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Compensatory responses to insulin resistance in obese African-American and Latina girls

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Summary

Purpose: Insulin responses to oral and intravenous glucose markedly differ by ethnicity. This study examined whether ethnic differences in pancreatic insulin secretion, hepatic insulin extraction and clearance explain these disparate findings in 35 obese African–American and 41 Latina girls (Tanner Stages: IV–V; ages: 14–18; body mass index percentile: 85.9–99.8%).

Methods: Pancreatic insulin secretion, hepatic insulin extraction and clearance were estimated by C-peptide and insulin modeling during an oral glucose tolerance test. Insulin sensitivity (SI), acute insulin response to glucose (AIR_G) and disposition index were derived from a frequently sampled intravenous glucose tolerance test.

Results: Compared to Latinas, obese African–American adolescents had lower pancreatic insulin secretion (21.3%; $P < 0.01$), glucose incremental area under the curve (IAUC) (41.7%, $P = 0.02$), C-peptide IAUC (25.1%, $P < 0.01$) and S_I (33.7%; $P < 0.01$). There were no ethnic differences in hepatic insulin extraction and clearance (P's > 0.05).

Conclusions: Compensatory mechanisms to insulin resistance do not appear to explain the ethnic differences in insulin responses to oral and intravenous glucose in obese African–American and Latina girls.

Keywords: African–American, hepatic insulin extraction, Latina, pancreatic insulin secretion.

Insulin responses to intravenous and oral glucose markedly differ by ethnicity. Previous research has consistently reported a greater acute insulin response to intravenous glucose (AIR_G) (1,2) as well as a greater insulin response to oral glucose ingestion in African–Americans compared to their Latino (3) and non-Latino white counterparts (4). Our laboratory recently demonstrated insulin sensitivity (S_I), derived from a frequently sampled intravenous glucose tolerance test (FSIGT) was significantly lower in obese African–American boys and girls compared to Latinos, independent of total and visceral fat mass (2). Moreover, pancreatic beta-cell function (as reflected by a greater disposition index [DI]) and AIR_G was significantly higher in African–Americans compared to Latinos (2). Interestingly, in the same group of participants, the exaggerated insulin response reported during the FSIGT was not observed during

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an oral glucose tolerance test (OGTT) (2). Specifically, insulin incremental area under the curve (IAUC) was similar in both ethnic groups (2).

One explanation for the greater AIR_G in African–Americans during the FSIGT may be related to ethnic differences in the compensatory responses to insulin resistance (5). We previously demonstrated that African–American children display profound hyperinsulinemia in response to intravenous glucose, partly explained by a lower hepatic insulin extraction, whereas Latino children have an increased second phase insulin secretion (5). It is unclear whether these findings in normal weight African–American and Latino children (Tanner stages I-III) are similar in a more severely obese adolescent population, and more importantly, whether or not these compensatory mechanisms explain our disparate findings between intravenous and oral glucose ingestion in African–American youth. Therefore, the primary objective of this study was to compare pancreatic insulin secretion, hepatic insulin extraction and clearance derived from an OGTT in obese African–American and Latino adolescents at a later stage of pubertal development (Tanner stages IV-V). It was hypothesized that pancreatic insulin secretion would be higher and/or hepatic insulin extraction and clearance would be lower in African–Americans compared to Latinos.

Participant characteristics and general procedures used in this study have been previously reported (1,2,6); however, the most relevant information is described below. OGTT modeling data was only completed in 51 African–Americans (16 males/35 females) and 66 Latinos (25 males/41 females); therefore the present analysis is based on a subsample (females only) of the original study population. All participants met the following inclusion criteria: age- and gender-specific BMI ≥ 85th percentile, African–American or Latino ethnicity (all four grandparents were of the same ethnic group as the child in the study), and attending grades 9th–12th grade (approximately 14–18 years of age). The University institutional review board approved this study.

Participants arrived at the University of Southern California (USC) General Clinical Research Center (GCRC) at ~7:30 am after completing an overnight fast. Upon arrival, a licensed pediatric healthcare provider conducted a medical/family history and physical examination. Total body composition was assessed using dual-energy X-ray absorptiometry using a Hologic QDR 4500W (Hologic, Bedford, MA, USA). Plasma glucose, insulin and C-peptide IAUC were measured during a 3-h OGTT (2). The extended Combined Model method was used to estimate pancreatic insulin secretion, hepatic insulin extraction and clearance (7). Approximately 7–14 d after the outpatient visit, participants were admitted to the GCRC in the evening hours and completed a FSIGT (2) the following morning.

