adjusted HR: 1.73; 95% CI: 0.70-4.28). No significant association was found between total

For author disclosure information, see page 785.

number of pregnancies, abortion and stillbirth and risk of maternal diabetes later in life. Our results suggest that the association between high parity and diabetes is mediated by known risk factors of diabetes.Women who experience more than two miscarriages are at around two times higher risk of diabetes later in life. Miscarriage may be considered as a sex-specific predictor for diabetes, and thus could be considered as an indicator for diabetes risk factor monitoring and preventive measures.

1277-P

Exercise and Dietary Intervention Increases Physical Activity, Promotes Healthy Diet and Reduces Excessive Gestational Weight Gain in Pregnant Women: A Randomized Controlled Trial in Urban Community

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The aim of this randomized, controlled trial was to determine the effect of a dietary and exercise intervention during pregnancy on excessive gestational weight gain (EGWG). Non-diabetic, pregnant women (< 26 weeks gestation) from a single urban centre were recruited and randomized to either the intervention or control group. Participants in the intervention group attended a weekly group exercise program and received dietary counseling. They also received a home exercise program. Physical activity and food intake surveys were provided to all participants at the enrolment and 8 weeks after enrolment. Gestational weight gain was determined from pre-pregnancy body mass index and body weight taken at the time of delivery. A total of 190 women, 102 in the intervention group and 88 in the control group, completed the study. The intervention significantly increased physical activity levels at 2 months after enrolment compared to baseline or to the control condition ($p < 0.001$). The intervention also led to decreased daily intakes of total calorie ($p < 0.01$), carbohydrate ($p < 0.05$), fat ($p < 0.001$), saturated fat ($p < 0.001$) and cholesterol ($p < 0.001$) compared to the control group. The prevalence of EGWG in the intervention group (n = 36, or 35%) was significantly lower than the control group (n = 48, or 55%) according to 2009 guidelines of the Institute of Medicine ($p < 0.05$). The results of the present study suggest that an exercise and dietary intervention prevents EGWG secondary to increased physical activity and the adoption of a healthy diet in pregnant women in an urban setting.

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1278-P

Hepatic Insulin Resistance Is an Early Determinant of Declining Beta-Cell Function in the 1st Year Postpartum Following Glucose Intolerance in Pregnancy

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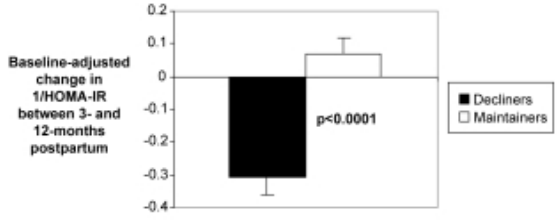
Glucose intolerance in pregnancy identifies women who are at risk of future type 2 diabetes. This risk is mediated by deterioration of their beta-cell function, which occurs as early as the 1st year postpartum. In this context, we sought to identify determinants of declining beta-cell function in the 1st year postpartum. In this study, 166 women with recent glucose intolerance in pregnancy underwent oral glucose tolerance tests at both 3- and 12-months postpartum. The women were stratified into 2 groups: those in whom beta-cell function (Insulin Secretion-Sensitivity Index-2 (ISSI-2)) declined between 3- and 12-months (*decliners*, n=92) and those in whom it did not (*maintainers*, n=74). Although glycemic measures were similar between the groups at 3-months, the decliners had higher 2-hr post-load glucose levels by 12-months (6.7 vs 5.9 mmol/L, p=0.0007). Over this time, the groups did not differ with respect to changes in exercise, waist, BMI, or whole-body insulin sensitivity (Matsuda index). However, they exhibited very different changes in hepatic insulin sensitivity (1/HOMA-IR), which decreased in decliners but not in maintainers (p<0.0001).



On multiple linear regression analysis, the change in 1/HOMA-IR emerged as the sole independent predictor of the change in ISSI-2 between 3- and 12-months (t=5.5, p<0.0001). Furthermore, on logistic regression analysis, an increase in 1/HOMA-IR independently predicted a lower likelihood of declining beta-cell function (OR=0.13, 95%CI 0.06-0.29, p<0.0001). In summary, in women with recent glucose intolerance in pregnancy, worsening hepatic insulin sensitivity is associated with falling beta-cell function in the 1st year postpartum. Hepatic insulin resistance thus emerges as an early determinant of beta-cell dysfunction in this high-risk population.

