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Time to Glucose Peak During an Oral Glucose Tolerance Test Identifies Prediabetes Risk

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Summary

Context—Morphological characteristics of the glucose curve during an OGTT (time to peak and shape) may reflect different phenotypes of insulin secretion and action, but their ability to predict diabetes risk is uncertain.

Objective—To compare the ability of time to glucose peak and curve shape to detect prediabetes and β -cell function.

Design and participants—In a cross-sectional evaluation using an OGTT, 145 adults without diabetes (age 42 ± 9 y (mean $\pm$ SD), range 24–62 y, BMI 29.2 ± 5.3 kg/m², range 19.9–45.2 kg/m²) were characterized by peak (30 mins vs. >30 mins) and shape (biphasic vs. monophasic).

Main Outcome Measures—Prediabetes and disposition index (DI) – a marker of β -cell function.

Results—Prediabetes was diagnosed in 36% (52/145) of participants. Peak >30 mins, not monophasic curve, was associated with increased odds of prediabetes (OR: 4.0 vs. 1.1; $P < 0.001$). Both monophasic curve and peak >30 mins were associated with lower DI ($P = 0.01$). Time to glucose peak and glucose AUC were independent predictors of DI (adjR²=0.45, $P < 0.001$)

Conclusion—Glucose peak >30 mins was a stronger independent indicator of prediabetes and β -cell function than the monophasic curve. Time to glucose peak may be an important tool that could enhance prediabetes risk stratification.

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Keywords

Oral glucose tolerance test; pancreatic function; insulin secretion; glucose curve; insulin sensitivity; prediabetic phenotype

INTRODUCTION

Prediabetes significantly increases the risk for developing diabetes and is independently associated with higher mortality rates¹. Established screening guidelines, using fasting and 2-hour glucose thresholds derived from the oral glucose tolerance test (OGTT)^{2, 3} are effective for diagnosing prediabetes, but the predictive ability may vary by race/ethnicity and incidence of diabetes in the population^{4, 5}. Up to 10–30% of individuals who developed diabetes were normoglycemic on initial evaluation^{6–8}. Yet impaired insulin secretion relative to insulin resistance is a fundamental pathophysiologic feature in normoglycemic individuals at highest risk for disease progression,⁹ and highlights the need for enhancing diabetes risk prediction models¹⁰.

Assessing the morphological characteristics of the glucose curve (e.g. time to glucose peak and curve shape) during an OGTT could be a useful indicator of prediabetes risk because it may reflect different phenotypes of insulin secretion relative to insulin sensitivity. Recently, the monophasic shape has been proposed as a risk predictor for β -cell function and diabetes in adults^{11–14}, children^{15–17} and pregnant women¹⁸. Yet there is heterogeneity in the glucose curve shape¹³; consistent shape characterization is poorly reproducible¹⁹ and varies with duration of the OGTT¹⁴. In contrast, the time to maximal glucose peak was the most reproducible parameter in a study of healthy volunteers that evaluated 5 morphological features of the OGTT glucose curve (time to insulin peak, shape of the glucose curve, glucose nadir below baseline, 1-h post challenge glucose and time to glucose peak)²⁰. In normoglycemic insulin sensitive individuals, the time to glucose peak commonly occurred at or before 30 minutes^{21–23} and a later time to glucose peak (> 60 minutes) was observed in adults with type 2 diabetes²¹.

These data suggest the close physiological relationship between β -cell function and morphological characteristics of the OGTT. Yet, glucose curve shape has several limitations which may limit its widespread use for risk stratification. Therefore, we characterized the glucose response curve during an OGTT using these two morphological parameters and compared the ability of each parameter to detect prediabetes and β -cell function relative to insulin sensitivity in adults without diabetes.

MATERIALS AND METHODS

Study Population and Design

Data from 145 participants (48 African-American women, 31 African immigrant women, 38 African immigrant men and 28 white women; age 42 $\pm$ 9y (mean $\pm$ SD), range 24–62y; BMI 29.2 $\pm$ 5.3 kg/m², range 19.9–45.2 kg/m²) who were enrolled in two cross-sectional studies to evaluate cardiometabolic health in African immigrant men and women (The Africans in America Cohort, NCT00001853) and African immigrant, African-American and white

women employed by the federal government (The Federal Women's Study, NCT01809288) were used in the present analysis. There were no differences in physical characteristics, prevalence of prediabetes or distribution of morphological features of the OGTT by study group. Therefore, participants were combined into one group for this analysis. Recruitment was by newspaper advertisements, flyers and the NIH website. The National Institute of Diabetes, Digestive and Kidney Diseases Institutional Review Board approved the studies which conformed to the US Federal Policy for the Protection of Human Subjects. All participants gave written informed consent.

