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Ethnic differences in beta cell adaptation to insulin resistance in obese children and adolescents

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Abstract *Aims/hypothesis:* The prevalence of altered glucose metabolism in obese children and adolescents is growing at a significant rate, especially in ethnic minorities. It is not clear whether young people of different ethnic backgrounds differ in their adaptive mechanisms to obesity-related insulin resistance. The aim of this study was to evaluate the early insulin response and insulin clearance in response to an oral glucose load in obese children and adolescents. *Methods:* Seven hundred and nine obese children and adolescents underwent an OGTT. Indices of the early insulin response and insulin clearance were compared in participants of White European, African American and Hispanic origin. *Results:* Participants of the three ethnic groups demonstrated similar mechanisms of adaptation to increasing insulin resistance, but with different magnitudes. African American subjects had a greater early insulin response and decreased insulin clearance than their White European and Hispanic counterparts. This happened regardless of whether the cohort was divided by glucose tolerance level or by level of insulin sensitivity. IGT across ethnic groups was characterised by a marked decline in the acute insulin response in the context of severe insulin resistance and very low insulin clearance. *Conclusions/interpretation:* In obese children and adolescents, mechanisms of adaptation to obesity related to insulin resistance are similar across ethnic groups. The greater early insulin

response needed to maintain glucose tolerance in young people of ethnic minorities may partially explain their greater tendency to develop type 2 diabetes.

Keywords Ethnic · Insulin clearance · Insulin response · Insulin sensitivity · Obesity

Abbreviations EIR: early insulin response · EIS: estimated insulin sensitivity · HOMA-IR: homeostasis model assessment of insulin resistance · IGI: insulinogenic index · WBISI: whole-body insulin sensitivity index

Introduction

The epidemic of childhood obesity in the USA and other Western countries [1] has been accompanied by a rise in the prevalence of IGT [2] and type 2 diabetes [3] in the paediatric age group. In African American and Hispanic young people, type 2 diabetes is more common than in people of White European origins [4]. The ethnicity-related clustering of type 2 diabetes is attributed to a greater degree of obesity and severity of insulin resistance [5]. Numerous groups have reported that African American children have lower insulin sensitivity with higher than expected acute plasma insulin responses to exogenous glucose than children of White European origin [6, 7]. Earlier studies [8] indicated that the higher insulin levels in African American children can in part be attributed to increased secretion as well as decreased insulin clearance. Similarly, other groups [9] suggested that Hispanic and African American young people have greater insulin resistance than children of White European origin and greater plasma insulin responses, in part because of reduced hepatic extraction of insulin.

The plasma insulin concentration in response to a glucose challenge is a complex function, not only of the coexisting plasma glucose concentration but also of beta cell responsiveness to changing glucose levels and the rate of insulin clearance, both of which are modulated by the prevailing degree of insulin resistance [10, 11]. In insulin-resistant states, an increased beta cell response to glucose

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and reduced insulin clearance are viewed as adaptive mechanisms that allow maintenance of NGT. A recently published study [12] proposed the possibility that the increased rates of type 2 diabetes in African American obese adolescents are a consequence of a limited capacity of the beta cell to compensate for the ambient insulin resistance. Although this hypothesis is very attractive, it is based mainly on studies performed in a small number of obese adolescents. The relative contributions of increasing insulin resistance and declining beta cell function in the development of altered glucose metabolism in obese young people of different ethnic backgrounds are unclear. Identification of ethnicity-specific tendencies for defects in glucose homeostasis may enable clinicians to tailor specific therapies and interventions for children and adolescents at risk of type 2 diabetes.

To gain insights into the pathophysiology of type 2 diabetes in young people, we did a longitudinal study in a multi-ethnic cohort of obese children and adolescents. Launched in 2000, the study used the OGTT to characterise alterations in glucose homeostasis. This relatively simple technique allowed us to explore ethnic differences in beta cell adaptation to peripheral insulin resistance in a large group of young obese subjects.

Subjects and methods

Subjects

Participants in this study were children and adolescents referred for an OGTT from the Yale Pediatric Obesity Clinic as part of a longitudinal study on the natural history of type 2 diabetes. Some of these subjects have been described in previous publications [13, 14]. To be eligible for this analysis, all had to be between the age of 4 and 20 years, obese (BMI Z-score >2.0), of White European, African American or Hispanic background, otherwise healthy, on no medications that could affect glucose homeostasis, and had a 2-h glucose level below 11.1 mmol, i.e. have NGT or IGT. For subjects who underwent more than one OGTT, only a single OGTT was used for the analysis. The study was approved by the Yale University Human Investigation Committee. Parental informed consent and child assent were obtained from all participants.