1279-P

Is Detemir Regimen Able To Obtain the Same Clinical Results of CSII (Continuous Subcutaneous Insulin Infusion) in Type I Diabetic Pregnant Women?

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Most studies emphasize the role of a thigh glycemic control in order to improve fetal and maternal outcomes in type I diabetic pregnant women. Even if the cost benefit ratio in the use of CSII is discussed, this is considered the gold standard in treatment of these patients. Objective: To verify if MDI (multiple daily injections) regimen with rapid analogues and Detemir is of equal efficacy to CSII in metabolic control and maternal fetal outcome in type 1 diabetic pregnant women. Study design: 29 type I diabetic women that decided to continue the same treatment used before pregnancy were studied: 18 were treated with CSII with Aspart and 11 with MDI (pre-meal bolus with Aspart and basal Detemir insulin). All women followed a standard nutritional therapy and performed daily self -monitoring of blood glucose from the first trimester to the end of gestation. Glycemic targets were pre-prandial < 90 mg/dl and 1 h postprandial < 120 mg/dl. Ultrasound scans were performed every two weeks from 28 to 38 weeks of gestation to assess fetal growth and fetal fat mass. Results: There were no significant differences in CSII and MDI group in HbA1c (I trimester:6,4% vs 7,2%; II trimester:5,8% vs 6,2%; III trimester:5,5% vs 5,5%) and in total fasting and postprandial mean glycemic levels (fasting:91 mg/dl vs 96 mg/dl; 1st hour:121 mg/dl vs 124 mg/dl; 2nd hour:104 mg/dl vs 105 mg/dl). Fasting glycemic levels until the 19th week are significantly higher in MDI vs CSII group, successively declining to a comparable level. The rate of fetal fat mass growth and maternal fetal outcome do not differ significantly between CSII and MDI group (birthweight 3235±383gr vs 3147±803gr, PI 2.67± 0.13 vs 2.69± 0.25, incidence of LGA 27% vs 36%, incidence of PI>90° percentile 5% vs 9%, non elective cesarean section rate 15,7% vs 26%). All babies were born without malformations. Conclusions: In our experience treatment with Detemir in MDI regimen gives the same results of CSII in terms of maternal and fetal outcomes with lower costs.

1280-P

Managing Weight Gain in Type 2 Diabetic Pregnancy: A Role for Metformin

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Metformin (MF) is unlicensed for use in pregnancy. NICE guidelines (UK) endorsed its use in 2008 and our clinical practice changed from using insulin alone in all Type 2 diabetic (T2DM) pregnancies to continuation of MF. Use of MF during pregnancy is associated with less weight gain in gestational diabetes but the effect of it in T2DM pregnancy is unknown. We wanted to examine the impact our change in practice had on weight gain among T2DM women treated with and without MF during their pregnancy.

We performed a case note review with statistical analysis of 34 consecutive pregnancies with pre-existing T2DM (2006-2010) with an emphasis on their pre-pregnancy/booking and 6 months post-partum weight. 17 were treated with insulin alone, 17 received MF+/- insulin during pregnancy.

Women came from an ethnically mixed population with no statistical difference in baseline characteristics (mean age, duration of diabetes, parity, delivery week, HbA1c, weight/BMI, pre-pregnancy treatment and insulin dose). The follow-up frequency, education, postnatal treatment and care were similar in each group. The mean weight change between pre and post-partum was +9.7±1.0kg in those treated with insulin alone vs -0.2±1.0kg in those who received MF (p<0.0001). The average weight change was +11% in the insulin group vs 0% in the MF group (p<0.0001). The BMI changed from 33.4 (pre-) to 37.0 (post-partum) in the insulin group vs 34.3 to 34.2 in those who received MF. At 6 months no woman treated with insulin alone was lighter than pre-pregnancy vs 41% who received MF+/-insulin. Prior to delivery women who took MF required on average 46% less insulin to meet their glucose targets (p=0.04). HbA1c did not change significantly between the two groups (p=0.68).

