Changes in OGTT-derived biomarkers in response to lifestyle intervention among Latino adolescents with obesity

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Summary

Background: Glucose concentrations during an oral glucose tolerance test (OGTT) have been used as biomarkers to differentiate type 2 diabetes risk phenotypes. No studies have examined changes in OGTT-glucose phenotypes following lifestyle intervention among high-risk youth.

Objective: To examine changes in OGTT-glucose phenotypes following lifestyle intervention and to explore differences in insulin sensitivity and β-cell function among post-intervention phenotypes.

Methods: Latino adolescents with obesity ($n = 48$, age 15.4 ± 1.0, BMI% 98.2 ± 1.4, female 56.3%) completed a 12-week lifestyle intervention that included weekly nutrition education and physical activity. At baseline and 12 weeks, youth completed a 2-h OGTT with glucose and insulin concentrations assessed at $0'$, $30'$, $60'$, $90'$ and $120'$. Glucose concentrations during the OGTT were used to identify biomarkers, 1-h glucose, glucose response curve and time to glucose peak.

Using these respective biomarkers, high-risk (1-h glucose   155 mg/dl, Monophasic, Late Peak) and lower-risk phenotypes (1-h glucose < 155 mg/dl, Biphasic, Early Peak) were categorized. Insulin sensitivity was estimated by whole-body insulin sensitivity index (WBISI) and β-cell function by oral disposition index (oDI).

Results: Following intervention, the prevalence of Monophasic phenotypes decreased from 81% to 67% ($p = 0.048$) and 1-h glucose   155 mg/dl from 38% to 10% ($p = 0.054$). Although Late Peak phenotypes did not significantly change (from 58% to 29%, $p = 0.200$), Early Peak phenotypes at post-intervention demonstrated significantly higher WBISI compared to Late Peak (2.3 ± 0.1 vs 1.7 ± 0.2, $p = 0.023$).

Conclusions: OGTT-glucose phenotypes improve following lifestyle intervention among high-risk youth. These findings further support their potential utility as clinical biomarkers to identify diabetes risk and risk reduction in youth.

Keywords

diabetes prevention; exercise; health behaviour; nutrition; physical activity

1 | INTRODUCTION

There is increasing interest in glucose concentrations during an oral glucose tolerance test (OGTT) as biomarkers that differentiate type 2 diabetes risk among youth and adults.[1–10] These biomarkers include 1-h glucose concentrations,[2,3,11] the shape of the glucose response curve,[1,7,12,13] and the time to glucose peak.[3,5,9,14] Each biomarker has been characterized into high (1-h glucose   155 mg/dl, Monophasic/Incessant-Increase, Late Peak) or lower (1-h glucose   155 mg/dl, Biphasic, Early Peak) risk phenotypes, hereafter termed OGTT-glucose phenotypes. Cross-sectional studies have exhibited an increased risk of type 2 diabetes among high-risk OGTT-glucose phenotypes as demonstrated by significantly reduced insulin sensitivity and β-cell function,[5,11] a blunted incretin response[3] and glucose intolerance[7] compared to respective lower-risk phenotypes among youth.

Few studies have prospectively examined changes in type 2 diabetes risk factors among OGTT-glucose phenotypes. In a study of Latino youth with obesity, 1-h glucose   155 mg/dl predicted β-cell deterioration after 8 years of follow-up, compared to 1-h glucose < 155 mg/dl phenotypes.[11] Using data from the TODAY study (Treatment Options for Type 2 Diabetes in Adolescents and Youth), youth with type 2 diabetes who were characterized by Monophasic or Incessant-Increase phenotypes demonstrated greater glycemic failure rates (42.3% and 58.3%, respectively) compared to the Biphasic phenotype group (39.1%).[1] Another longitudinal study among youth with obesity and polycystic ovary syndrome demonstrated that 40% of Late Peak youth developed impaired glucose tolerance (IGT) after a two-year follow-up period, whereas no youth with the Early Peak phenotype developed IGT.[15] These prospective studies expand upon previous work and demonstrate that high-risk OGTT-glucose phenotypes may confer future type 2 diabetes risk.