OGTT

Subjects were studied in the General Clinical Research Center of Yale University School of Medicine at 08.00 h following a 10–12 h overnight fast. A standard OGTT (1.75 g/kg body weight, up to 75 g) was performed in all children and adolescents to establish glucose tolerance status [15]. After the local application of a topical anaesthetic cream containing 2.5% lidocaine and 2.5% prilocaine, one antecubital i.v. catheter was inserted for blood sampling and maintained patent by a normal saline drip. Two baseline samples were then obtained at –15 and 0 min for

measurements of plasma glucose, insulin and C-peptide. Thereafter, flavoured glucose (Orangedex; Custom Laboratories, Baltimore, MD, USA) was given orally, and blood samples were obtained every 30 min for 180 min for the measurements of plasma glucose, insulin and C-peptide.

Calculations

Parameters reflecting insulin sensitivity, early insulin response (EIR) and insulin clearance were derived from the OGTT. Estimated insulin sensitivity (EIS) was calculated using the Matsuda index [16] (whole-body insulin sensitivity index [WBISI]), which we have previously validated by comparison with euglycaemic–hyperinsulinaemic clamp studies in obese children and adolescents [17]. The index was calculated according to the following formula:

$$\text{WBISI} = 10\,000 / \sqrt{[(\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean glucose} \times \text{mean insulin})]}$$

The EIR was calculated using the insulinogenic index (IGI) [18] using fasting and 30-min levels of glucose (mmol/l) and insulin (pmol/l) according to the following formula:

$$\text{IGI} = \Delta \text{insulin}(0-30) / \Delta \text{glucose}(0-30).$$

We found that the relation of IGI with first-phase insulin secretion as measured by hyperglycaemic clamp in obese children and adolescents is $r=0.56$ ($p<0.001$). Insulin clearance was calculated using the molar ratio of the AUC of insulin and C-peptide for the complete length of the study (180 min). This calculation avoids potential pitfalls of calculating these ratios at discrete time points [19]. The incremental AUC for glucose, insulin and C-peptide were calculated using the trapezoidal rule.

Relation between OGTT-derived indices of secretion and sensitivity

Since the OGTT represents an oral route of the glucose challenge, indices of secretion and sensitivity derived from this test may differ from similar indices derived from studies using an i.v. route of glucose administration. Despite this, we hypothesised that the estimates of insulin secretion and sensitivity should maintain the physiological feedback relation, reflecting the tight communication between the beta cell and the ambient peripheral sensitivity. We hypothesised that the curvilinear relation would most appropriately characterise the relation between WBISI and IGI, as proposed by Kahn et al. [20]. Therefore, we modelled log-transformed IGI as a function of log-transformed WBISI.

Simple linear regression suggested that the log–log transformed curvilinear model was a better fit than the untrans-

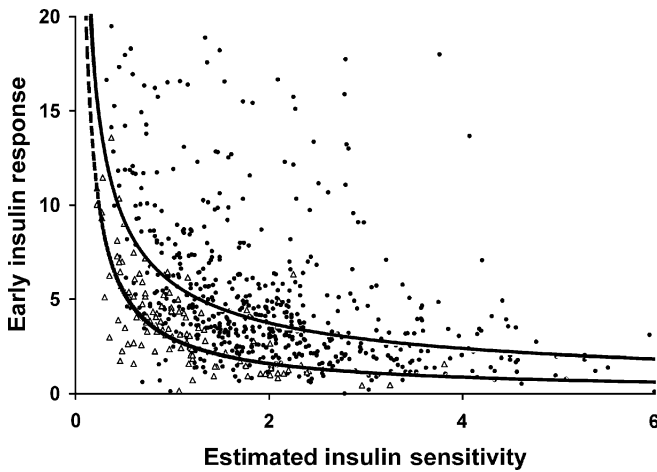


Fig. 1 Relation of the estimated insulin sensitivity and the early insulin response in subjects with NGT and IGT. NGT, circles and solid line; IGT, triangles and dashed line

formed straight-line model ($r^2=0.16$ and 0.04 , respectively). The estimated model for the log–log transformed data was:

$$\log \text{IGI} = -0.53 \log \text{WBISI} + 1.7 \quad (1)$$

Kahn et al. [20] demonstrated that the hyperbolic function $\log(y) = -\log(x) + c$ (alternatively stated as $xy = \text{constant}$) adequately explained the relation between sensitivity and secretion measures derived from the IVGTT. The results from our regression analysis suggest that, in obese children and adolescents, a similar curvilinear relation exists between the log IGI and the log of the square root of WBISI (Eq. 1). This leads to our calculation of the relation between them (OGTT-derived disposition index) as the product of IGI and the square root of WBISI. The two hyperbolas representing subjects with NGT and IGT in this cohort are shown in Fig. 1. We performed a similar analysis of the relation of log IGI and the log $1/\text{IR}$ (where IR is insulin resistance according to the homeostasis model assessment

index of insulin resistance [HOMA-IR]) derived from the fasting sample. The slope of the relation was -0.52 , i.e. it demonstrated a relation almost identical to that of the WBISI. The Spearman correlation coefficient between the disposition indices calculated with the WBISI and with HOMA-IR was 0.98 .