Before analysis, data were evaluated for normality and log transformed when necessary. Ethnic differences in physical characteristics were tested using independent-sample t-tests and Chi-square tests. Ethnic differences in body composition, OGTT and FSIGT parameters were tested using analysis of covariance, after controlling for Tanner stage, sex, total fat mass and fat-free mass. All analyses were performed using SPSS version 18.0 (Chicago, IL, USA) with significance level set at $\alpha < 0.05$.

Participant characteristics are shown in Table 1. Compared to Latinas, a smaller percentage of African–Americans were in Tanner stage IV, had higher body weight, fat-free mass and body fat percentage (all P's < 0.05). There were no significant differences in age, body mass index (BMI), BMI z-score, BMI percentile, total fat mass, impaired fasting glucose and impaired glucose tolerance by ethnicity (all P's < 0.05).

The values for the key variables from the OGTT and FSIGT are shown in Table 2. During the OGTT, African–Americans had significantly lower fasting insulin and C-peptide values, glucose and C-peptide IAUCs compared to Latinas (all P's < 0.05; see Fig. 1). C-peptide-to-glucose ratio also tended to be lower in African–Americans compared to Latinas ($P = 0.051$). Pancreatic insulin secretion ($P < 0.01$) was significantly lower in African–Americans compared to Latinas; however, there were no significant ethnic differences reported in fasting glucose, insulin IAUC, hepatic insulin extraction and clearance (all P's > 0.05). During the FSIGT, S_I was significantly lower in African–Americans compared with Latinas ($P = 0.02$). AIR_G and DI were 40 and 20% higher, respectively, in African–Americans compared to Latinas; however, these differences were not significant (P's > 0.05).

Contrary to our hypotheses, this study demonstrates that in response to oral glucose ingestion, pancreatic insulin secretion is significantly lower in obese African–American girls compared to their Latina counterparts. Acknowledging that glucose is a major stimulus for pancreatic insulin secretion, we also examined the ratio of C-peptide-to-glucose concentrations during the OGTT. Again, African–Americans had a lower C-peptide-to-glucose ratio than compared to Latina girls ($P = 0.051$). These findings are generally consistent with our previous findings (5) and confirm increased secretion is the

Table 1 Participant characteristics

	African–Americans ($n = 35$)	Latinas ($n = 41$)	*P*-value
Tanner stage (%)			<0.01
Stage IV	5.7	34.1	
Stage V	94.3	65.9	
Age (years)	15.5 ± 0.2	15.3 ± 0.2	0.51
Weight (kg)	93.9 ± 3.7	84.7 ± 2.7	0.05
BMI (kg/m^2)	35.1 ± 1.2	33.2 ± 0.9	0.24
BMI z-score	2.1 ± 0.7	2.0 ± 0.7	0.31
BMI percentile	97.3 ± 0.5	96.5 ± 0.6	0.27
Fat-free mass (kg)	53.9 ± 1.4	47.8 ± 1.1	<0.01
Fat mass (kg)	35.5 ± 2.1	34.5 ± 1.6	0.70
Percentage of body fat	38.6 ± 1.0	41.2 ± 0.8	<0.01
IFG (%)	5.7	7.3	0.78
IGT (%)	11.4	22.0	0.23
IFG and IGT (%)	2.9	2.4	0.91

Data are unadjusted mean ± standard error. Significant at $p < 0.05$. BMI, body mass index; IFG-impaired fasting glucose; IGT-impaired glucose tolerance. *P*-values reflect significant differences by ethnicity and were calculated using chi-square and Student's t-tests. While unadjusted means are reported here for all variables, analyses were based on log scores for age, weight, BMI and BMI percentile.

