Insulin Resistance and Associated Compensatory Responses in African-American and Hispanic Children

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OBJECTIVE — The objective of this study was to compare insulin resistance relative to body fat and the associated compensatory responses in 57 healthy children living in Los Angeles, California (14 Caucasians, 15 African-Americans, and 28 Hispanics).

RESEARCH DESIGN AND METHODS — Insulin sensitivity and acute insulin response were determined by intravenous glucose tolerance test. Insulin secretion, hepatic insulin extraction, and insulin clearance were estimated by C-peptide and insulin modeling.

RESULTS — Insulin sensitivity was significantly lower in Hispanics and African-Americans compared with Caucasian children, and acute insulin response was significantly higher in African-American children. No ethnic differences were noted in the first-phase secretion, but second-phase insulin secretion was significantly higher in Hispanic children than in African-American children (200 ± 53 vs. 289 ± 41 nmol/min; $P = 0.03$). The greater acute insulin response in African-Americans, despite lower secretion, was explained by a lower hepatic insulin extraction in African-Americans compared with Hispanics (36.6 ± 2.9 vs. 47.3 ± 2.2%; $P = 0.0006$).

CONCLUSIONS — In conclusion, Hispanic and African-American children are more insulin resistant than Caucasian children, but the associated compensatory responses are different across ethnic groups.

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Type 2 diabetes is a significant health issue in overweight African-American and Hispanic adults (1). In addition, type 2 diabetes has recently emerged as a significant health issue in overweight adolescents (2), especially overweight African-American, Hispanic-American, and Native American adolescents (2). The pathogenesis of type 2 diabetes has not yet been examined in children but is likely to have some characteristics similar to those in adults. In adults, progression to type 2 diabetes is linked to the effect of increased adiposity, possibly visceral adiposity, on insulin resistance (3) and the subsequent inability of the β-cell to adequately compensate for insulin resistance (4). In children, this process is likely to be similar but exacerbated by transient insulin resistance that occurs during the middle of puberty (5,6) and may further contribute to β-cell demand. There is no clear explanation, however, of why certain ethnic groups should be at higher risk for type 2 diabetes. Detailed studies of the underlying physiological factors contributing to type 2 diabetes (i.e., body fat, insulin sensitivity, insulin secretion, insulin clearance, β-cell compensation) are helpful in attempting to reveal why certain subgroups of the population may be at increased risk. Previous studies of this nature have focused on African-Americans, and there is a distinct paucity of information in the Hispanic population. Studies in young children are of increased significance because they allow examination of potentially underlying differences across subgroups of the population to be performed in the absence of potentially confounding factors such as smoking, alcohol, aging, and menopausal status.

Data from the Bogalusa Heart study (7,8) was the first to show evidence of increased insulin resistance in African-American children compared with Caucasian children based on measures of fasting insulin. Subsequently, other studies using more direct measures have demonstrated lower insulin sensitivity and greater acute insulin response in African-American children (9,10), and these differences are independent of body fat, visceral fat, dietary factors, and physical activity (11). Previous studies in African-American children compared with Caucasian children have suggested that the lower insulin sensitivity is associated with a higher-than-expected acute insulin response to glucose (9) and that the higher insulin levels in African-Americans are partly attributable to increased secretion and decreased hepatic extraction (12).

Studies of obesity, insulin resistance, insulin secretion, and the β-cell response in the Hispanic population are limited. Compared with non-Hispanic whites, Hispanics are reported to have greater fasting and postchallenge insulin level (13) and greater insulin resistance (14,15). However, some previous studies show no difference in insulin action or secretion between Hispanic and non-Hispanic whites, after adjusting for BMI and waist-to-hip ratio, suggesting that obesity accounted for this ethnic difference (13). Because only crude anthropometric indexes were used in this adjustment, further

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Abbreviations: FSIGTT, frequently sampled intravenous glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial on p. 2350.

studies using more detailed body measures are needed. One prior study in third-grade children in Corpus Christi, Texas (16), showed that Hispanic children had significantly higher levels of fasting insulin than non-Hispanic white children. However, it was not clear whether this difference remained significant after accounting for differences in obesity, and the outcome measures were limited to fasting insulin and crude anthropometric indexes.