Statistical analysis

Data are presented as mean \pm SD or as the mean and a 95% CI where appropriate. Parameters that were not normally distributed were log-transformed for analysis. Multiple pairwise comparisons of subjects with NGT and with IGT were performed using ANOVA with post hoc Bonferroni correction for multiple comparisons between pairs. Comparisons of IGT subjects and the lowest tertile of sensitivity of the NGT participants were performed using Student's t test. Adjustment of comparisons for potential confounders was performed using analysis of covariance with main effects for glucose 120 min, age, sex, pubertal status, BMI Z-score, ethnicity and other relevant covariates where appropriate (using the general linear model procedure). A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS 12.0 for Windows.

Results

Anthropometric characteristics of the cohort

A total of 709 obese children and adolescents, 597 with NGT (246 of White European origin, 189 African American and 162 Hispanic) and 112 with IGT (53 of White European origin, 31 African American and 28 Hispanic), participated in this study (Table 1). Among the subjects with NGT, the African American participants were heavier and had a higher BMI and BMI Z-score than their counterparts of White European and Hispanic origin. Among the IGT subjects, Hispanic participants were

Table 1 Anthropometric data of participants

	NGT			IGT		
	White European	African American	Hispanic	White European	African American	Hispanic
No.	246	189	162	53	31	28
M/F	98/148	74/115	79/83	18/35	10/21	8/20
Age (years)	12.8 \pm 3.0	12.9 \pm 2.8	12.6 \pm 3.2	14.3 \pm 3.2	12.9 \pm 2.9	12.3 \pm 2.6 ^c
Height (cm)	157 \pm 14	159 \pm 12 ^a	155 \pm 15	162 \pm 13	161 \pm 14	155 \pm 12
Weight (kg)	89.3 \pm 28.3	96.7 \pm 27.3 ^b	87.7 \pm 28.2	102.8 \pm 33.1	106.5 \pm 31.4	90.9 \pm 29.3
BMI (kg/m ²)	35.2 \pm 7.3	37.4 \pm 7.2 ^c	35.6 \pm 7.3	38.3 \pm 8.5	40.5 \pm 8.9	37.2 \pm 7.4
BMI Z-score	2.40 \pm 0.33	2.51 \pm 0.27 ^d	2.48 \pm 0.37	2.46 \pm 0.36	2.61 \pm 0.35	2.53 \pm 0.35
Prepubertal/pubertal	57/189	38/151	41/121	5/48	6/25	4/24

^a $p=0.008$ for African Americans vs Hispanics

^b $p=0.02$ and $p=0.008$ for African Americans vs White European Americans and Hispanics, respectively

^c $p=0.005$ and $p=0.05$ for African Americans vs White European Americans and Hispanics, respectively

^d $p=0.002$ for African Americans vs White European Americans

^e $p=0.01$ for Hispanics vs White European Americans

slightly younger than other participants, while weight, BMI and BMI Z-score were similar among the three ethnic groups. In the NGT and IGT groups, pubertal status was similar between subjects of the three ethnic groups. Overall, there were more prepubertal children in the NGT group (136 of 597) compared with the IGT group (15 of 112; $p=0.02$, χ^2 test).

After adjusting for age, sex and ethnicity, the weight of the participants with IGT was greater than that of the participants with NGT (100.8 ± 32.0 vs 91.2 ± 28.1 kg, $p=0.001$), as were BMI (38.67 ± 8.39 vs 36.02 ± 7.36 kg/m², $p=0.002$) and BMI Z-score (2.52 ± 0.36 vs 2.46 ± 0.33 , $p=0.004$).