Lifestyle intervention is the first-line approach to preventing type 2 diabetes[16] and results in improvements in insulin sensitivity and β-cell function.[17] However, the literature is void

of studies that assess the effects of lifestyle intervention on OGTT-glucose phenotypes and whether lifestyle-induced transitions of high- to lower-risk phenotypes (or vice versa) are associated with improvements in type 2 diabetes risk factors. Therefore, the purpose of this study is twofold and includes (1) to assess the effects of lifestyle intervention on OGTT-glucose phenotypes among a high-risk population of adolescents and (2) to explore whether post-intervention OGTT-glucose phenotypes are differentiated by insulin sensitivity and β-cell function following lifestyle intervention.

2 | METHODS

This study represents a secondary data analysis from a randomized controlled trial testing the efficacy of a 12-week lifestyle intervention among Latino adolescents with obesity. Details of the parent study as well as the primary outcomes have been previously published.[18,19]

2.1 | Participants

Inclusion criteria for participation in the parent study were (1) self-identification as Latino, (2) ages 14–16 years at enrollment and (3) obesity as defined as body mass index (BMI) 95th percentile for age and sex or BMI $30 kg/m^2$. Exclusion criteria included (1) taking medication(s) or diagnosed with a condition that influences carbohydrate metabolism, physical activity, or cognition, (2) type 2 diabetes, (3) enrollment in a formal weight loss program within 6 months of the start of the study period, or (4) diagnosed with depression or any other condition that may impact quality of life. The classification of OGTT-derived phenotypes requires glucose concentrations from five time points during OGTT (described below); therefore, the current analysis focuses on youth enrolled in the intervention arm of the original study that had complete OGTT-glucose values at baseline and post-intervention ($n = 48$). A consort diagram of the original study can be found elsewhere.[20] All youth provided written assent and a parent/guardian provided written informed consent. This study was approved by the Arizona State University (ASU) Bioscience Institutional Review Board.

2.2 | Lifestyle intervention

The 12-week intervention included weekly nutrition education and 3 days/week of physical activity. The nutrition education classes were delivered by bilingual health educators to youth and parents/guardians and targeted reductions in sugar-sweetened beverages and saturated fat and increases in fruit, vegetable and fiber intake. The physical activity sessions were delivered by certified trainers to groups of youth and designed to elicit an average heart rate of 150 beats per minute for each 60-minute session. Adherence to the lifestyle intervention was expressed as a percentage of nutrition education classes and physical activity sessions attended along with average heart rates during physical activity sessions, which were measured by Polar (Bethpage, NY) heart rate monitors.

2.3 | Procedures

All participants arrived at the ASU clinical research unit after a 10–12 h fast. Height and weight were measured to the nearest 0.1 cm and 0.1 kg to calculate BMI and BMI% according to CDC Growth Charts.[21] Pubertal growth stage was estimated by the pubertal

development scale.[22] Family history of type 2 diabetes including in utero exposure to gestational diabetes was measured by parental report. Body fat percent was estimated by bioelectric impedance scale (TBF-300A; Tanita Corporation of America, Arlington Heights, IL). A 75-g OGTT was administered with blood samples collected at $0'$, $30'$, $60'$, $90'$ and $120'$ to measure insulin and glucose concentrations before and after the lifestyle intervention.

2.4 | Biochemical assessment

Insulin was measured using the Stellux Insulin Chemiluminescence ELISA kit by ALPCO Diagnostics (Windham, NH). Glucose was measured by the cobas c111 analyser from Roche Diagnostics (Indianapolis, IN). Pre- and post-samples were used to analyse glucose and insulin concentrations were batched and measured in duplicate under identical conditions.

2.5 | Classification of OGTT-glucose phenotypes

For the 1-h glucose biomarker, a $60'$ glucose concentration of 155 mg/dl served as the threshold to differentiate high (155 mg/dl) and lower-risk phenotypes (<155 mg/dl).[3] For the glucose response curve, biphasic phenotypes were classified as increasing to glucose peak before dropping by 4.5 mg/dl and increasing again by 4.5 mg/dl throughout the OGTT.[7,23] Youth that did not meet the second rise in glucose by 4.5 mg/dl as with a biphasic shape were classified as Monophasic phenotypes. Youth that did not present an initial drop in glucose by 4.5 mg/dl were classified as Incessant-Increase phenotypes.[12,13] Time to glucose peak phenotypes were differentiated by the time point of glucose peak with a $30'$ peak classified as Early Peak and a peak any time after $30'$ considered Late Peak.[3,5]