Therefore, we undertook the current study to examine two major hypotheses. First, by combining detailed measures of insulin action and secretion with detailed measures of body composition, we hypothesized that African-American and Hispanic children would be more insulin resistant than non-Hispanic white children, even after adjusting for differences in body fat content. Second, we hypothesized that the compensation to this insulin resistance, in terms of acute insulin response, insulin secretion, hepatic insulin extraction, and insulin clearance, would be similar in African-American and Hispanic children.

RESEARCH DESIGN AND METHODS

Subjects

Children were recruited by newspaper and radio advertisements, presentations at local schools, mailings to University and Hospital employees, and word of mouth. None of the children were taking medications known to affect body composition (e.g., methylphenidate, growth hormone), had syndromes or diseases known to affect body composition or fat distribution (e.g., Cushing's disease, Down's syndrome, type 1 diabetes), or had any major illness since birth. Ethnicity was determined by self-report and was based on all four grandparents being of the same ethnic group as the child in the study. The Institutional Review Board of the University of Southern California approved this study. Both parents of each child provided informed consent, and each child signed a child assent form before testing commenced. The data presented are all from newly recruited subjects that have not been part of any previous publication from our research group.

Protocol

Children were admitted to the General Clinical Research Center (GCRC) in the late afternoon for an overnight visit. In the afternoon, a detailed medical history was obtained, a physical examination was performed, and total body composition was assessed by dual-energy X-ray absorptiometry. The children were served dinner and an evening snack; all food was consumed before 8:00 P.M. Consumption of only water and noncaloric, noncaffeinated beverages was permitted between 8:00 P.M. and the time of testing the following morning, when intravenous lines were inserted and a frequently sampled intravenous glucose tolerance test (FSIGTT) test was performed. Testing was completed by ~12:00 P.M.

Tanner staging

Tanner stage was determined by a physician and was based on breast stage and pubic hair development in girls and on genitalia development in boys. Because insulin sensitivity falls between Tanner stages I and III and then recovers by Tanner stage V, for the purpose of this analysis, only children at Tanner stages I–III were included, allowing for linear adjustment of the effects of Tanner stage development on insulin sensitivity.

Tolbutamide-modified FSIGTT

Before initiation of FSIGTT, fasting venous blood samples were collected for determination of fasting levels of glucose, insulin, C-peptide, and free fatty acids. Insulin sensitivity, acute insulin response, disposition index (product of insulin sensitivity and acute insulin response), glucose effectiveness, and glucose effectiveness at zero insulin were determined by FSIGTT in the early morning after an overnight fast, as previously reported (9). Sera were analyzed in duplicate for glucose using a Yellow Springs Instrument 2700 Analyzer (Yellow Springs Instrument, Yellow Springs, OH) and a glucose oxidase kit was used to measure insulin (radioimmunoassay; Diagnostic Products, Los Angeles, CA), C-peptide (double antibody radioimmunoassay; Diagnostic Products), and free fatty acids (only fasting samples; Wako Diagnostics, Richmond, VA). Values for glucose and insulin were entered into the MINMOD computer program (version 3.0, Richard N. Bergman) for determination of insulin sensitivity, acute insulin response, glucose effectiveness, and disposition index.

Prehepatic insulin secretion rates were calculated using the extended Combined Model method (17). The extended Combined Model describes the relationship between plasma insulin and C-peptide to derive estimates of prehepatic insulin secretion, fractional hepatic insulin extraction, and descriptive kinetic parameters for both insulin and C-peptide. The model-predicted insulin secretion rates are per-unit C-peptide distribution volume and were corrected to mass per time by assuming a 6.02% body weight C-peptide distribution space (18). All curve fitting was performed using MLAB software (Civilized Software, Bethesda, MD) with a weighted nonlinear least-squares approach. Weights for parameter identifications were estimated using the internal weighting function of MLAB. This function uses a five-point moving average to smooth and estimate the SD of the data. Weights are then determined as the inverse variance.

Total body fat

Whole-body composition (fat mass and fat-free mass) was measured by dual-energy X-ray absorptiometry using a Hologic QDR 4500W densitometer (Hologic, Bedford, MA).

