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The Role of Glycemia in Insulin Resistance in Youth with Type 1 and Type 2 Diabetes

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Abstract

Background—Hyperglycemia has traditionally been considered a major contributor to insulin resistance (IR) in type 1 diabetes (T1D), yet studies examining the relationship between HbA1c and IR are conflicting. Glucose measures captured by continuous glucose monitoring (CGM) (e.g. peak glucose, standard deviation, hypoglycemia) in youth have not been explored as predictors of insulin sensitivity (IS).

Objective—Assess the relationship between IS and glycemia in youth with T1D and type 2 diabetes (T2D).

Methods—Sedentary 12-19 year olds with diabetes had peripheral IS measured by hyperinsulinemic-euglycemic clamp. HbA1c and 3 days of CGM data were also collected. Spearman correlation coefficients were calculated to examine the association between variables.

Results—Participants included 100 youth with T1D (46% male, median BMI 74thile, HbA1c 8.5%) and 42 with T2D (26% male, BMI 99thile, HbA1c 6.9%). Nineteen with T1D and 13 with T2D also wore CGM. In T2D youth, higher HbA1c, average sensor glucose, area under the CGM curve, and metabolic syndrome characteristics correlated with lower IS. In T1D youth, higher BMI thile, waist circumference, triglycerides, and LDL cholesterol, but not HbA1c, correlated with lower IS. Moreover, higher CGM overnight mean glucose correlated with greater IS, and CGM hypoglycemia correlated with lower IS.

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Conclusions—Markers of metabolic syndrome and hyperglycemia predicted decreased IS in T2D youth. Paradoxically, *hypoglycemia* predicted decreased IS in T1D youth and *hyperglycemia*, particularly overnight, predicted improved IS. These preliminary results imply different mechanisms underlying IR in T1D vs. T2D and suggest a role for non-insulin therapies in T1D to improve IR.

Keywords

type 1 diabetes; insulin resistance; hyperinsulinemic-euglycemic clamp; continuous glucose monitoring

Introduction

Insulin resistance (IR) plays a central role in the pathogenesis of type 2 diabetes and directly leads to hyperglycemia by interfering with insulin action. However, IR is not typically considered a contributor to the pathophysiology of type 1 diabetes, a disease where hyperglycemia stems primarily from insulin deficiency. IR has been strongly implicated as a risk factor for cardiovascular disease in the general population as well as in individuals with type 2 diabetes, and more recently in type 1 diabetes (1, 2). The presence of impaired insulin sensitivity (IS) has been well documented in adults with type 1 diabetes (3, 4) and our group has previously reported significant decreases in IS in normal weight youth with type 1 diabetes when compared to healthy pubertal stage, BMI and activity matched controls (5, 6). In this adolescent cohort, lower IS correlated with impaired functional exercise capacity and early markers of cardiovascular dysfunction, suggesting that morbidity from IR in type 1 diabetes begins early in the disease process.

The phenotype of IR in youth with type 1 diabetes, however, differs from youth with type 2 diabetes, the latter being nearly universally obese, with predominant features of the metabolic syndrome. Youth with type 1 diabetes, in contrast, can be normal weight, and often lack the typical metabolic syndrome phenotype, yet have marked decreases in IS, suggesting unique etiologies of IR in type 1 diabetes. Hyperglycemia has been reported to lower IS in type 1 diabetes (7, 8), although thorough physiology studies in youth are limited. For example, in an early 1990's study by Arslanian et al. (9), youth with type 1 diabetes and HbA1c levels >10.4% had lower IS as measured by hyperinsulinemic-euglycemic clamp than those with HbA1c levels <10.4%. However, methods for diabetes monitoring, types of insulin, and modes of insulin delivery have changed greatly since this study was conducted. Moreover, HbA1c-based conclusions are difficult, as poor diabetes control also equates to other factors beyond hyperglycemia that also may contribute to lower IS (elevated free fatty acids and other dyslipidemia, a catabolic state, other hormonal dysregulation, etc.).