Participants self-identified as healthy, did not report a history of diabetes and were not taking medications that influenced glucose or lipid metabolism. Participants had 3 outpatient visits at the NIH Clinical Center, Bethesda MD. At visit 1, a medical history, physical examination, urinalysis, and electrocardiogram were performed, and routine laboratory tests confirmed the absence of anemia, liver, renal, and thyroid disease. Participants returned to the NIH Clinical Center after a 10–12 hour overnight fast for visits 2 and 3, ~ 7–14 days apart. At visit 2, a 2-hour 75gram OGTT was performed, and plasma glucose, insulin and C-peptide concentrations were measured at 0, 30, 60, 90 and 120 minutes after glucose ingestion. At visit 3, one intravenous catheter was placed in each arm near or in the antecubital veins, baseline blood samples were obtained and an IM-FSIGT was performed, with plasma glucose and insulin concentrations obtained at 32 time points between baseline and 180 minutes²⁴.

Definitions

Prediabetes—Using the values obtained during the OGTT, prediabetes was defined as: fasting glucose ≥ 5.6 and <7.0 mmol/L, and/or 2-hour glucose ≥ 7.8 and <11.1 mmol/L².

Morphological Parameters of the Glucose Curve

1. Time to glucose peak was dichotomized as maximal glucose peak occurring at or after 30 minutes during the OGTT.
2. Shape of the glucose curve was characterized as biphasic or monophasic as previously described¹³. Curves were classified as monophasic if glucose increased to a maximum between 30–90 minutes followed by a decrease until 120 minutes¹³. Curves were classified as biphasic if glucose peaked at 30 or 60 minutes, followed by a nadir and second peak by 120 minutes. Prior to shape classification, the upward or downward change in glucose between time points was defined as a glucose difference of >0.22 mmol/L. This value was based on the upper limit of the coefficient of variation of glucose samples run at the NIH Clinical Center laboratory. One individual whose glucose curve increased monotonically was categorized as “Unclassified” and was excluded from further group analysis.

Calculations and Variables

Assessment of Insulin sensitivity and β -cell function—The insulin sensitivity index (S_I) was determined by the minimal model (MinMOD Millennium v.6.02)²⁵. β -cell

function was determined in two ways: (1) the acute insulin response to glucose (AIRg), calculated as the area under the insulin curve above basal between 0 and 10 minutes, and (2) the disposition index (DI), calculated as $S_I \times \text{AIRg}$.

Analyses—Glucose concentrations were measured in serum using an enzymatic hexokinase assay on the Cobas 6000 instrument (Roche Diagnostics, Indianapolis, IN). Insulin and C-peptide were measured in serum via electrochemiluminescence on the Cobas 6000 instrument (Roche Diagnostics, Indianapolis, IN). Hemoglobin A1c was determined by HPLC-D10 instrument (BioRad Laboratories, Hercules CA) in 144 patients. One patient had hereditary persistence of fetal hemoglobin and HbA1c could not be determined. Total percent body fat was determined using whole body dual-energy X-ray absorptiometry (DXA) scans (Hologic Discovery, Bedford, MA).

Modeling Changes in Morphological Parameters of OGTT in Hypothetical Subjects—A longitudinal-dynamic (differential equation) model for whole-body glucose and insulin homeostasis²⁶ was used to simulate a hypothetical subject prone to glucose intolerance. The model was used as a tool to simulate OGTTs at 3 time points (baseline, 2 and 5 years) and assess the changes in the glucose curve shape and time to glucose peak along the progression to diabetes. Details of the model are provided in the Supplemental materials.