Data analysis

Variables that were not normally distributed were log-transformed before analysis (fasting insulin, insulin sensitivity, acute insulin response, insulin secretion, and disposition indexes). For ease of interpretation, data are presented in the measured untransformed scale. General linear models were used to examine the effects of ethnicity. The dependent variables examined were insulin sensitivity, acute insulin response, fasting insulin, fasting C-peptide, disposition index, first- and second-phase insulin secretion, total insulin secretion, hepatic insulin extraction, and fractional disappearance rate of insulin. The covariates for all models were Tanner stage and total fat mass. Tanner stage was included as a covariate because insulin sensitivity is known to decrease and insulin secretion is known to increase between Tanner stages I and III (5); children beyond Tanner stage III were not included in the current analysis. Body fat was included as a covariate because fat mass is the most significant contributor to

Table 1—*Physical characteristics of children in three ethnic groups*

	Hispanics (n = 28)	African-Americans (n = 15)	Caucasians (n = 14)
Age (years)	10.0 ± 1.9	10.1 ± 1.5	10.8 ± 1.9
Tanner stage	1.4 ± 0.7	1.7 ± 0.9	1.6 ± 0.8
Weight (kg)	49.2 ± 18.0	44.4 ± 12.5	44.4 ± 16.1
BMI (kg/m^2)	24.0 ± 5.8	21.5 ± 4.7	20.7 ± 5.0
Fat-free mass (kg)	30.1 ± 8.9	30.3 ± 6.3	29.8 ± 8.3
Fat mass (kg)	17.0 ± 9.4	12.0 ± 7.3	12.5 ± 8.2
Percentage of body fat	32.7 ± 8.0	25.2 ± 10.0	25.7 ± 10.6
Fasting glucose (mg/dl)	91.4 ± 4.5	90.0 ± 5.2	91.8 ± 7.0

Data are unadjusted data ± SD.

insulin sensitivity in children (9), and our hypothesis was to examine whether ethnic differences were independent of fat mass. The results were largely identical when fat-free mass was also included in the model to account for relative fatness. Sex was not included because this factor was not significant in any of the models presented. The model for acute insulin response also included insulin sensitivity as a covariate. In all models, the overall statistical effect of ethnicity was examined by the P value of ethnicity when included in the model as a fixed factor. Differences across the various ethnic groups were examined using least-square means. All analyses were conducted using SPSS statistical software (version 9.0; SPSS, Chicago, IL), and data are presented as means ± SD. This study was powered to detect lower insulin sensitivity in Hispanic and African-American children (relative to Caucasian children), similar to what we have shown previously when comparing African-American and Caucasian children. Assuming a lower insulin sensitivity of 2.2×10^{-4} min^{-1}/(μIU/ml), with a within-group SD of 2.0×10^{-4} min^{-1}/(μIU/ml), provides 80% power at $\alpha = 0.05$ with a sample size of 14 per group for an independent Student's t test (PS power and sample size calculations).

RESULTS — The mean physical characteristics of the three ethnic groups are shown in Table 1. No significant difference in age or Tanner stage was shown across the three groups. Hispanic children tended to be heavier, with greater fat mass (effect of ethnicity was not significant for these variables), and percentage of body fat was significantly higher in the Hispanic children ($P = 0.016$) despite no difference in lean body mass.

There was no difference in fasting glucose levels across ethnic groups. The adjusted values for the key variables associated with insulin action and secretion are shown in Table 2, and the insulin and C-peptide values during the FSIGTT are shown in Fig. 1. For insulin sensitivity, there was an overall effect of ethnicity ($P = 0.04$) due to the lower values in Hispanic children ($P = 0.05$) and African-American children ($P = 0.02$) compared with Caucasian children. For fasting insulin, there was an overall effect of ethnicity ($P = 0.005$) due to lower fasting insulin in Hispanic children compared with Caucasian children ($P = 0.04$) and African-

Table 2—*Least-square mean differences in insulin action and secretion parameters for three ethnic groups*