IR has also been implicated in the cardiovascular complications seen in type 1 diabetes (10, 11), although the mechanisms are unclear and reported findings are not universal. The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, a large type 1 diabetes epidemiology study, did not find that hyperglycemia predicted cardiovascular events (12). Although direct measures of IS were not available, estimated IS in the EDC study correlated inversely with cardiovascular events. In the Coronary Artery Calcification in Type 1

(CACTI) study in adults with type 1 diabetes, IS was measured by a three-stage hyperinsulinemic-euglycemic clamp, and lower IS, not HbA1c, predicted coronary artery calcification (13). Moreover, the CACTI study did not find a correlation between IS and glycemic control as measured by HbA1c nor continuous glucose monitoring (CGM) (13). However, individuals in CACTI were selected to have much better glycemic control than the Arslanian study, as mean HbA1c was $7.5 \pm 0.9\%$, and no youth were studied. Finally, there have been no comparisons between the role of hyperglycemia and IS in type 1 vs. type 2 diabetes. The aim of this report, therefore, is to describe the relationship between IS and glycemia across a broader spectrum, as measured by HbA1c and CGM, in youth with type 1 diabetes and type 2 diabetes.

Research Design and Methods

Participants

Adolescents with type 1 diabetes and type 2 diabetes were recruited from the University of Colorado Denver (UCD) pediatric diabetes clinics and by advertisement. Inclusion criteria included age 12-19 years, sedentary status (<3 h regular exercise/week, as confirmed by questionnaire and accelerometer use), and puberty Tanner stage >1 to minimize pubertal and training effects. Type 1 diabetes was defined by American Diabetes Association (ADA) criteria plus the presence of glutamic acid decarboxylase, islet cell or insulin autoantibodies, as well as insulin requirement. Type 2 diabetes was defined by ADA criteria and the absence of glutamic acid decarboxylase, islet cell or insulin autoantibodies, insulin requirement, or secondary causes of diabetes. Exclusion criteria included resting blood pressure $>140/90$ mmHg, hemoglobin <9 mg/dl, serum creatinine >1.5 mg/dl, macroalbuminuria, HbA1c $>12\%$, smoking, inability to wean from metformin prior to the insulin clamp, use of medications known to affect insulin sensitivity (ex. oral glucocorticoids, atypical antipsychotics, immunosuppressants), pregnancy, oral contraceptives, severe illness or DKA within 2 months, and weight >300 lbs or BMI $<5\%$ ile. The study was approved by the Colorado Multiple Institutional Review Board and appropriate consent and assent were obtained.

Screening included a history, physical examination including height and weight, blood pressure and waist circumference, Tanner staging, and fasting laboratory testing (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], lipid panel, serum creatinine, HbA1c, and urine microalbumin:creatinine ratio). Participants wore an accelerometer for seven days to measure routine levels of physical activity. A 3-day fixed-macronutrient diet (55% carbohydrates, 30% fat, 15% protein) was provided by the UCD Clinical & Translational Research Center (CTRC) metabolic kitchen for consumption prior to admission for the euglycemic clamp and a subset wore a continuous glucose monitor (CGMS, Medtronic MiniMed, Inc Northridge, CA) during the 3-day study diet period. Subjects were instructed to monitor blood glucose at least four times per day during the period of CGM wear.

Activity and diet questionnaires

A 3d pediatric physical activity recall questionnaire was used to estimate habitual physical activity (14), reported as a 3d average of daily metabolic equivalents. Body composition by dual-energy x-ray absorptiometry was performed by standard methods (15).

Insulin sensitivity

Subcutaneous insulin was discontinued at dinner 24 hours prior to admission, in all patients with type 1 and type 2 diabetes. All participants with type 2 diabetes were asked to discontinue metformin three days prior to the clamp, as in previous studies, to remove acute effects on insulin sensitivity (16). Upon admission, home insulin was replaced with an inpatient overnight IV insulin infusion to normalize blood sugar levels to a target goal of 100 mg/dL by 4 AM or earlier. Fasting blood and urine were collected and assayed by standard methods. Subjects were excluded if large urine ketones were present on admission. All participants fasted overnight, and not one had blood sugars <70 mg/dl during this pre-clamp, overnight observation period. A 3 hour hyperinsulinemic-euglycemic clamp ($80 \text{ mU/m}^2 \times \text{min}$ insulin) was performed the following morning to estimate insulin sensitivity (16). During the clamp glycemia was monitored every 5 min using a Yellow Springs Instruments (YSI, Yellow Springs, OH) glucose analyzer, and 20% dextrose infusion was titrated to maintain an average blood glucose of 95 mg/dl. There were no significant differences in mean blood glucose (Table 1) between the groups at the conclusion of the clamp. Blood samples were drawn at baseline, 150, 160, 165, 170, 175, and 180 min to determine glucose and insulin. Glucose infusion rate (GIR) was determined from the average glucose infusion rate during the last 20 min of the clamp and expressed as milligrams per kilogram body mass per minute (mg/kg/min) and as milligrams per kilogram fat-free mass per minute (mg/kg FFM/min, obtained from dual-energy x-ray absorptiometry scan on a Hologic machine, Marlborough, MA).