2.6 | Type 2 diabetes risk factors

Insulin sensitivity was estimated by the whole-body insulin sensitivity index (WBISI), which is derived by the following equation[24]:

$$\frac{10\,000}{\sqrt{I_0 \times G_0 \times \text{Mean}(I_0, I_{30}, I_{60}, I_{90}, I_{120}) \times \text{Mean}(G_0, G_{30}, G_{60}, G_{90}, G_{120})}},$$

where I and G represent insulin and glucose concentrations at the respective sample collection time points listed in subscript text (in minutes). The WBISI has been validated against the gold standard and the hyperinsulinemic euglycemic clamp technique, among adults and youth with obesity.[24,25] Insulinogenic index (IGI) was used to estimate insulin secretion (insulin$30'$–$0'$/ glucose$30'$–$0'$),[26,27] and β-cell function was estimated by the oral disposition index (oDI) as WBISI $\times$ IGI.[27]

2.7 | Analytical approach

Baseline differences between respective OGTT-glucose phenotypes were examined by independent t tests. Agreement of risk classification between respective high and lower risk OGTT-glucose phenotypes was examined by Cohen's Kappa statistic (K), where <0 = Less than chance agreement, 0.01–0.20 = Slight agreement, 0.21–0.40 = Fair agreement, 0.41–0.60 = Moderate agreement, 0.61–0.80 = Substantial agreement and 0.81–0.99 = Almost

perfect agreement.[28] Changes in the prevalence of OGTT-glucose phenotypes (additionally grouped by high vs. lower risk) were examined using a chi-square statistical test. Youth were then classified into response phenotypes, which were based on the phenotype classification after the intervention. For example, an individual who maintained or transitioned into a Biphasic phenotype in response to the intervention was considered a Biphasic responder (i.e., Biphasic at post-intervention), and this example applied to all other response OGTT-glucose phenotypes examined. A paired t test was used to examine pre-/post-intervention changes in insulin sensitivity, β-cell function and glucose area under the curve (AUC) among all 48 youth. To analyse differences in insulin sensitivity and β-cell function after lifestyle intervention between OGTT-glucose response phenotypes, we applied an analysis of covariance (ANCOVA) model, adjusting for age, sex, BMI and the dependent variable (either WBISI or oDI) at baseline.[29] SPSS Version 25 (Chicago, IL) was used with significance set at the 0.05 alpha level. Data are presented as mean ± SD or adjusted mean ± SE.

3 | RESULTS

Comparisons of baseline characteristics between respective OGTT-glucose phenotypes are presented in Table 1. It should be noted that using the glucose response curve biomarker, only two youth were classified as Incessant-Increase phenotypes. Given that Monophasic and Incessant-Increase phenotypes are high-risk phenotypes and to maximize sub-sample sizes, the two Incessant-Increase phenotypes were combined with Monophasic phenotypes. Of the high-risk phenotypes, 38%, 81% and 58% of adolescents were classified as 1-h glucose   155 mg/dl, Monophasic and Late Peak, respectively. Agreement across OGTT-glucose phenotypes at baseline was fair for all comparisons: 1-h glucose and glucose response curve ($\kappa = 0.243$, $p = 0.010$), 1-h glucose and time to glucose peak ($\kappa = 0.360$, $p = 0.007$) and glucose response curve and time to glucose peak ($\kappa = 0.302$, $p = 0.015$).

Comparisons of insulin sensitivity and β-cell function between respective OGTT-glucose phenotypes are listed in Table 1. The 1-h glucose   155 mg/dl phenotype presented with 38.1% lower insulin sensitivity and 63.2% lower β-cell function ($p < 0.05$) compared to 1-h glucose < 155 mg/dl phenotype. For the glucose response curve biomarker, Monophasic phenotypes demonstrated 50.0% lower β-cell function ($p < 0.05$), with no difference in insulin sensitivity. For the time to glucose peak biomarker, Late versus Early Peak phenotypes were similar in insulin sensitivity and β-cell function at baseline.

Changes in the prevalence of OGTT-glucose phenotypes in response to lifestyle intervention are presented in Figure 1. There were significant reductions in the prevalence of Monophasic phenotypes ($p = 0.048$) and a trend for reductions in the prevalence of 1-h glucose   155 mg/dl ($p = 0.054$) following lifestyle intervention. The prevalence of Late Peak phenotypes after lifestyle intervention was reduced, but was not significant ($p = 0.200$).