Table 2 OGTT and FSIGT parameters for African–American and Latina girls

	African–Americans ($n = 35$)	Latinas ($n = 41$)	*P*-value
OGTT			
Fasting glucose (mmol/L)	5.0 ± 0.1	5.0 ± 0.1	0.32
Fasting insulin (pmol/L)	160.36 ± 14.4	182.7 ± 11.2	<0.01
Fasting C-peptide (nmol/L)	0.9 ± 0.1	1.1 ± 0.1	<0.01
Glucose IAUC (nmol/min/L)	74.6 ± 7.1	105.7 ± 7.7	0.02
Insulin IAUC (nmol/min/L)	347.3 ± 43.1	393.6 ± 35.4	0.13
C-peptide IAUC (nmol/min/L)	21.5 ± 1.6	26.9 ± 1.5	<0.01
Ratio C-peptide:glucose concentrations	0.09 ± 0.005	0.10 ± 0.004	0.05
Pancreatic insulin Secretion (nmol/min)	895.6 ± 112.2	1088.1 ± 108.0	<0.01
Hepatic insulin extraction (%)	55.7 ± 2.3	60.5 ± 2.1	0.24
Fractional disappearance of insulin (% per min)	38.5 ± 2.5	36.6 ± 1.9	0.66
FSIGT			
Insulin sensitivity (x 10^{-4} min^{-1}/pmol/L)	8.6 ± 0.9	11.5 ± 0.9	0.02
AIR_G (pmol/L x 10 min)	15998.7 ± 1886.1	9558.6 ± 672.3	0.16
DI (x 10^{-4} min^{-1})	2264.2 ± 241.9	1813.8 ± 110.5	0.08

Data are mean ± standard error. Significant at $P < 0.05$. OGTT, oral glucose tolerance test; IAUC, incremental area under the curve; FSIGT, frequently sampled intravenous glucose tolerance test; AIR, acute insulin response to glucose; DI, disposition index. Analyses were based on log scores for fasting glucose, fasting insulin, pancreatic insulin secretion, hepatic insulin extraction, fractional disappearance of insulin, insulin sensitivity, AIR and DI. *P*-values reflect significant differences by ethnicity and were calculated using analyses of covariance, covarying for Tanner stage, total fat, fat-free mass and insulin sensitivity (for AIR_G and pancreatic secretion only).

primary mechanism by which obese Latina girls compensate for insulin resistance.

Hepatic insulin extraction and clearance were similar in both ethnic groups. These findings are in contrast to our previous findings where normal weight African–American children had significantly lower hepatic insulin extraction and clearance compared to Latino children (5). It is possible that with greater obesity, the ability of the liver to compensate for insulin resistance by reducing insulin extraction in African–Americans becomes compromised (8). Although this compensatory mechanism may be able to maintain the already low levels of insulin sensitivity in normal weight African–American youth in