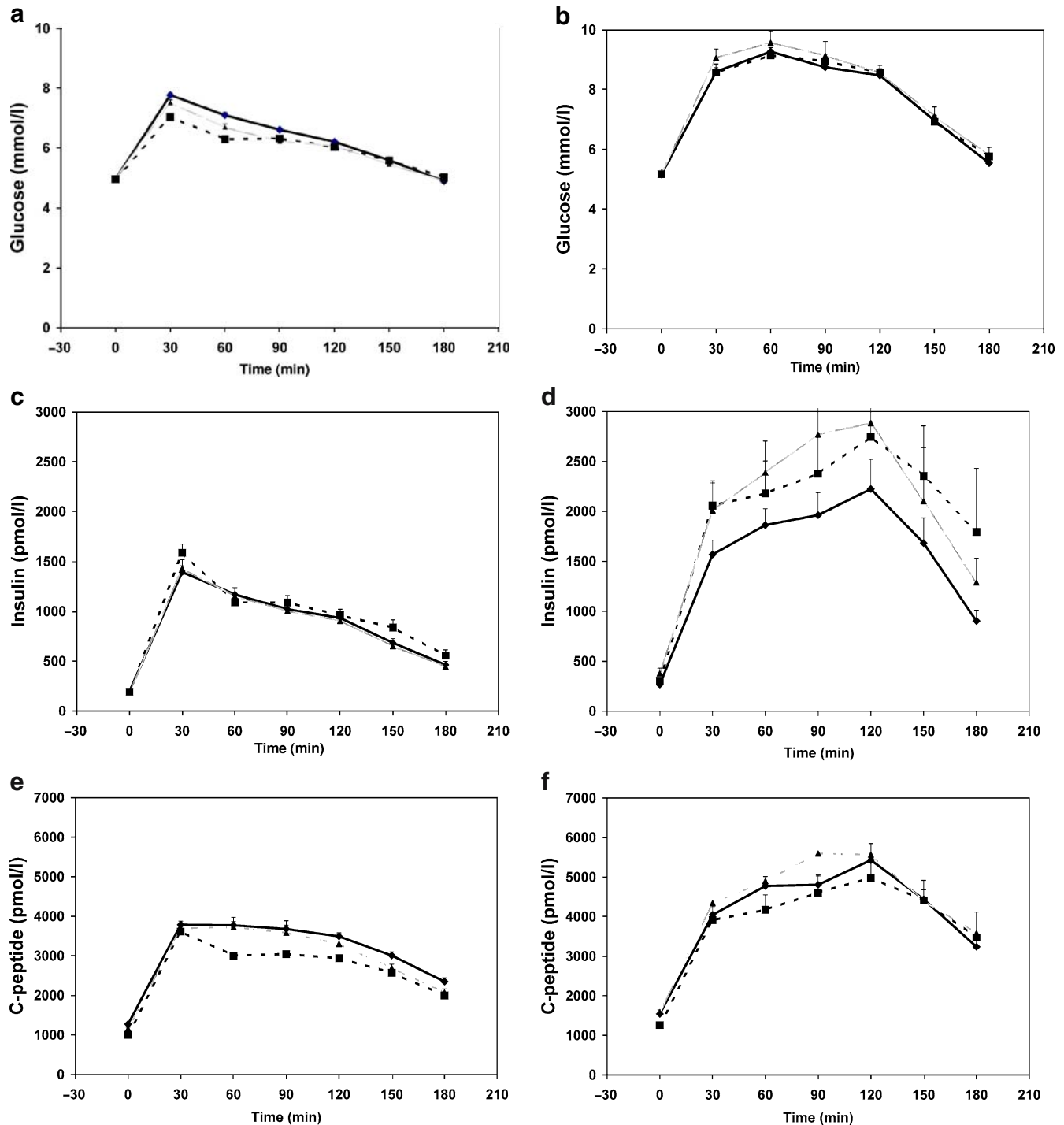


Fig. 2 Glucose (a, b), insulin (c, d) and C-peptide levels (e, f) during the OGTT in obese subjects with NGT (a, b, c) and IGT (d, e, f). White European Americans, *solid black line*; African Americans, *dashed line*; Hispanics, *solid grey line*

Plasma glucose, insulin and C-peptide responses to the OGTT

In subjects with NGT, fasting plasma glucose and insulin levels were similar in all three ethnic groups, whereas fasting C-peptide was significantly lower in African Americans ($1,005 \pm 366$ pmol/l) than in obese participants of White European ($1,274 \pm 660$ pmol/l, $p < 0.001$) and Hispanic ($1,154 \pm 468$ pmol/l, $p = 0.04$) origin (Fig. 2). Following the oral glucose load, plasma glucose levels rose in all three groups, reaching a peak level at 30 min and decreasing gradually thereafter, reaching similar levels at 180 min. After adjusting for sex, age, BMI Z-score and 2-h glucose level, the mean increment in plasma glucose at 30 min was significantly lower in African Americans than in subjects of White European origin ($p < 0.001$). Despite lower plasma glucose levels in African Americans, the adjusted plasma insulin response was similar in all three groups. Adjusted plasma C-peptide responses (AUC for the entire OGTT) were lower in African Americans than in subjects of White European origin ($p < 0.001$ and $p = 0.016$ vs White European and Hispanics, respectively). In subjects with IGT, there were no statistically significant differences among the three ethnic groups in basal and stimulated glucose, insulin and C-peptide levels.