CGM data

For each participant that wore a CGM, 48 hours of data, with an equal number of sensor values (i.e., 576), were analyzed. Typical hours for daytime (6am-12am) and nighttime (12am-6am) glucose distributions were determined. Nighttime hours were selected to represent expected, average timeframes during which adolescents were most likely to be sleeping and not eating.

Laboratory assays were performed by the UCD CTSC core laboratory or the Children's Hospital Colorado clinical laboratory. HbA1c levels were measured by (DCCT-calibrated) ion-exchange high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA). Measurements of total cholesterol, high density lipoprotein cholesterol, and triglyceride were performed enzymatically on a Hitachi 917 autoanalyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Low density lipoprotein cholesterol levels were calculated by the Friedewald equation. AST and ALT were measured via chemical reaction on a Vitros® 5600 chemistry system (Ortho Clinical Diagnostics, Rochester, NY). Serum insulin was analyzed with radioimmunoassay (Millipore, Billerica, MA).

Statistical analysis

The distributions of all variables were examined prior to analysis. Descriptive statistics were reported as mean and standard deviation for continuous variables with normal distributions and median (25thile, 75thile) for continuous variables with non-normal distributions. Groups were compared using t-tests, the Wilcoxon rank-sum test, chi-square tests, or Fisher's exact test, as appropriate. Spearman correlation coefficients were calculated for GIR and glycemic variables. All analyses were performed using SAS for Windows (version 9.4).

Results

142 adolescents were included in the analysis. 100 had type 1 diabetes and 42 had type 2 diabetes. Baseline characteristics of both groups are presented in Table 1. The median participant age was 16 years and was similar between groups. Participants with type 2 diabetes had higher BMI z-score, waist circumference, systolic blood pressure, triglycerides, and lower high density lipoprotein (HDL) cholesterol, all features of the metabolic syndrome. Youth with type 1 diabetes tended to have a normal BMI%ile and lipid profile. Youth with type 1 diabetes had a higher HbA1c than youth with type 2 diabetes. Both groups of youth had much lower IS compared to our historical, lean controls (where mean GIR was 15.3±4.7 mg/kg/min and 19.8±4.6 mg/lean kg/min) (6) and, as expected, the youth with type 2 diabetes had lower IS than those with type 1 diabetes.

CGM data (Table 1) were available in a consecutively enrolled subgroup of the overall cohort, as this data collection was added to the protocol later in the course of the primary study when funding became available. Baseline characteristics of the CGM subgroup were similar to that seen in the overall cohort. Youth with type 1 diabetes compared to those with type 2 diabetes had a greater degree of hyperglycemia (as reflected by average sensor glucose, peak sensor glucose, area under the curve, time spent >200), greater glucose variability (standard deviation), and more hypoglycemia.

Table 2 presents correlations between baseline group characteristics and GIR with and without correction for fat free mass. HbA1c correlated negatively with GIR (i.e., hyperglycemia correlated with decreased IS) in the overall group of youth with type 2 diabetes. Other variables correlating with lower GIR in type 2 diabetes youth included ALT, diastolic blood pressure (DBP), total cholesterol, triglycerides, and waist circumference. Variables correlating with lower GIR in the overall group of youth with type 1 diabetes – BMI%ile, total cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, waist circumference – included some metabolic syndrome markers. HbA1c, however, did not correlate with IS in youth with type 1 diabetes.

Correlations between glycemia as measured by CGM and GIR are presented in Table 3. In youth with type 2 diabetes, higher average sensor glucose and glucose area under the curve correlate with lower IS. Maximum sensor glucose also tended to (p=0.05) correlate with lower IS. In youth with type 1 diabetes, however, higher overnight glucoses – as represented by night average, maximum, and minimum sensor glucose and by area under the CGM glucose curve – predicted greater IS. Furthermore, more time spent in hyperglycemia

>200mg/dl also predicted greater IS while more time spent hypoglycemic <70 mg/dl predicted decreased IS.