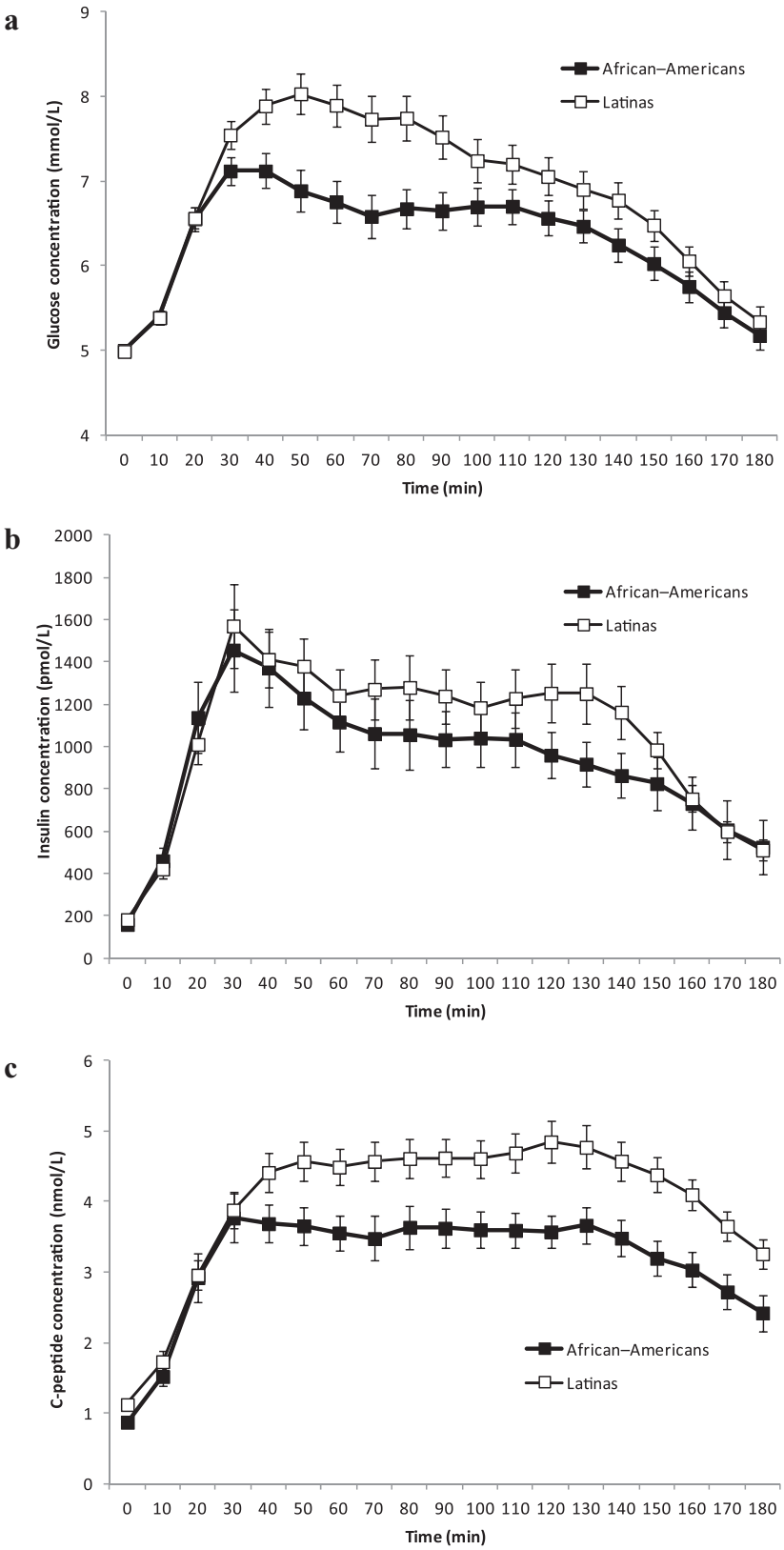

Figure 1 Incremental area under the curves during the oral glucose tolerance test for (a) glucose, (b) insulin and (c) C-peptide.

the short term, with greater obesity this mechanism may eventually lead to failure of the beta-cell and progression towards type 2 diabetes in this ethnic group. Further research using a longitudinal design is needed to better examine the pathophysiology of type 2 diabetes progression in African–American youth.

Interestingly, FSIGT measures of insulin sensitivity demonstrate African–Americans were more insulin resistant compared to Latinas, whereas lower pancreatic insulin secretion, glucose and C-peptide IAUCs during the OGTT suggest African–Americans are more insulin sensitive. There are several factors that may explain these disparate findings. First, previous research has reported lower Glucagon-like peptide-1 (GLP-1) levels in response to oral glucose ingestion in obese African–American adolescents compared to non-Latino whites (4,9), thus highlighting the potential role for ethnic differences in incretin hormones. However to date, no study has compared incretin responses in African–American and Latina girls. Second, it is also plausible that these disparate OGTT and FSIGT findings are explained by the different methods in which glucose was administered (ingestion vs. intravenous, respectively) (10). Previous research has reported differences by test type in pancreatic secretory responses and pancreatic beta-cell rate of exposure to nutrients (10). Therefore, it is likely that intravenous and oral glucose tests capture unique aspects of the insulin response. Specifically, the higher AIR_G (within the first few minutes) previously observed in obese African–Americans during the FSIGT may be the result of the immediate release of previously docked insulin secretory granules on the beta-cell (10,11), whereas the rapid depletion of these granules and greater reliance on granule transport may drive insulin and C-peptide responses during the OGTT. Hence, these findings emphasize the importance of understanding test-related differences in the assessment of insulin and C-peptide dynamics when examining ethnic differences in type 2 diabetes risk in obese African–American and Latino adolescents. Several limitations of this study should be noted. First, data limitations precluded analysis of other factors known to influence insulin and C-peptide dynamics in this analysis including genetic admixture (12). In addition, the poor reproducibility of the OGTT has been previously noted (13) and the reliance on mathematical modeling of insulin sensitivity and secretion rather than direct measurements (14) may have influenced the interpretation of the present findings. Finally, given the large variability in OGTT- and FSIGT-derived insulin and glucose indices, some of our analyses may have been underpowered, inhibiting our ability to generalize our findings to other populations. Despite these limitations, we were able to replicate some of our previous findings and detect significant differences in pancreatic insulin secretion, glucose and C-peptide IAUCs between obese African–American and Latina girls. Future research should continue to address the question of underlying mechanisms that contribute to metabolic abnormalities in obese African–American and Latino adolescents.

Conflict of interest statement

The authors have no conflict to disclose.

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