Statistical Analyses

Data are presented as mean $\pm$ SD, except where otherwise indicated. The area under the curves (AUC) during the 2-hour OGTT for glucose, insulin and C-peptide were calculated using the trapezoid rule. Within group comparisons for each parameter (glucose peak at 30 mins vs. >30 mins and monophasic vs. biphasic) were performed with Student's t-tests for continuous variables and chi-square for categorical variables. The skewness and kurtosis test was used to determine the normality of all variables, and the Kruskal Wallis test was used for within-group analysis of non-parametric variables (insulin, C-peptide, S_I , AIRg and DI). Linear regression analyses were used to examine the association of predictor variables (time to glucose peak, curve shape, and glucose AUC) on DI (dependent variable). The disposition index was logarithmically transformed for regression analysis. Logistic regression was used to determine the relationship of predictor variables (time to glucose peak and curve shape) on prediabetes (outcome variable). Linear and logistic regression models were adjusted for the following covariates (ethnicity, sex, age, BMI and family history of diabetes). Receiver operator characteristic (ROC) AUC for prediabetes were computed for the two features (glucose peak >30 mins and monophasic curve). The ROC AUC were compared with the Mann-Whitney U statistics (for correlated ROC curves). P-values <0.05 were considered statistically significant and analyses were performed with STATA, v14.2 (College Station, Texas).

RESULTS

Prediabetes in the Cross-sectional Cohort (Supplemental Table 1)

Prediabetes was diagnosed in 36% (52/145) of participants and was associated with older age, higher hemoglobin A1c, higher fasting and 2-hour glucose concentrations. Otherwise, there were no differences in race/ethnicity, sex, BMI or other physical characteristics in those with and without prediabetes.

Glucose Curve Classification by Time to Glucose Peak vs. Curve Shape

A glucose peak >30 mins and a monophasic curve were the most common morphological features identified. All 145 individuals could be characterized by time to glucose peak: 33% (48/145) had a glucose peak at 30 mins and 67% (97/145) had a glucose peak >30 mins (Table 1). Glucose curve shape was classified as biphasic in 32% (46/145) of participants and monophasic in 67% (98/145). One individual was “Unclassified” (see Methods). The two morphological parameters were correlated in the participants who had glucose peak >30 mins – monophasic: 78% (76/97) vs. biphasic: 22% (21/97), $P<0.01$. In individuals with a glucose peak at 30 mins there was an equal chance of having either curve shape – monophasic: 45% (22/48) vs. biphasic: 54% (26/48).

Figure 1 illustrates the mean glucose, insulin and C-peptide curves classified by time to glucose peak (Figure 1A–C) and curve shape (Figure 1D–F). The morphology of the insulin and C-peptide curves for each parameter were similar to the corresponding glucose response curve.

Physical and Metabolic Characteristics by Morphology of Glucose Curve (Table 1)

Time to Glucose Peak—Glucose peak >30 mins was associated with older age ($P=0.03$), higher BMI ($P=0.02$), greater percent body fat ($P=0.04$), larger waist circumference ($P=0.03$), higher rates of prediabetes ($P<0.001$) and higher overall glycemia during the OGTT ($P<0.01$). Fasting and 2-hour C-peptide, and 2-hour insulin were higher in the group with glucose peak >30 mins, ($P<0.01$).

Shape of the Glucose Curve—The monophasic curve was more common in individuals with a family history of diabetes (Table 1). Otherwise, there were no differences in physical characteristics such as age, sex, BMI or body composition between participants with a monophasic vs. biphasic curve. Fasting glucose, insulin and C-peptide concentrations and rates of prediabetes were similar in individuals with monophasic and biphasic curves. Individuals with a monophasic curve had higher 2-hour and AUC concentrations for glucose, insulin and C-peptide ($P=0.01$).

To account for potential sex differences in the relationships with metabolic characteristics, we repeated the analyses using only women or men and found no differences in the results (data not shown).

Relationship of Morphology of Glucose Curve to β -cell function (Figure 2)

Figure 2 depicts the Tukey Box and Whisker Plots for S_I , AIRg and DI by morphology of the glucose curve. A glucose peak >30 mins was associated with significantly lower AIRg (~25%), and DI (~50%) with a trend for lower S_I (~20%) (Figure 2A–C). The monophasic vs. biphasic curve was associated with lower DI (~30%) but no difference in S_I or AIRg (Figure 2D–F).

The relative contribution of the two morphological parameters to DI is shown in Table 2. Time to glucose peak and glucose AUC were independent predictors of DI ($\text{adj}R^2=0.45$, $P<0.001$) in all participants and in those with normal glucose tolerant individuals ($\text{adj}R^2=0.49$, $P<0.001$). In the individuals with prediabetes, glucose AUC was the most significant predictor of DI ($\text{adj}R^2=0.44$, $P<0.001$). Glucose curve shape was not a significant determinant of DI in any of the above models before or after adjusting for covariates (Table 2).