Discussion

We found that youth with type 1 diabetes, in contrast to youth with type 2 diabetes, have paradoxically improved IS in the face of hyperglycemia. By using CGM to measure glycemic variations, a novel finding of this study is that greater time spent in hypoglycemia and overnight with lower blood sugars correlated with decreased IS in type 1 diabetes youth. Even in this small type 1 diabetes subgroup, multiple CGM measures showed a significant positive correlation with improved IS, particularly overnight glucose values. These findings challenge the general assumption that hyperglycemia is the predominant contributor to IR in type 1 diabetes.

One possible mechanism to explain of the relationship of lower IS with greater hypoglycemia includes the contributions of counter-regulatory hormones. Progressive declines in plasma glucose elicit a physiologic response in healthy individuals. When glucose levels fall below a threshold physiologic range, counter-regulatory hormones (glucagon, growth hormone, epinephrine, and cortisol) are secreted and impair IS (17) to protect against further decreases in plasma glucose concentrations. In individuals with uncontrolled diabetes or recurrent hypoglycemia, these thresholds are shifted to higher glucose concentrations (18, 19). Yki-Jarvinen et al. described lower glucose infusion rates (GIR) by hyperinsulinemic-euglycemic clamp in males with type 1 diabetes following exposure to a period of prolonged hyperglycemia. From these data, the authors concluded that hyperglycemia induced IR. However, counter-regulatory hormones were also higher at clamp start after the blood glucose dropped to euglycemia following hyperglycemia, and the degree to which these hormones contributed to impairment in IS in their study was not determined (8, 20).

The concept that chronic hyperglycemia induces IR has been derived from various studies documenting 1) an inverse correlation between IS and glycated hemoglobin (9), 2) improvement of insulin action with improved glycemic control via continuous subcutaneous insulin infusion (CSII) (21, 22), and 3) decreases in insulin-mediated glucose disposal with experimentally induced hyperglycemia (8). In the study by Arslanian et al. (9), youth with type 1 diabetes and HbA1c levels >10.4% had lower IS as measured by hyperinsulinemic-euglycemic clamp than those with HbA1c levels <10.4%, although notably, the youth with higher HbA1c also had significantly higher growth hormone concentrations at clamp start, and lower BMI, showing a catabolic state. In the study by Simonson et al. (22), after 4-8 months of CSII, eight adults with type 1 diabetes were found to have improvements, but not normalization, in IS and a decrease in HbA1c from 10.2% to 7.1%. These participants had a mean fasting plasma glucose prior to clamp start of 140 ± 17 mg/dl pre-CSII versus 106 ± 16 mg/dl post-CSII, thus a decrease from higher glucose levels to a maintenance glucose of 88 mg/dl during the hyperinsulinemic-euglycemic clamp may have resulted in differing counter-regulatory hormone responses between groups. Furthermore, whether CSII decreased hypoglycemia or affected IS by providing more physiologic insulin replacement compared to NPH and regular insulin is unclear as CGM data were not available. Lastly, in

this paper, the authors themselves acknowledged that the changes in IS post-CSII were modest and significant impairments in IS remained compared to controls that was unaccounted for post-CSII. Our study controlled overnight pre-clamp glucoses to avoid glucose fluctuations and to normalize glucoses several hours preceding clamp start. This report is one of the first to describe the relationship between clamp-derived IS measures obtained under such conditions and CGM findings in youth, with novel associations found when assessing nighttime and overall CGM glycemic variables.

The association between hyperglycemia (% time >200 mg/dl on CGM) and improved IS observed in these type 1 diabetes youth may also be a reflection of underinsulinization, as increased peripheral insulin has been associated with down-regulation of peripheral insulin receptors (23, 24). Hyperinsulinemia-induced IR has been described in mice transfected with extra copies of the insulin gene leading to insulin excess, and in vivo studies in humans have induced lower IS after exposure to hyperinsulinemia (24-26).