As a whole, the intervention led to significant increases in insulin sensitivity (from 1.7 ± 0.2 to 2.1 ± 0.1, $p = 0.015$) and β-cell function (from 6.7 ± 0.7 to 10.0 ± 1.3, $p = 0.006$), and reductions in glucose AUC (from 16122.0 ± 320.4 to 14973.4 ± 291.6 mg h/dl, $p = 0.002$) among the 48 participants (Figure 2). Differences in insulin sensitivity and β-cell function

between each respective OGTT-glucose response phenotype after lifestyle intervention are plotted in Figure 3. The most robust finding was that Early Peak response phenotypes demonstrated 35.3% ($p = 0.023$) greater insulin sensitivity after lifestyle intervention compared to Late Peak response phenotypes. No other differences in insulin sensitivity or β-cell function were found after lifestyle intervention between the respective OGTT-glucose phenotype comparisons. Within-group effects across all potential transition phenotypes are described in Table S1.

Attendance was not significantly different between respective glucose response curve (Monophasic at post-intervention: 85.6%, Biphasic at post-intervention: 86.8%, $p = 0.809$) and time to glucose peak response phenotypes (Late Peak at post-intervention: 87.4%, Early Peak at post-intervention: 82.5%, $p = 0.324$), but was significantly greater among 1-h glucose < 155 mg/dl compared to 1-h glucose   155 mg/dl response phenotypes (87.9% vs 69.7%, p = 0.011). Average heart rates during the exercise portion of the intervention were not significantly different between any respective OGTT-glucose response phenotype (1-h glucose   155 mg/dl at post-intervention: 154.1 beats/min, 1-h glucose < 155 mg/dl at post-intervention: 153.7 beats/min, $p = 0.921$), (Monophasic at post-intervention: 152.0 beats/min, Biphasic at post-intervention: 157.1 beats/min, $p = 0.058$) and (Late Peak at post-intervention: 152.8 beats/min, Early Peak at post-intervention: 154.1 beats/min, $p = 0.630$).

4 | DISCUSSION

Previous studies have established a differential risk for type 2 diabetes between respective OGTT-glucose phenotypes among youth.[1,3,7,11–13] Our findings add novelty to the body of knowledge in this field and suggest that higher risk OGTT-glucose phenotypes, namely, Monophasic and 1-h glucose   155 mg/dl, may be responsive to lifestyle intervention among a high-risk youth population. Furthermore, transitioning into an Early Peak phenotype after lifestyle intervention may be associated with increases in insulin sensitivity.

Studies among youth demonstrate that 1-h glucose   155 mg/dl and Monophasic glucose response curve at baseline are prospectively associated with worsening type 2 diabetes profiles (e.g., β-cell deterioration, glycemic failure) compared to their healthier phenotype counterparts.[1,11] The present investigation extends these findings and suggests that these phenotypes can improve among high-risk youth in response to lifestyle intervention. However, the mechanisms that mediate changes and the clinical significance of transitioning from a high-risk phenotype to a lower-risk phenotype have yet to be elucidated, particularly since we found no significant differences in insulin sensitivity and β-cell function between respective glucose response curve (Biphasic vs. Monophasic) and 1-h glucose (1-h glucose < 155 mg/dl versus 1-h glucose   155 mg/dl) response phenotypes following lifestyle intervention. It is important to consider that the 1-h glucose   155 mg/dl group at post-intervention only included five adolescents, and thus, interpretations should be made with caution.

It is expected that changes in insulin sensitivity and β-cell function would contribute to changes in OGTT-glucose phenotypes given that these factors contribute largely to the