Impact of ethnicity and glucose tolerance status on indices of insulin sensitivity, secretion and clearance

As shown in Table 2, EIS, calculated as HOMA-IR or WBISI, was comparable among the three groups in subjects with NGT, even though African American subjects had a greater BMI Z-score. Despite a similar degree of insulin resistance, after adjusting for age, sex, pubertal status and BMI Z-score, indices of insulin sensitivity were still similar between the three ethnic groups while the EIR was sig-

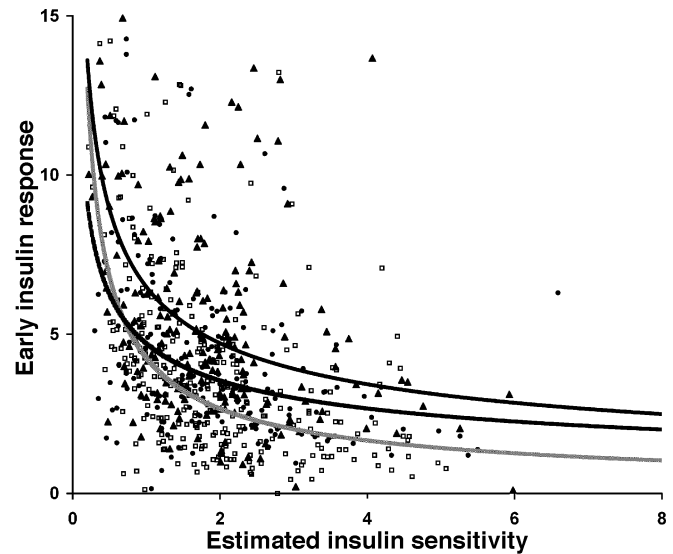


Fig. 3 Relation of estimated insulin sensitivity and the early insulin response in study participants. White European Americans, open squares and dotted line; African Americans, black triangles and black line; Hispanics, black circles and grey line. The disposition index curve, after adjustment for age, sex, pubertal status, BMI Z-score and glucose at 120 min, is shifted to the right for African Americans ($p < 0.001$ for African American vs White European Americans and Hispanics). No significant difference was seen between the curves for White European Americans and Hispanics ($p = 0.59$)

nificantly greater in African Americans than in subjects of White European and Hispanic origin ($p < 0.001$), as was insulin clearance ($p < 0.001$ and $p = 0.003$ vs White European and Hispanics, respectively). In subjects with IGT, indices of EIS were similar among the three ethnic groups. The EIR was greater in African Americans than in subjects of White European origin ($p = 0.02$). Insulin clearance was greater in the latter than in African Americans and Hispanics.

Table 2 OGTT-derived indices in obese subjects with NGT and IGT by ethnicity

	NGT			IGT		
	White European	African Americans	Hispanics	White European	African Americans	Hispanics
Insulin sensitivity indices						
HOMA-IR	7.352±4.95	7.24±4.27	7.18±4.43	10.06±7.55	11.75±7.31	13.96±7.98
WBISI	2.02±1.12	2.02±1.16	2.07±1.12	1.23±0.67	1.07±0.64	0.87±0.67
30-min changes						
ΔGlucose 30–0 (mmol/l)	2.78±1.17	2.06±1.00 ^a	2.56±1.06	3.44±0.94	3.39±1.56	3.78±1.17
ΔInsulin 30–0 (pmol/l)	1170±924	1392±1158	1236±912	1266±942	1752±1236	1596±1158
ΔC-peptide 30–0 (pmol/l)	2511±1319	2610±1633	2543±1321	2443±1475	2654±1417	2807±1693
Insulin secretion indices						
IGI (pmol/l per mmol/l)	467±410	837±768 ^b	563±507	368±239	536±331 ^c	433±271
Insulin clearance index						
Insulin clearance	4.26±1.58	3.50±1.38 ^c	4.14 ±1.56	3.39±1.41 ^d	2.63±1.05	2.60±0.98

^a $p < 0.001$ for African Americans vs White European Americans and Hispanics, $p = 0.04$ for Hispanics vs White European Americans

^b $p < 0.001$ for African Americans vs. White European Americans and Hispanics

^c $p = 0.001$ and $p = 0.003$ for African Americans vs White European Americans and Hispanics, respectively

^d $p = 0.05$ and $p = 0.04$ for White European Americans vs African Americans and Hispanics

^e $p = 0.02$ for African Americans vs White European Americans

Relation of EIS and EIR in the three ethnic groups

As shown in Fig. 3, obese children and adolescents from the three ethnic groups demonstrated a distinct relation of the EIR and the EIS, African Americans demonstrating a clear shift to the right compared with their counterparts of White European and Hispanic origin. Indeed, after adjustment for age, sex, pubertal status, BMI Z-score and 2-h glucose on the OGTT, the disposition index of African Americans was significantly greater ($p<0.001$) than in the other groups, while it was comparable between subjects of White European origin and Hispanics ($p=0.59$).

EIR and insulin clearance by strata of EIS

In order to adjust for the wide variation in insulin sensitivity observed in obese participants with NGT [21], we divided the subjects into tertiles of insulin sensitivity. EIS was similar among the three ethnic groups within each tertile (Table 3, Fig. 4). Fasting C-peptide was lower in African Americans than in subjects of White European origin and Hispanics in tertiles 2 and 3. Despite significantly lower plasma glucose elevations, the increments in both plasma insulin and C-peptide levels in the African American group were of similar magnitude to those seen in White Europeans and Hispanics in each tertile.