Loss of endogenous insulin secretion into the portal circulation and peripheral exogenous insulin replacement also lead to relative underinsulinization of the liver and overinsulinization of peripheral tissues. Endogenous insulin secretion typically results in portal vein insulin concentrations three times higher than that seen peripherally and subcutaneous insulin alone is insufficient to restore this gradient (27). A study of combined kidney-pancreas transplantation compared different anastomoses of the pancreatic vein and described lower peripheral tissue IS with systemic anastomoses versus portal anastomoses (28). Another study in type 1 diabetes patients found normalization of IS at both the hepatic and skeletal muscle level after undergoing intrahepatic islet transplantation, despite being on low-doses of immunosuppressive agents (29), demonstrating the importance of adequate hepatic concentrations of insulin on IS. From these studies, one could hypothesize that higher overnight fasting glucoses are a reflection of increased hepatic glucose output, so that increased basal insulin doses correlate with lower hepatic glucose output. This hypothesis could explain why those with the lowest overnight glucoses in our study may in fact have the greatest peripheral hyperinsulinization and thus more IR.

Of note, in our cohort, a relationship between hypoglycemia and IS was not demonstrated in youth with type 2 diabetes. One potential explanation is that our participants with type 2 diabetes had minimal hypoglycemia detected on CGM as very few of the type 2 diabetes youth were on insulin therapy. Another likely factor is that in type 2 diabetes, IR combined with relative insulin deficiency causes hyperglycemia; thus, it is expected that IR and hyperglycemia would correlate in type 2 diabetes. In contrast, in type 1 diabetes, hyperglycemia occurs primarily from absolute insulin deficiency. Thus the differing pathologic mechanisms influencing glycemia in these two populations likely contribute to the differences in our findings. Furthermore, hypoglycemia starts at a young age in children with type 1 diabetes and despite newer insulin analogs, insulin pump therapy, and CGM technology, rates of hypoglycemia remain high (30-32). The potential long-term impacts of these early, recurrent events on IS require further study.

Limitations of our study include the small number of participants with CGM data. These data are exploratory and findings from this subgroup should be considered hypothesis-

generating. Despite the small numbers, a consistent pattern between glycemia and IS in type 1 diabetes youth, that differed from type 2 diabetes youth, was demonstrated. Furthermore, multiple significant correlations between glycemia as measured by CGM and IS were found. Also, when considering glucose extremes, in this study, while the HbA1c range was much wider than in the CACTI study, youth with HbA1c >12% were still excluded, therefore the role of marked hyperglycemia in IS was not assessed in this study. It is possible that marked hyperglycemia may be associated with impaired IS, however, further studies would be needed to isolate glucose effects from other consequences of insulin deficiency and metabolic instability. Although we postulate several mechanisms other than hyperglycemia to explain the lower IS detected in type 1 diabetes youth, further studies including measures of counter-regulatory hormones are required to explore these hypotheses and larger studies are needed to verify these findings. Stable isotope tracer studies to determine the relationship between hyperglycemia and hepatic and adipose IR are also underway.

In conclusion, our findings suggest that hyperglycemia alone is not responsible for the impairments in IS seen in adolescents with type 1 diabetes. CGM outcomes in this study provide evidence for alternate etiologies of insulin resistance, such as hypoglycemia, although the true mechanisms require further study. Lastly IR is present in type 1 diabetes, regardless of glucose control and despite current technology and modes of insulin delivery, implying a need for non-insulin agents in these youth to improve IS and its associated morbidity.