regulation of glucose in the post-prandial state.[30] Reductions in type 2 diabetes incidence in the Diabetes Prevention Program were associated with enhancements in β-cell function supported by improvements in insulin secretion relative to insulin sensitivity among high-risk adults.[17] The Yale Bright Bodies Healthy Lifestyle Program was an adapted DPP for youth with IGT that demonstrated significant increases in insulin sensitivity but no significant changes in insulin secretion, or β-cell function compared to a standard clinical care group.[31] Our study exhibited differential effects on insulin sensitivity only among one of the respective phenotype comparisons with no differences in insulin secretion (data not shown) or β-cell function following lifestyle intervention. Studies that assess β-cell function relative to insulin sensitivity in response to lifestyle intervention in youth are scarce.[32] Therefore, it is difficult to speculate whether improvements in β-cell function after lifestyle intervention are predominantly due to changes in insulin secretion or insulin sensitivity among high-risk youth. It is possible that reductions in type 2 diabetes risk occur through increases in insulin sensitivity and that more aggressive interventions may be needed to improve β-cell function measures in youth. Furthermore, other factors related to glucose regulation during an OGTT, such as endogenous glucose production,[33] the incretin response,[3,8] glucose retention in the splanchnic beds[34] and sex,[35] may contribute to changes in OGTT-glucose phenotypes. Future research is warranted to understand the mechanisms responsible for inducing changes in OGTT-glucose phenotypes in response to intervention.

Although we found no significant changes in the prevalence of time to glucose peak phenotypes following lifestyle intervention, insulin sensitivity was significantly increased among Early Peak responders compared to Late Peak responders. Previous work has demonstrated significantly increased prevalence of T-risk allele *TCF7L2 rs7903146* variants among high-risk youth with Late Peak phenotypes compared to Early Peak phenotypes.[15] The *TCF7L2 rs7903146* variant has been negatively associated with insulin sensitivity and an increased risk for type 2 diabetes among high-risk youth.[36] It is plausible that the time to glucose peak biomarker is not responsive to detecting changes in respective high- and lower-risk phenotypes following lifestyle intervention. A previous study among adolescent girls with obesity or overweight identified hepatic steatosis and inflammation as differentiating Early and Late Peak phenotypes.[3] Given that both liver fat[37] and inflammatory processes[38] are associated with insulin resistance, these factors may have contributed to the observed differential response in insulin sensitivity between Early and Late Peak response phenotypes. Furthermore, Late Peak phenotypes have been characterized by a blunted incretin response as measured by lower glucagon-like peptide-1 (GLP-1) compared to Early Peak phenotypes.[3] GLP-1 is known to influence insulin dynamics and post-prandial glucose regulation[39] and is responsive to lifestyle changes.[40,41] Therefore, it stands to reason that other factors not measured in the current study such as liver fat, inflammation, incretins and key genetic risk factors for type 2 diabetes may differentiate Early Peak and Late Peak response phenotypes. Further examination is warranted to understand the mechanisms that may differentiate the response of insulin sensitivity among Early Peak response phenotypes compared to Late Peak.

This study is the first to assess changes in OGTT-glucose phenotypes in response to lifestyle intervention among a high-risk youth population and adds to the growing body of knowledge about the utility of glucose phenotypes to identify type 2 diabetes risk.

Our findings provide novel information to suggest that these phenotypes are malleable to a lifestyle intervention and therefore may support their utility as clinical biomarkers to assess diabetes risk reduction. Despite these strengths, we acknowledge that our study is not without limitations. This study was a secondary analysis and thus was not powered to detect significant changes in OGTT-glucose phenotypes prevalence or changes in type 2 diabetes risk factors between response phenotypes. Time to glucose peak phenotypes are classified by a 5-sample OGTT with 30′ sampling intervals, thereby limiting more precise glucose peak phenotyping methods that include more frequent sampling. Furthermore, time to insulin peak and area under the curve are differentiated by insulin sensitivity and β-cell function (relative to insulin sensitivity)[42] and warrant future research. This study was conducted among Latino adolescents with obesity, and thus, the findings may not be generalizable to other populations. Our measures to estimate insulin sensitivity and β-cell function were derived from the OGTT and are not the gold standard in the field.[25,27] Therefore, autocorrelation may influence our findings since biomarkers and risk factors examined used the insulin and glucose values from the same OGTT. Future research is needed to confirm these results using gold-standard measures of insulin sensitivity and β-cell function.