EIS was similar between the three ethnic groups within each tertile of the NGT subjects (Fig. 4). Subjects with IGT had insulin sensitivity similar to that of the most resistant subjects with NGT. In subjects with NGT, after adjustment for age, sex, ethnicity, BMI Z-score, 2-h glucose and insulin clearance, EIR was higher in African Americans than in White Europeans ($p<0.001$) at any given tertile of insulin sensitivity, while Hispanics had a higher EIR than subjects of White European origin ($p=0.02$). Importantly, the interaction between sensitivity category and ethnicity was not significant, i.e. the magnitude of difference in the EIR across tertiles of sensitivity was similar across ethnic groups. Subjects with IGT had insulin sensitivity similar to that of the most resistant tertile of the NGT group while EIR was significantly lower ($p<0.001$), indicating a deterioration in beta-cell function leading to IGT.

Insulin clearance decreased with decreasing insulin sensitivity, and in subjects with IGT it was similar to that in insulin-resistant subjects with NGT. After adjusting for age, sex, BMI Z-score and 2-h glucose, at any given tertile of insulin sensitivity the clearance of insulin was lower for African American participants with NGT ($p<0.001$ vs White Europeans and Hispanics). Hispanics had greater clearance than subjects of White European origin ($p=0.002$). Importantly, the magnitude of the difference in insulin clearance was similar for the three ethnic groups across tertiles of insulin sensitivity. The ethnic differences in insulin clearance disappeared in subjects with IGT.

Table 3 Obese subjects with NGT according to tertiles of insulin sensitivity

	Tertile 1 (most sensitive)			Tertile 2			Tertile 3 (most resistant)		
	White European	African American	Hispanic	White European	African American	Hispanic	White European	African American	Hispanic
No.	72	56	58	87	66	50	86	67	54
M/F	29/43	19/37	29/29	34/53	26/40	27/23	35/51	29/38	23/31
Age (years)	11.9±3.2	12.9±3.0	11.6±3.4	13.1±3.2	12.9±2.8	13.23±3.1	13.3±2.4	12.7±2.5	13.2±2.6
Height (cm)	151±15	157±12	150±18	158±13	159±13	156±113	162±11	160±11	159±11
Weight (kg)	79.1±29.2	92.2±28.1 ^a	73.5±24.2	87.8±23.2	96.8±30.0	90.6±25.3	99.9±28.7	100.4±23.4	100.2±28.4
BMI Z-score	2.38±0.32	2.47±0.28	2.36±0.36	2.36±0.33	2.49±0.31	2.51±0.40	2.47±0.33	2.59±0.22 ^f	2.57±0.31
Prepubertal/pubertal	28/44	15/41	20/38	22/65	16/50	11/39	16/70	14/53	13/41
HOMA-IR	3.58±1.15	3.94±1.43	3.83±1.19	6.20±1.49	6.07±1.46	6.01±1.23	11.71±5.88	11.18±4.69	11.85±4.59
Fasting glucose (mmol/l)	4.89±0.39	4.78±0.33	4.89±0.28	4.94±0.39	4.94±0.44	4.94±0.33	5.06±0.39	5.11±0.39	5.11±0.39
Fasting insulin (pmol/l)	96±30	108±36	102±30	168±36	162±36	162±30	312±144	294±120	52±18
Fasting C-peptide (pmol/l)	915±577	749±237	832±341	1161±419	942±239 ^d	1136±326	1667±759	1267±383 ^g	16158±422
ΔGlucose 30–0	2.67±1.17	1.83±1.00 ^b	2.33±1.22	2.78±1.17	1.94±0.94 ^c	2.56±0.94	3.00±1.11	2.39±0.89 ^h	2.67±0.89
ΔInsulin 30–0	576±402	762±498 ^c	684±324	978±504	1068±576	1092±420	1848±1116	2250±1458	1962±1170
ΔC-peptide 30–0	1949±1087	1976±836	2010±1017	2356±1187	2432±1777	2511±1185	3125±1389	3282±1735	3143±1486

^a $p=0.02$ vs White European Americans and $p=0.17$ vs Hispanics

^b $p=0.001$ vs White European Americans and $p=0.047$ vs Hispanics

^c $p=0.03$ vs White European American

^d $p<0.001$ and $p=0.02$ vs White European Americans and Hispanics, respectively