The majority of women with T2DM entered pregnancy obese. Women who received only insulin during pregnancy were on average 10kg heavier 6 months post-partum. Women who took MF+/-insulin had significantly reduced insulin requirements during pregnancy and readily returned to their pre-pregnancy weight. Our data in a real clinical setting highlights the problem of weight gain in T2DM pregnancy and supports the use of MF for aiding weight management.

1281-P

Predictors of Congenital Anomalies in Offspring of Mothers with Pre-Gestational Diabetes

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This study quantifies the risk and investigates predictors of major structural congenital anomalies in offspring of women with pre-gestational diabetes.

We linked birth data for 1996-2008 from the Northern Diabetes in Pregnancy (NorDIP) and Northern Congenital Abnormality (NorCAS) Surveys in the North of England. Prevalence of congenital anomalies in singleton pregnancies resulting in miscarriages at ≥20 weeks gestation, terminations of pregnancy for congenital anomalies, stillbirths and live births was compared between women with pre-gestational diabetes and those without, using rate ratios (RR) with 95% confidence intervals (95% CI). Multiple logistic regression was used to analyse the relationship between potential predictors and congenital anomalies in offspring of women with diabetes.

There were 120 affected offspring among 1677 pregnancies in women with diabetes, 71.6 per 1000 compared to 19.1 per 1000 in women without diabetes (RR 3.8, 95% CI 3.2-4.5). In univariate analysis, lack of pre-conception folic acid, poor pre-conception glycemic control (higher levels of A1C three months pre-pregnancy), nephropathy diagnosed pre-pregnancy and more deprived socioeconomic status (area-based Index of Multiple Deprivation score) were significant predictors of congenital anomalies in offspring of women with diabetes. Mean first trimester A1C, type or duration of diabetes, fetal sex, BMI, retinopathy or neuropathy pre-pregnancy were not associated with the risk of a congenital anomaly. In a multivariate analysis, only poor pre-conception glycemic control and nephropathy were independent predictors of congenital anomaly: OR 1.2 (95% CI 1.1-1.4) and 2.1 (1.01-4.6). In women with type 1 diabetes, lack of preconception folic acid use was also a significant predictor.

Offspring of women with diabetes have nearly four-fold increased risk of congenital anomalies, with nearly 1 in 13 offspring affected. Poor pre-conception glycemic control and pre-pregnancy nephropathy were independent significant predictors of congenital anomalies in offspring of women with pre-gestational diabetes.

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EPIDEMIOLOGY

[*See also: Presidents Posters 426-PP to 431-PP, page A118.*]

Guided Audio Tour: Epidemiology of Type 1 Diabetes and Youth
(Posters 1282-P to 1289-P), see page 15.

1282-P

Progression of Cardiovagal Dysfunction in a Cohort of Children and Adolescents with Type 1 Diabetes: The Wisconsin Diabetes Registry Study

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Cardiovagal dysfunction (CD) is associated with higher prevalence of cardiovascular morbidity and increased mortality in patients with type 1 diabetes (T1D); however, little is known about the burden and evolution of CD in children and adolescents from population-based studies. There is a further question whether changes in glycemic control can modify the course of CD in the same age groups.

We evaluated 422 children and adolescents with T1D from the Wisconsin Diabetes Registry study who were followed from diagnosis to up to 20 years and had ≥1valid deep breathing test conducted at ≥10 years of age. CD was defined as an expiration-inspiration difference (EID, beats per minute [bpm]) <2.5th age-specific percentile of normative data. Tracking of cardiovagal function was evaluated in 57 subjects (10-17 years old at diagnosis) who had EID measurements at baseline and 20 years later, using age-adjusted correlation coefficients (r_p). In the total sample, repeated measurements of EID were regressed on diabetes duration using random effects models. We tested the effect of glycated hemoglobin A1c (HbA1c averaged over one year before each deep breathing test) on EID, adjusting for age at diagnosis, duration and body weight.

The prevalence of CD ranged from 5.5% (95% CI: 1.8%, 9.3%) at diagnosis to 24.4% (95%CI: 17.0%, 28.5%) at 20 years. EID declined at a constant rate of 0.5 bpm/year (p<0.001), independently of age at diagnosis, and showed moderate tracking from childhood to adulthood (r_p=0.46, p<0.001). EID was inversely associated with HbA1c in the fully adjusted model: there was a mean EID difference of 0.3 bpm by percent point of HbA1c (p<0.001). There was no evidence that the effect of HbA1c on EID changed with disease duration (p-interaction=0.111).