In conclusion, OGTT-glucose phenotypes may be responsive to lifestyle intervention among Latino adolescents with obesity. Furthermore, maintaining or transitioning into an Early Peak phenotype may be associated with increases in insulin sensitivity. Future larger trials are warranted to examine potential predictors of response and understand mechanisms that may explain the response of OGTT-glucose phenotypes. Such research may support the use of OGTT-glucose phenotypes as clinical biomarkers to assess risk and risk reduction among high-risk youth populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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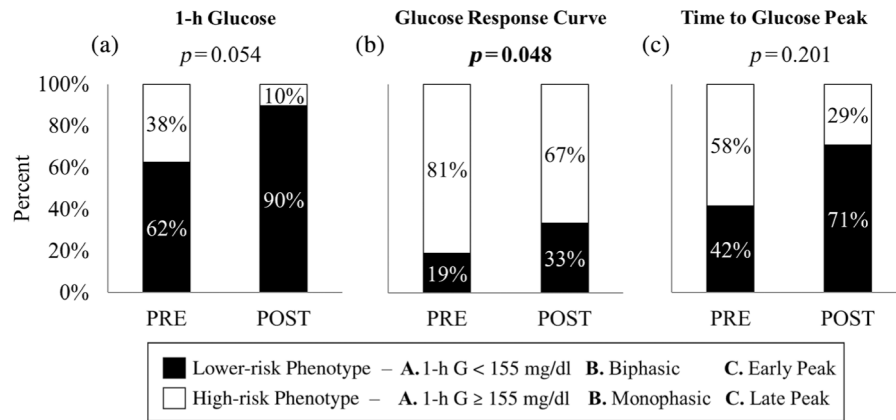
Significance alpha level set at *p* < 0.05

FIGURE 1.

Prevalence of respective high and lower-risk OGTT-glucose phenotypes before (PRE) and after (POST) lifestyle intervention. Significance alpha level set at *p* < 0.05
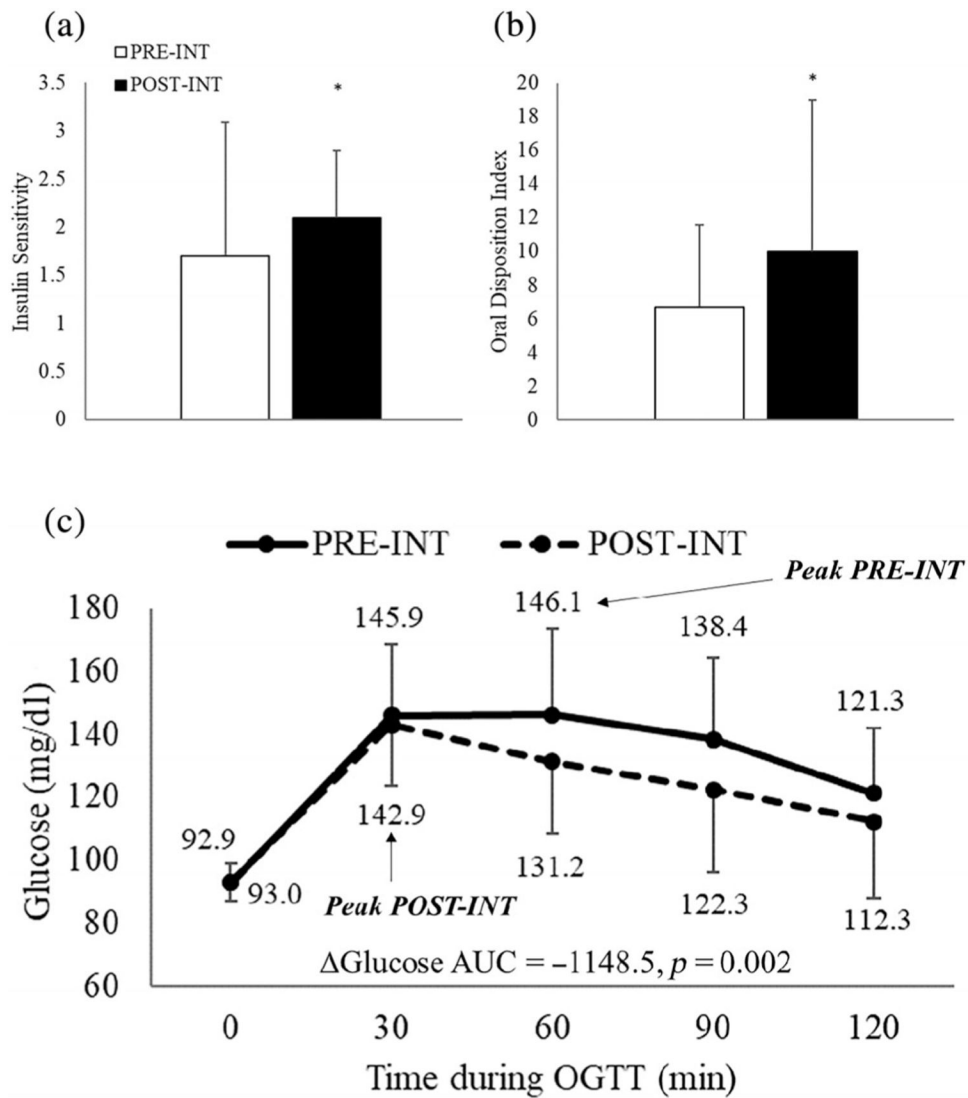
FIGURE 2.