Relationship of Morphology of Glucose Curve to Prediabetes

In the unadjusted logistic regression, glucose peak >30 mins was associated with a 4-fold increased odds of prediabetes (OR: 4.0; 95% CI: 1.7, 9.6, $P=0.001$) vs. the monophasic curve (OR: 1.1; 95% CI: 0.5, 2.5, $P=0.90$). After adjusting for covariates (ethnicity, sex, age, BMI and family history of diabetes), the magnitude of the odds ratio effects of time to glucose peak was larger (OR: 4.7; 95% CI: 1.8, 12.6, $P=0.002$) and no change in odds ratio associated with curve shape (OR: 1.2; 95% CI: 0.5, 2.6, $P=0.73$).

The sensitivity and specificity for detecting prediabetes in individuals with glucose peak >30 mins were 84% and 43% respectively. Individuals with a monophasic curve had a sensitivity and specificity for detecting prediabetes of 75% and 36% respectively. The ROC AUC for prediabetes tended to be higher for the parameter glucose peak >30 mins vs. monophasic curve (ROC AUC: 0.64, 95% CI (0.57, 0.71) vs. 0.55, 95% CI (0.47, 0.63), $P=0.06$).

Dynamic-Longitudinal Modeling - Simulated OGTTs in Hypothetical Subjects

—The simulations of glucose curves during the progression to diabetes in a hypothetical subject showed that with time the glucose peak progressively shifted to the right, remained monophasic and was associated with greater glucose AUC as hyperglycemia worsened (Supplemental Figure 1). The delay in the timing of the glucose peak with progression to diabetes coincided with ~60% lower S_I and ~60% and ~80% lower β -cell function at 2 and 5 years respectively (Supplemental Figure 1).

DISCUSSION

This comparative analysis highlights the limitations of using the glucose curve shape parameter and provides additional evidence to support time to glucose peak parameter as a potential prediabetes risk stratification tool. The time to glucose peak >30 mins was an independent indicator of prediabetes and lower β -cell function in an otherwise healthy multi-ethnic adult cohort. A later time to glucose peak was associated with a worse metabolic profile during the OGTT (Table 1) and higher odds of prediabetes (OR: 4.0, $P<0.001$). Using a reliable measure of β -cell function relative to insulin sensitivity, glucose peak >30 mins

was associated with lower DI, even after adjusting for glucose AUC during the OGTT (Table 2). Therefore, the association of time to glucose peak with β -cell function was independent of overall glycemia during the OGTT and suggests that this parameter could be used in addition to glucose thresholds in risk prediction models. Moreover, our findings highlight the limitations of using glucose curve shape as a screening tool for prediabetes. The monophasic curve was not associated with increased odds for prediabetes (Table 2) and tended to have a lower ability to detect prediabetes (ROC AUC) compared to the glucose peak parameter.

Additional support for the dynamic nature of the time to glucose peak compared to the curve shape was provided by the dynamic-longitudinal model²⁶. The simulations predicted that the failure of β -cell function and mass to compensate for insulin resistance was reflected in differences in both time to glucose peak and glucose AUC in OGTTs simulated at various time points during the progression to diabetes (Supplemental Figure 1). In contrast, glucose curve shaped remained monophasic with no shift observed as hyperglycemia worsened. In the model, both the decline in S_I and the loss of β -cell function contributed to the shift in the time to glucose peak. This model observation is consistent with the strong association between DI and time to glucose peak in our clinical observations.

The monophasic curve was proposed as a useful predictor of prediabetes because of its association with lower DI (derived from clamp indices²⁷) and ~2-fold increase in progression to type 2 diabetes over a 7–8 year period¹². Compared to the biphasic curve, the monophasic shape was linked to a worse cardiometabolic profile among adults and children^{12–15, 27}. However, the monophasic curve may have low sensitivity for identifying individuals at high risk for prediabetes because it is ubiquitous and up to 20% of participants could not be easily characterized into a monophasic or biphasic shape category¹⁴. More recently, the monophasic curve was found to be poorly reproducible and associated with significant heterogeneity in 70% of individuals over a 3-year period¹⁹. The marked variability in curve shape was independent of glucose tolerance status, although a persistent curve shape was associated with higher odds for impaired fasting glucose. The limited predictive ability of the monophasic shape for impaired glucose tolerance¹⁹ is further compounded by its co-linearity with overall glycemia²⁸. In our study, only one individual could not be easily classified as monophasic or biphasic. Nevertheless, curve shape did not differentiate physical and metabolic risk groups (Table 1) and tended to have lower sensitivity and specificity for prediabetes when compared to the time to peak parameter. Since the relationship of curve shape with lower β -cell function was mediated by overall glycemia (Table 2), this further limits its use as a glucose independent risk factor.