^e $p<0.001$ vs White European Americans and $p=0.004$ vs Hispanics

^f $p=0.002$ vs White European Americans

^g $p<0.001$ vs White European Americans and $p=0.004$ vs Hispanics

^h $p<0.001$ vs White European Americans and $p=0.004$ vs Hispanics

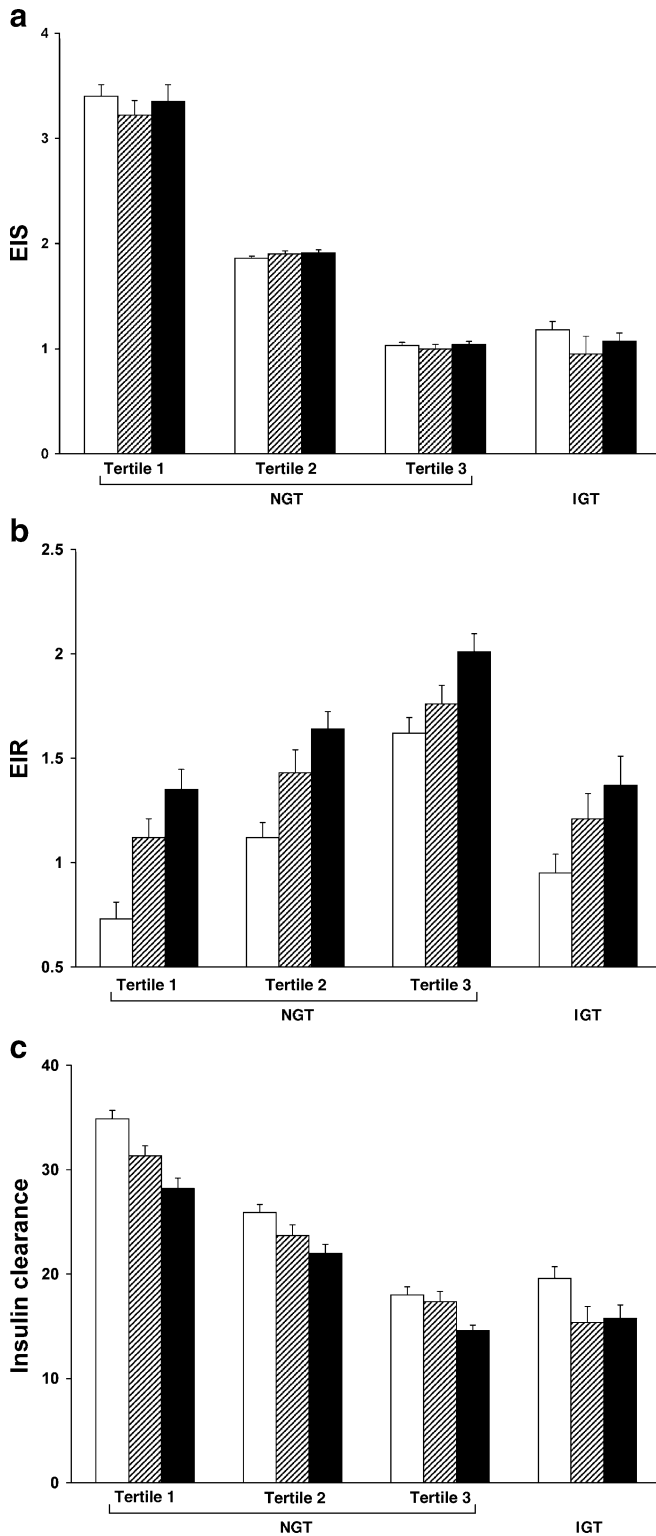


Fig. 4 Adjusted insulin sensitivity (a), secretion (b) and clearance (c) in subjects with NGT stratified by tertiles of insulin sensitivity (tertile 1, most insulin-sensitive; tertile 3, most insulin-resistant) and in subjects with IGT. White European Americans, *white bars*; African Americans, *black bars*; Hispanics, *hatched bar*

Discussion

In this study we examined the EIR to an oral glucose load in a large cohort of non-diabetic obese children and adolescents of three ethnic backgrounds and the relation between the degree of insulin resistance and clearance of insulin. Our main findings are that obese children and adolescents of White European, African American and Hispanic background demonstrate similar mechanisms of adaptation to increasing insulin resistance when glucose tolerance is normal. This adaptation is manifested as an increased EIR alongside a reduction in insulin clearance. Obese children with IGT were as insulin-resistant as subjects with NGT in the lowest tertile of insulin sensitivity yet had a lower insulin response, which was insufficient and could not be compensated for by further reductions in insulin clearance. Obese African American children and adolescents demonstrated a shift to the right of the relation between the EIR and EIS, indicating a seemingly greater disposition index.

In this study we compared ethnic differences in EIRs using parameters of insulin secretion derived from the OGTT. Interestingly, African American subjects had a greater EIR than obese young people of White European origin at any level of insulin sensitivity or glucose tolerance, even after controlling for anthropometric parameters, insulin clearance and glucose tolerance, while Hispanic children displayed a pattern intermediate to White European and African Americans. These observations are reflected by a shift to the right of the relation between the EIR and EIS in African Americans.