Change in WBISI (Panel A), oDI (Panel B) and glucose AUC (Panel C) among the entire cohort of analysis ($n = 48$)
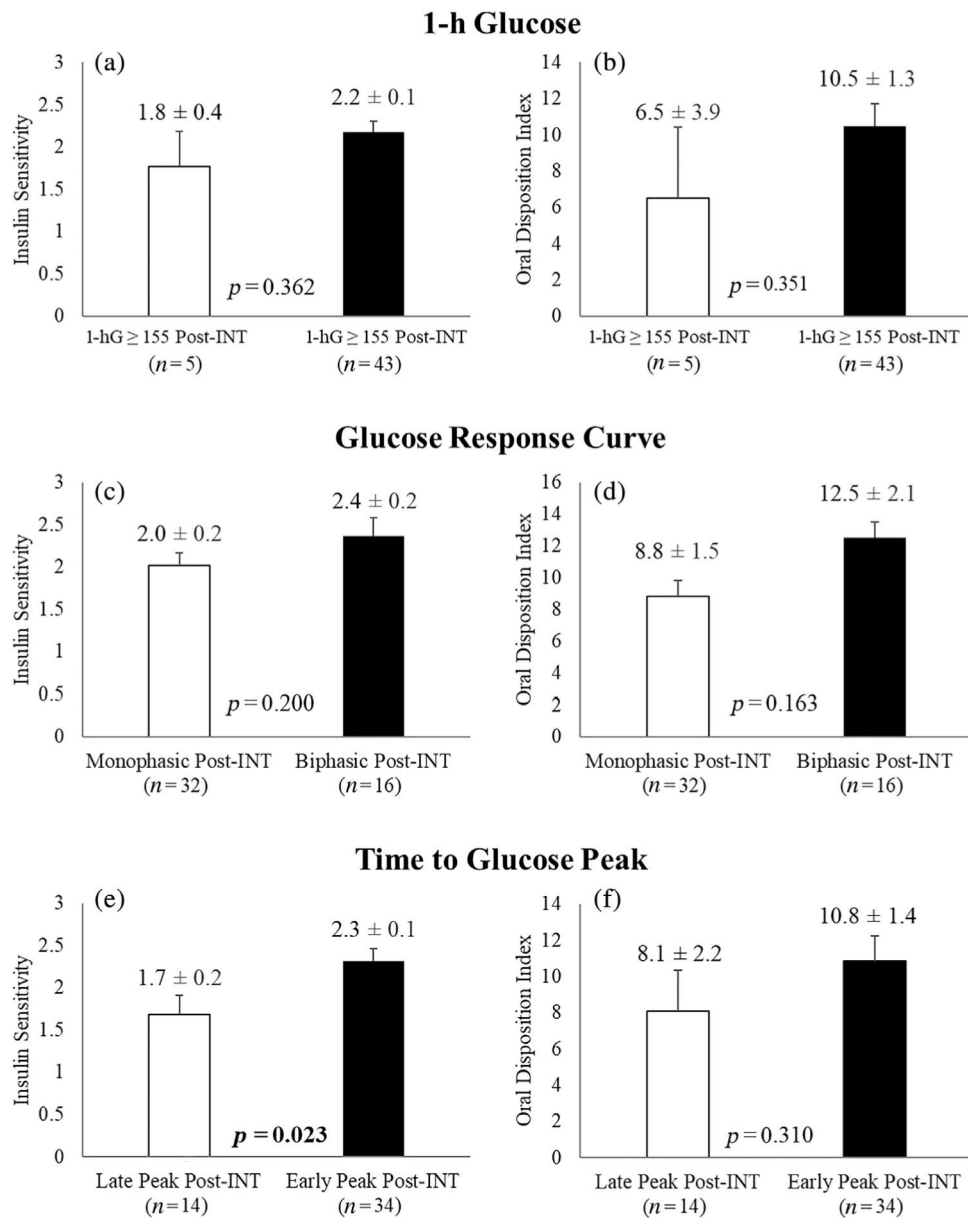
1-h Glucose

Glucose Response Curve

Time to Glucose Peak

INT: intervention; 1hG: 1-h glucose
Data are presented as Mean±SE, Significance alpha level set at p<0.05

FIGURE 3.