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Table 1

Descriptive statistics for overall study cohort and CGM sub-groups

	Type 1 Diabetes	Type 2 Diabetes	P	Type 1 Diabetes - CGM subgroup	Type 2 Diabetes-CGM subgroup	P
N	100	42		19	13	
Female, N (%)	54 (54)	31 (74)	0.03	11 (58)	10 (77)	0.45
Age (yr)	16 (15, 18)	16 (14, 18)	0.66	16 (15, 17)	17 (14, 18)	0.98
Diabetes duration (yr)	3.8 (1.0, 7.5)	1.7 (0.2, 3.8)	0.0002	3.8 (1.5, 7.5)	1.8 (0.2, 3.0)	0.01
BMI %	74 (46, 88)	99 (95, 99)	<0.0001	0.5 (-0.4, 1.2)	1.9 (1.8, 2.3)	<0.0001
Tanner Stage, N (%)			0.02			0.23
I	1 (1)	-		-	-	
II	3 (3)	1 (2.4)		2 (11)	-	
III	11 (11)	4 (9.5)		1 (5)	-	
IV	24 (24)	2 (4.8)		5 (26)	1 (8)	
V	61 (61)	35 (83)		11 (58)	12 (92)	
Ethnicity, N (%)	83 (83)	8 (19)	<0.0001	17 (89)	2 (15)	<0.0001
Caucasian	10 (10)	24 (57)		2 (11)	7 (54)	
Hispanic	2 (2)	9 (21)		-	3 (23)	
Black	5 (5)	1 (2)		-	1 (8)	
Other						
Waist circumference (cm)	77 (69, 84)	106 (97, 118)	<0.0001	78 (71, 89)	102 (97, 111)	<0.0001
Systolic blood pressure	117±11	122±11	0.04	118±14	119±12	0.75
Diastolic blood pressure	70±8	71±9	0.39	67±10	67±11	0.89
Lipids						
Cholesterol (mg/dl)	141 (127, 159)	152 (133, 186)	0.05	149 (131, 161)	153 (122, 166)	0.74
LDL cholesterol (mg/dl)	80 (67, 96)	84 (66, 95)	0.65	85 (73, 100)	87 (73, 91)	0.52
HDL cholesterol (mg/dl)	45 (41, 50)	35 (31, 44)	<0.0001	46 (43, 50)	35 (33, 39)	0.002
Triglycerides (mg/dl)	74 (56, 102)	142 (81, 230)	<0.0001	73 (59, 101)	94 (75, 188) ^{94 (75, 188)}	0.07
AST	19 (11, 28)	25 (15, 33)	0.02	25 (17, 29)	24 (18, 31)	0.85
ALT	26 (16, 29)	29 (18, 53)	0.03	15 (12, 22)	24 (16, 39)	0.03
Hemoglobin A1c (%)	8.5 (7.5, 9.5)	6.9 (6.2, 10.0)	0.008	8.4 (7.6, 8.9)	6.7 (6.2, 9.9)	0.20
Clamp glucoses (mg/dl)	140 (120-158)	114 (108, 135)	0.002	139 (128, 152)	113 (110, 122)	0.002
Overnight mean glucose	113 (100-129)	102 (96, 120)	0.03	113 (97, 139)	105 (96-112)	0.32
Glucose, time 0 min	98 (93-102)	98 (95-101)	0.55	98 (93, 102)	97 (94, 100)	0.71
Glucose, time 180 min						
GIR (mg/kg/min)	8.3 (5.5, 10.2)	4.0 (2.4, 5.8)	<0.0001	6.8 (5.3, 10.3)	4.1 (3.3, 5.9)	0.02
GIR (mg/kg fat free mass/min)	11.6±4.3	7.5±4.0	<0.0001	10.4 ±3.9	8.2±4.4	0.18

	Type 1 Diabetes	Type 2 Diabetes	P	Type 1 Diabetes - CGM subgroup	Type 2 Diabetes-CGM subgroup	P
Continuous Glucose						
Monitoring Variables						
Average sensor glucose						
Average daytime glucose				164 (126, 188)	124 (103, 194)	0.17
Average night glucose				158 (135, 202)	123 (107, 214)	0.17
				122 (101, 177)	115 (98, 148)	0.60
Maximum sensor glucose				373 (261, 400)	177 (155, 400)	0.02
Maximum daytime glucose				366 (261, 400)	177 (155, 400)	0.02
Maximum night glucose				216 (170, 304)	131 (114, 332)	0.08
Minimum sensor glucose				51 (40, 58)	71 (63, 90)	0.01
Minimum daytime glucose				55 (46, 62)	79 (71, 90)	0.0002
Minimum night glucose				68 (47, 84)	83 (67, 114)	0.14
Standard deviation						
Daytime SD				73 (48, 82)	22 (15, 49)	0.01
Night SD				74 (46, 87)	21 (15, 52)	0.01
				43 (26, 51)	12 (7, 39)	0.02
Area under the curve (AUC)						
Daytime AUC				4.7×10 ⁵ (3.6×10 ⁵ , 5.4×10 ⁵)	3.5×10 ⁵ (3.0×10 ⁵ , 5.6×10 ⁵)	0.17
Nighttime AUC				3.2×10 ⁵ (2.7×10 ⁵ , 4.1×10 ⁵)	2.5×10 ⁵ (2.2×10 ⁵ , 4.3×10 ⁵)	0.17
				1.0×10 ⁵ (8.4×10 ⁴ , 1.5×10 ⁵)	9.7×10 ⁴ (8.3×10 ⁴ , 1.2×10 ⁵)	0.66
% time spent >140 mg/dl				51 (33, 64)	18 (12, 86)	0.27
% time spent >200 mg/dl				26 (8, 45)	0 (0, 0)	0.07
% time spent >300 mg/dl				6 (0, 11)	0 (0, 1)	0.17
% time spent <60 mg/dl				2 (0, 9)	0 (0, 0)	0.001
% time spent <70 mg/dl				5 (1, 13)	0 (0, 2)	0.01