Interestingly, this index of insulin secretion correlated only moderately with first-phase secretion data derived from hyperglycaemic clamps. This observation may be explained by the different stimuli (enteral vs parenteral) of glucose in the two techniques and highlights the potentially greater role of incretin [22] and autonomic stimulation [23] of the beta cell in response to an oral glucose challenge. It remains to be determined whether obese African American children differ in their incretin response [24] to an oral glucose challenge or in their autonomic tone [25, 26] compared with obese children of White European and Hispanic origin.

Several studies have suggested that obese African American children and adolescents are more insulin-resistant than their White European and Hispanic peers. In our large cohort, EIS, whether assessed by the WBISI or HOMA-IR, was similar among subjects of the three ethnic groups with the same glucose tolerance, despite the fact that African American young people with NGT were more obese. In agreement with this observation, other groups [27] have shown, using euglycaemic-hyperinsulinaemic clamps, that African American obese children have similar peripheral insulin sensitivity to their White European counterparts. It seems that the degree of obesity in these young people masks the ethnic differences seen at normal weight or in less severely obese young subjects.

Our analytical approach enabled us to examine the separate adaptation mechanisms used by obese young people in the face of decreasing insulin sensitivity and changing glucose tolerance. The findings show a similar pattern and magnitude of increase in the EIR coupled to a decrease in insulin clearance in obese children with NGT with lower insulin sensitivity, regardless of ethnic background. Although the changes in EIR across tertiles of insulin sensitivity were of similar magnitude in the three ethnic groups studied, African Americans had a greater absolute EIR than their counterparts of White European and Hispanic origin. Similarly, insulin clearance was lower in African Americans for a given insulin sensitivity tertile. Our finding that insulin clearance is lower in African Americans than in subjects of White European origin, thus contributing to higher peripheral insulin concentrations, is in agreement with several other studies [28, 29]. The finding of a similar pattern of EIR adaptation to increasing insulin resistance across ethnic groups is at odds with a previous study [30], which demonstrated failure of such compensation in obese African American young people. In contrast, other groups [31] reported similar findings to ours in adults. In addition, others have reported a similar pattern of the acute insulin response in healthy children of the three ethnic groups using an IVGTT [32]. A potential explanation for these discrepancies may be the use of the hyperglycaemic clamp and not the OGTT by some groups and limited sample sizes in several studies.

Our results show that African American children and adolescents with NGT had a lower glucose increment at 30 min of the OGTT while having similar increments in insulin. The systemic glucose level at this time point is of critical importance, as it represents the glucose stimulus for the EIR. This finding may be explained by several mechanisms, such as differences in glucose absorption kinetics, a greater proportion of the glucose load deposited in the liver and splanchnic bed and not reaching the systemic circulation [33], or faster suppression of hepatic glucose production of the fasting state, resulting in a lower early glucose excursion. We could not look into these mechanisms using our data, but they deserve further investigation.

The greater EIRs observed in African American and Hispanic children and adolescents at any given level of glucose tolerance or insulin sensitivity, in the setting of a cross-sectional analysis, can be interpreted in several ways. One possibility is that the beta cells of obese African American children and adolescents differ in sensitivity to the glucose stimulus or the insulin-resistant milieu, and that this manifests as an exaggerated response compared with White European and Hispanic subjects. Indeed, African Americans had lower early glucose excursions during the OGTT yet manifested greater secretion responses. Gower et al. [34] used C-peptide modelling of IVGTTs in children to demonstrate that first-phase beta-cell sensitivity to glucose was greater in African Americans than in subjects of White European origin. Another potential mechanism is that the relation of insulin sensitivity and secretion in African Americans lies on a different feedback curve that is shifted

more to the right than those of their counterparts of White European and Hispanic origin. Indeed, the OGTT-derived disposition index of African Americans was higher whether the cohort was divided by glucose tolerance or by tertiles of insulin sensitivity and, in the IGT group, African Americans had a greater absolute insulin response in the face of comparable insulin sensitivity and clearance (Fig. 4) that was not sufficient to maintain NGT. As the IGI used in this study reflects the early (or first-phase) insulin response, possible ethnic differences in the second phase of insulin secretion may explain the discrepancy between the seemingly improved disposition index of African Americans and their greater likelihood of developing type 2 diabetes.

The findings shown here reflect the similarity of the overall mechanisms of adaptation for increasing insulin resistance across ethnic groups in obese young people. When insulin clearance reaches a trough, as seen in most insulin-resistant subjects with NGT and in subjects with IGT, the beta cell can no longer compensate by increased secretion, and thus fails. It should be noted that the African Americans and Hispanics with NGT had a greater absolute EIR and develop IGT while having a greater early response than subjects of White European origin. This cannot be explained by differences in peripheral insulin sensitivity. These observations imply that the demand on the beta cell to maintain glucose tolerance is greater in obese children and adolescents of ethnic minorities, specifically of African American background, and may also partially explain the greater prevalence of type 2 diabetes in obese young people from these two ethnic groups.

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