In contrast, time to glucose peak was a strong predictor of β -cell function in our multi-ethnic population at high risk for diabetes, 1/3 of whom already had prediabetes. Our findings are in agreement with cross-sectional analyses that have linked later time to glucose peak with impaired glucose tolerance and type 2 diabetes^{20, 21}. The predictive ability of the time to glucose peak parameter is further demonstrated by a longitudinal analysis in 532 postpartum predominantly white women²⁹. Compared to an unchanged glucose peak, both a shift in the glucose peak to a later time point and an unchanged glucose peak at 60 minutes were associated with declining insulin secretion and worsening glucose tolerance over a 9-month

period. The dynamic nature of the time to glucose peak coincided with changes in 2-hour glucose values in normal glucose tolerant women and provide insight into early changes in β -cell function. We now extend these observations to African-immigrant, African-American and white overweight/obese men and women who were otherwise healthy. Additional analyses are necessary to determine whether time to glucose peak could be a valuable epidemiological tool of β -cell function in populations with a high risk for diabetes but who have limited resources for complex metabolic phenotyping.

Although alternative OGTT indices of β -cell function are available, these parameters rely on insulin and glucose thresholds that require standardization of insulin assays and complex mathematical models^{30–34}. Because the glucose peak parameter is relatively easily obtained from a multiple sample OGTT, it would maximize the information gained from a single test without the added expense or inconvenience of assessing insulin concentrations. Our findings suggest that time to glucose peak could be a useful indicator of pancreatic function for clinical and epidemiological studies when complex metabolic phenotyping are not feasible.

Using the multiple sampled OGTT to characterize the time to glucose peak could also maximize the predictive value for cardiovascular disease. A recent meta-analysis of >1200 non-diabetic individuals identified cardiovascular risk was related to the timing and the height of the glucose peak³⁵. Moreover, the time of the glucose peak may be dynamic with the potential to assess changes in β -cell function relative to insulin sensitivity. Kramer et al. evaluated the oral disposition index in 63 patients with type 2 diabetes who were treated with short-term insulin therapy and demonstrated that the time to glucose peak shifted to an earlier time point in those with improved β -cell function²⁰.

The strength of this analysis is that reliable and independent measures of pancreatic function were used to test the ability of a simple parameter to aid in clinical and epidemiological evaluations of prediabetes risk. However, there are a few notable limitations. Our cross-sectional analysis in predominantly African descent individuals will require validation in a larger longitudinal study to assess whether this tool can be used to advise primary prevention guidelines for type 2 diabetes. Further, the reproducibility of the time to glucose peak parameter could be influenced by variations in gastric emptying or differences in pre-test carbohydrate loading. These factors were not assessed in the current study but would be informative in future evaluations of OGTT risk predictors. Of note, assessing the time to glucose peak parameter requires a multiple sample OGTT, while only 2 sampling time points (fasting and 2-hour glucose) are currently recommended for the diagnosis of prediabetes. The additional advantage of testing glucose levels at 30, 60 and 90 mins would be the ability to obtain a measure of β -cell function without increasing the time commitment of the patient and with a marginal increase in cost.

In conclusion, using a multiple sample 2-hour OGTT, the time to glucose peak is a stronger independent indicator of prediabetes and β -cell function than glucose curve shape. The glucose peak parameter maximizes the information obtained from a single OGTT and could prove to be a valuable tool of high clinical and epidemiological significance because it can

be simply derived and used in addition to glycemic thresholds to enhance prediabetes risk stratification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Glucose, insulin and C-peptide response curves during an oral glucose tolerance test characterized by time to glucose peak (A–C) and curve shape (D–E). Data are mean $\pm$ SEM. Peak at 30 mins (filled circle and solid line), peak >30 mins (filled square and dotted line), biphasic (filled triangle and solid line) and monophasic (filled triangle and dotted line).

Figure 2.