	Hispanic (n = 28)	African-Americans (n = 15)	Caucasians (n = 14)	Significant effects
Insulin sensitivity [$\times 10^{-4}$ min^{-1}/(μIU/ml)]	4.5 ± 0.5	4.1 ± 0.6	6.3 ± 0.6	H versus C: $P = 0.05$; AA versus C: $P = 0.02$
Fasting insulin (μIU/ml)	7.4 ± 1.0	10.4 ± 1.43	9.1 ± 1.4	H versus AA: $P = 0.001$; H versus C: $P = 0.04$
Fasting free fatty acids (mmol)	0.39 ± 0.02	0.41 ± 0.02	0.36 ± 0.02	None
AIR (μIU/ml)	938 ± 85	1,210 ± 116	747 ± 122	AA versus H: $P = 0.06$; AA versus C: $P = 0.003$
DI from AIR (min^{-1})	0.35 ± 0.05	0.45 ± 0.07	0.29 ± 0.07	None
Glucose effectiveness (% per min)	0.025 ± 0.001	0.027 ± 0.002	0.027 ± 0.002	None
GEZI (% per min)	0.023 ± 0.001	0.023 ± 0.002	0.023 ± 0.001	None
First-phase insulin secretion (nmol/min)	153 ± 18	123 ± 24	112 ± 25	None
Second-phase insulin secretion (nmol/min)	289 ± 41	200 ± 53	206 ± 56	AA versus H: $P = 0.03$
Total insulin secretion (adj for insulin sensitivity)	436 ± 53	302 ± 71	354 ± 76	AA versus C: $P = 0.08$; AA versus H: $P = 0.03$
DI from secretion (min^{-1})	34.3 ± 3.0	23.1 ± 3.9	34.7 ± 4.1	AA versus C: $P = 0.04$; AA versus H: $P = 0.03$
Hepatic insulin extraction (%)	47.3 ± 2.2	36.6 ± 2.9	49.1 ± 3.0	AA versus H: $P = 0.006$ AA versus C: $P = 0.004$
Fractional disappearance of insulin (% per min)	26.0 ± 1.1	20.9 ± 1.5	24.2 ± 1.5	AA versus H: $P = 0.009$

Data are least-square means ± standard error after adjusting for Tanner stage and total fat mass; the model for AIR also adjusted for insulin sensitivity; analysis was conducted on log-transformed data, but means are presented for non–log-transformed data for ease of interpretation. AIR, acute insulin response; DI, disposition index; GEZI, glucose effectiveness at zero insulin; H, Hispanic; C, Caucasian; AA, African-American.

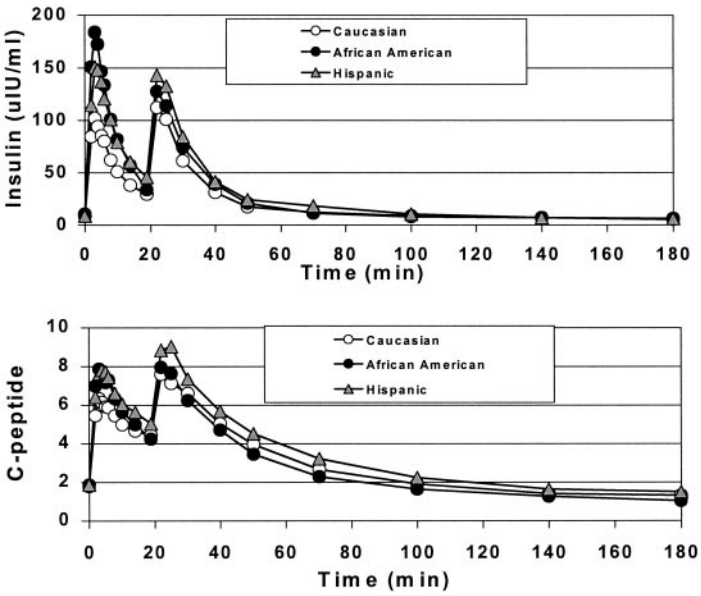

Figure 1—*Insulin and C-peptide levels during the FSIGTT. Insulin and C-peptide concentrations for 3 h after administration of glucose at time 0 and tolbutamide at 20 min.*

American children ($P = 0.001$). Insulin levels immediately after administration of glucose were highest in African-American children, followed by Hispanic and Caucasian children (Fig. 1). This pattern was mirrored in acute insulin response after adjusting for insulin sensitivity, where there was an overall effect of ethnicity ($P = 0.01$) due to the higher values in African-American children compared with Caucasian children ($P = 0.003$) and Hispanic children ($P = 0.06$). The higher acute insulin response in Hispanic children compared with Caucasian children did not reach statistical significance. The disposition index (product of insulin sensitivity and acute insulin response) was not significantly different across ethnic groups but was higher in African-American children and lower in Caucasian children.