Differences in insulin sensitivity by WBISI (Panels A, C, E) and β-cell function by oDI (Panels B, D, F) between respective OGTT-glucose phenotypes after intervention (Post-INT). INT, intervention; 1hG, 1-h glucose. Data are presented as mean ± SE, significance alpha level set at $p < 0.05$

TABLE 1

Baseline characteristics across OGTT-glucose phenotypes among Latino youth ($n = 48$)

Parameter	1-h Glucose			Glucose response curve			Time to glucose peak		
	1-h glucose < 155 ($n = 30$)	1-h glucose 155 ($n = 18$)	p value	Biphasic ($n = 9$)	Monophasic ($n = 39$)	p value	Early peak ($n = 20$)	Late peak ($n = 28$)	p value
Age, years	15.3 ± 1.0	15.4 ± 1.0	0.779	15.2 ± 1.1	15.4 ± 1.0	0.665	15.2 ± 1.1	15.5 ± 0.9	0.428
Female, N (%)	20 (66.7%)	7 (38.9%)	0.060	6 (66.7%)	21 (53.8%)	0.485	11 (55.0%)	16 (57.1%)	0.762
Prediabetes, N (%)	2 (22.2%)	11 (39.3%)	0.716	5 (16.7%)	8 (44.4%)	0.040	3 (15.0%)	10 (35.7%)	0.111
Family history, N (%)	13 (43.3%)	5 (27.8%)	0.281	3 (33.3%)	15 (38.5%)	0.775	7 (35.0%)	11 (65.0%)	0.883
PDS	2.7 ± 0.5	2.6 ± 0.4	0.418	2.8 ± 0.5	2.6 ± 0.5	0.346	2.7 ± 0.5	2.7 ± 0.5	0.915
BMI, kg/m^2	34.0 ± 4.9	35.5 ± 4.6	0.318	33.0 ± 2.7	34.9 ± 5.1	0.271	35.5 ± 4.3	33.9 ± 5.0	0.247
BMI%	98.0 ± 1.5	98.6 ± 0.9	0.071	97.9 ± 1.4	98.3 ± 1.4	0.459	98.6 ± 0.9	97.9 ± 1.6	0.083
WC, cm	106.9 ± 10.4	111.7 ± 13.7	0.181	106.4 ± 7.0	109.3 ± 12.7	0.520	112.3 ± 11.5	106.2 ± 11.6	0.076
G$_0$, mg/dl	91.8 ± 5.4	94.7 ± 6.8	0.104	92.5 ± 7.2	93.0 ± 5.8	0.844	94.6 ± 4.3	91.6 ± 6.8	0.091
G$_{120}$, mg/dl	114.7 ± 17.7	132.3 ± 20.7	0.003	117.3 ± 17.5	122.2 ± 21.3	0.528	112.3 ± 19.4	127.7 ± 19.1	0.009
HOMA-IR	4.9 ± 2.6	6.0 ± 3.1	0.161	5.1 ± 2.8	5.4 ± 2.8	0.773	5.9 ± 2.9	4.9 ± 2.7	0.223
WBISI	2.1 ± 1.2	1.3 ± 0.6	0.012	2.0 ± 1.2	1.7 ± 1.0	0.524	1.7 ± 1.0	1.8 ± 1.1	0.737
oDI	8.7 ± 5.5	3.2 ± 1.2	<0.001	11.2 ± 5.6	5.6 ± 3.6	0.002	6.9 ± 3.5	6.5 ± 6.1	0.832

Note: Data presented as Mean ± SD.

Abbreviations: G$_0$, fasting glucose; G$_{120}$, 2-h glucose during OGTT; HOMA-IR, homeostatic model assessment of insulin resistance; oDI, oral disposition index; PDS, pubertal development scale; WBISI, whole-body insulin sensitivity index; WC, waist circumference.