Tukey box and whiskers plot of the relationship of time to glucose peak with S_I (A), AIRg (B), DI (C) and glucose curve shape with S_I (D), AIRg (E), and DI (F).

Table 1

Patient characteristics by morphology of OGTT glucose curve.

	Glucose Peak at 30 mins (n=48)	Glucose Peak >30 mins (n=97)	P-value Peak at 30 vs. Peak >30 mins	Biphasic (n=46)	Monophasic (n=98)	P-value Mono vs. Biphasic
Age (y)	40±10	43±9	0.03	41.7±9.3	42.5±9.6	0.66
Female Sex	29 (60)	78 (80)	0.01	33(72)	73 (75)	0.04
Ethnicity			0.16			0.62
AI	27 (56)	42 (43)		19 (41)	49 (50)	
AA	11 (23)	37 (38)		17 (37)	31 (32)	
White	10 (21)	18 (18)		10 (22)	18 (18)	
BMI (kg/m ²)	27.8±5.1	29.9±5.2	0.02	29.0±4.9	29.4±5.4	0.71
WC (cm)	89.6±11.5	93.9±12.6	0.05	92.16±11.3	92.70±12.9	0.81
SBP (mmHg)	117±12	119±13	0.31	119±13.9	118±13	0.40
DBP (mmHg)	70±9	73±9	0.07	72±10	73±9	0.28
Total body fat (%)	31.0±10.0	35.3±8.2	<0.01	34.0±8.8	33.8±9.2	0.92
Family history of diabetes	29 (60)	52 (54)	0.44	25 (54)	55 (56)	0.04
Metabolic Characteristics						
Prediabetes	8 (17)	44 (46)	0.001	13 (28)	38 (39)	0.22
HbA1c (%)	5.36±0.37	5.41±0.39	0.40	5.39±0.37	5.42±0.40	0.64
HbA1c (mmol/mol)	35±4.0	36±4.3	0.40	35±4.0	36±4.4	0.64
Fasting glucose (mmol/L)	5.1±0.4	5.2±0.4	0.11	5.1±0.4	5.1±0.4	0.74
2h glucose (mmol/L)	6.3±1.0	7.5±1.5	<0.0001	6.7±1.3	7.2±1.5	0.06
Glucose AUC (mmol/L•min)	810±132	925±145	<0.0001	790±130	934±138	<0.0001
Fasting insulin (pmol/L)	34.2 (18.6–108)	46.8 (16.8–152.4)	0.20	35.4 (18.6–108)	44.4 (16.8–152.4)	0.26
2h insulin (pmol/L)	258 (96–942)	402 (96–1512)	0.001	264 (114–864)	396 (96–1560)	0.01
Insulin AUC (pmol/L•min)	43302 (22296–122856)	49236 (19998–140316)	0.49	39162 (19998–122856)	49422 (21234–141318)	0.01
Fasting C-peptide (nmol/L)	0.6 (0.3–1.0)	0.7 (0.4–1.4)	0.03	0.6 (0.3–1.1)	0.6 (0.4–1.4)	0.18
2h C-peptide (nmol/L)	2.3 (1.3–4.2)	3.0 (1.4–6.3)	<0.001	2.4 (1.4–4.4)	2.9 (1.4–6.3)	<0.01
C-peptide AUC (nmol/L•min)	266 (164–454)	285 (167–612)	0.31	263 (161–454)	287 (170–620)	0.01

Data are mean±SD, n (%) or median (25th–75th percentile). AI: African Immigrant, AA: African-American, SBP – systolic blood pressure, DBP – diastolic blood pressure, AUC – area under the curve.

Table 2

Predictors of disposition index (DI).

	Dependent variable – log DI					
	Total (n=144)		NGT (n=93)		Prediabetes (n=51)	
	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value
Peak at 30 mins	0.24 (0.1)	0.016	0.29 (0.1)	0.015	0.30 (0.2)	0.213
Biphasic Curve	0.10 (0.1)	0.286	0.15 (0.1)	0.168	0.10 (0.2)	0.575
Glucose AUC	0.00 (0.0)	<0.001	0.00 (0.0)	<0.001	0.00 (0.0)	<0.001
Adjusted R ²	0.44	<0.001	0.32	<0.001	0.40	<0.001

Model adjusted for ethnicity, sex age, BMI and family history; Peak >30 minutes and monophasic curve used as reference; NGT: normal glucose tolerance, AUC: area under the curve