*Baseline data are presented as mean±SD for normally distributed variables and median (25thile, 75thile) for non-normally distributed variables; BMI = Body mass index; LDL=low density lipoprotein; HDL=high density lipoprotein; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GIR=Glucose infusion rate

Correlations between baseline variables and Glucose Infusion Rate in participants with type 1 vs. type 2 diabetes

Table 2

	Type 1 Diabetes (overall cohort) N=100		Type 2 Diabetes (overall cohort) N=42	
	GIR (mg/kg/min)	GIR (mg/kg FFM/min)	GIR (mg/kg/min)	GIR (mg/kg FFM/min)
HbA1c	-0.18	-0.18	-0.35 *	-0.42 ‡
AST	-0.21 *	-0.17	-0.18	-0.17
ALT	0.01	0.01	-0.30	-0.27
SBP	-0.14	-0.15	-0.26	-0.27
DBP	-0.14	-0.07	-0.41 ‡	-0.39 *
BMI %ile	-0.40 ‡	-0.24 *	-0.16	-0.0
Cholesterol	-0.21 *	-0.21 *	-0.34 *	-0.32 *
LDL	-0.19	-0.21 *	-0.01	-0.01
HDL	0.13	0.15	0.27	0.31
Triglycerides	-0.34 ‡	-0.36 ‡	-0.57 ‡	-0.58 ‡
Waist circumference	-0.45 ‡	-0.37 ‡	-0.43 ‡	-0.36 *

GIR = Glucose infusion rate; FFM = fat-free mass; BMI = Body mass index; LDL=low density lipoprotein; HDL=high density lipoprotein; AST=aspartate aminotransferase; ALT=alanine aminotransferase; SBP = Systolic blood pressure; DBP = Diastolic blood pressure

* p<0.05,
‡ p<0.01,
‡ p<0.001

Table 3
Correlations between CGM variables and Glucose Infusion Rate in T1D and T2D participants

CGM variables	Type 1 Diabetes (CGM subgroup) N=16		Type 2 Diabetes (CGM subgroup) N=12	
	GIR (mg/kg/min)	GIR (mg/kg FFM/min)	GIR (mg/kg/min)	GIR (mg/kg FFM/min)
Average sensor glucose	0.46	0.43	-0.65 [*]	-0.64 [*]
Day avg	0.09	0.10	-0.62 [*]	-0.61 [*]
Night avg	0.78 [‡]	0.72 [‡]	-0.58 [*]	-0.52
Maximum sensor glucose	-0.22	-0.26	-0.57	-0.55
Day maximum	-0.24	-0.28	-0.57	-0.55
Night maximum	0.56 [*]	0.55 [*]	-0.48	-0.45
Min sensor glucose	0.18	0.26	-0.20	-0.23
Day min	0.05	0.15	-0.22	-0.21
Night min	0.64 [‡]	0.57 [*]	-0.21	-0.23
Standard deviation	-0.05	-0.09	-0.48	-0.47
Daytime SD	-0.11	-0.17	-0.50	-0.48
Night SD	0.31	0.40	-0.17	-0.17
MAGE	0.04	-0.06	-0.41	-0.41
Area under the curve	0.46	0.43	-0.65 [*]	-0.64 [*]
Daytime AUC	0.09	0.10	-0.62 [*]	-0.61 [*]
Nighttime AUC	0.78 [‡]	0.72 [‡]	-0.55	-0.52
% time spent >140 mg/dl	0.36	0.34	-0.24	-0.22
% time spent >200 mg/dl	0.50 [*]	0.46	-0.43	-0.43
% time spent >300 mg/dl	0.16	0.10	-0.25	-0.25
% time spent <60 mg/dl	-0.43	-0.46	-0.17	-0.10
% time spent <70 mg/dl	-0.49	-0.51 [*]	0.06	0.08

GIR = Glucose Infusion Rate; FFM = fat-free mass

^{*} p<0.05,

[‡] p<0.01,

[‡] p<0.001