Our results show that CD is present at diagnosis in children and adolescents with T1D and increases with disease duration. Our findings suggest that the course of CD can be effectively modified by improving glycemic control in agreement with the results of the Diabetes Control and Complications Trial.

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1283-P

Modifiable Factors Associated with Bone in Premenopausal Women with Type 1 Diabetes

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Bone fragility has been identified as a complication of type 1 diabetes (T1D). The reasons for skeletal compromise have yet to be determined. This study is a secondary data analysis of premenopausal women with T1D (n=89) who were part of the Wisconsin Diabetes Registry and matched controls (n=76). Peripheral (heel, wrist) and central (hip, spine) bone mineral density (BMD; g/cm^2), measures of bone formation (Osteocalcin and Bone-Specific Alkaline Phosphatase) and resorption (N-terminal cross-linked telopeptide and Tartrate-Resistant Acid Phosphatase Isoform 5b), and dietary and lifestyle factors were analyzed. Multivariable stepwise regression modeling was used to identify significant associations with BMD and bone turnover markers stratified by diabetes status; effect modification by diabetes status was also tested in the entire sample. BMI and vigorous physical activity were positively associated with central BMD in controls (p≤0.03) but not in women with T1D. Similarly, waist-to-hip ratio was positively associated with wrist BMD in controls (p=0.03) but not in women with T1D (interaction p=0.02). Use of estrogen contraception (former β=-0.02 and current β=-0.04) and higher A1C (%; β=-0.01) were detrimental to peripheral BMD in women with T1D (p≤0.03). Sun exposure was associated with higher hip BMD in women with T1D (p=0.01) but not in controls (interaction p=0.03). With regard to bone turnover, age was negatively associated with all four markers in controls (p≤0.04) but not women with T1D. Greater alcohol and caffeine consumption, and smoking were associated with altered bone resorption in women with T1D (p≤0.03;smoking interaction p=0.04). In conclusion, age, BMI and vigorous physical activity, traditional clinical predictors of bone fragility, may not be associated with bone in women with T1D. Estrogen contraception use, poor glycemic control, caffeine, alcohol, and smoking may negatively impact bone in women with T1D whereas sun exposure may have a positive effect on bone health. Modifiable behaviors play a large role in the bone health of women with T1D and offer several opportunities for education and intervention to improve bone in this population. **ADA-Funded Research**

1284-P

US Emergency Department Visits with Hyperglycemic Crisis, 2008

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Hyperglycemic crisis (including diabetic ketoacidosis and hyperglycemic hyperosmolar state) is a serious diabetes complication. However, estimates of the national emergency departments (ED) visit rates for hyperglycemic crisis do not exist. This study aimed to estimate and describe ED use for hyperglycemic crisis among persons with diabetes using the newly available National Emergency Department Sample. ED visits with hyperglycemic crisis as any listed diagnosis were identified using ICD-9-CM codes of 250.1-250.3. To obtain ED visit rates, we used 2008 estimates of ED visits with hyperglycemic crisis as any listed diagnoses for the numerator and the estimated number of people with diabetes from 2007-2009 National Health Interview Survey as denominator. In 2008, there were an estimated 226,000 (±12,000) ED visits with hyperglycemic crisis with charges totaling $0.44 billion for ED services. About 74.0% (±0.9) of these had hyperglycemic crisis listed as primary diagnosis; 85.8% (±1.1) resulted in a hospital admission; and 2.2% (±0.2) resulted in death (ranged from 0.5% (±0.1) for those 0-44 years to 10.6% (±1.1) for those 75 years or older). The overall rate of ED visits with hyperglycemia crisis as any listed diagnosis per 100 diabetic persons was 1.2 (±0.08). Rates decreased with age, ranging from 16.2 (±5.8) per 100 for persons aged 0-17 years to 0.4 (±0.04) per 100 for persons aged 75 years or older (P for trend <0.01), but the rates were similar by sex (1.2 per

For author disclosure information, see page 785.

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