There were no significant effects of ethnicity on first-phase insulin secretion, although the values tended to be higher in Hispanics and African-Americans compared with Caucasians. This trend is evident from the higher C-peptide levels in these two ethnic groups immediately after administration of glucose (Fig. 1). Second-phase insulin secretion was significantly higher in Hispanic children compared with African-American children ($P = 0.03$); this effect is evident from the higher C-peptide levels in Hispanics during the FSIGTT (Fig. 1). Total insulin secretion, adjusted for insulin sensitivity, and disposition index, calculated as the product of insulin sensitivity and insulin secretion over the 180 min, were both significantly higher in Hispanics than in African-Americans (Table 2). The greater acute insulin response in African-Americans despite lower insulin secretion was explained by a lower hepatic insulin extraction in African-Americans than in both Hispanics ($P = 0.0006$) and Caucasians ($P = 0.0004$). The overall fractional disappearance rate of insulin was significantly higher in Hispanics than in African-Americans ($P = 0.009$).

Fasting free fatty acid levels were not significantly different across ethnic groups before or after adjusting for differences in body fat content. In Caucasian and Hispanic children, there was no significant relationships between free fatty acid levels and insulin secretion, extraction, or sensitivity before or after controlling for body fat. However, in African-American children, there were significant relationships between fasting free fatty acid levels and second-phase insulin secretion (partial $r = 0.6$; $P = 0.01$ after controlling for body fat) and between fasting free fatty acid levels and insulin sensitivity (partial $r = -0.65$; $P = 0.01$ after controlling for body fat).

CONCLUSIONS — In the current study, we hypothesized that African-American and Hispanic children would be more insulin resistant than Caucasian children, even after adjusting for differences in body fat. We also hypothesized that the compensation for this insulin resistance, in terms of acute insulin response, insulin secretion, hepatic insulin extraction, and insulin clearance, would be similar in African-American and Hispanic children. Our major findings are as follows:

1. Our data support several previous studies showing that African-Americans have lower insulin sensitivity than Caucasians, independent of adiposity, and that African-Americans compensate with a greater-than-expected acute insulin response.
2. We extend these findings to confirm that Hispanic children are also more insulin resistant than Caucasian children, to an equal degree than African-American children. Similarly, this difference in insulin resistance is independent of adiposity.
3. Contrary to our hypothesis, these data support the finding that the compensatory response to the same degree of insulin resistance may be different in Hispanic children than in African-American children. African-American children compensated with a higher acute insulin response to glucose, and this effect may be due, in part, to a reduction in hepatic insulin extraction, which spares the need to increase insulin secretion. Hispanic children, on the other hand, compensated with greater insulin secretion.

Only a few studies have previously examined aspects of insulin action and secretion relative to adiposity in multiple ethnic groups. One previous study (19) assessed insulin action using the hyperglycemic clamp in healthy (glucose tolerant), nonobese young adults including Asian-Americans ($n = 18$), African-Americans ($n = 9$), Caucasians ($n = 34$), and Mexican-Americans ($n = 16$). There was no ethnic difference in fasting insulin, but Asian-Americans, African-Americans, and Mexican-Americans were more insulin resistant than Caucasians. Second-phase insulin response was significantly higher in the three ethnic groups than in the Caucasians. This difference, however, was not apparent after controlling for insulin sensitivity, suggesting adequate β-cell compensation in all three ethnic groups. However, second-phase insulin

response was determined by the sum of insulin levels between 130 and 180 min, a crude index of insulin secretion, and no indicators of hepatic insulin extraction were included. Our results are generally consistent with these findings, except that we did not detect significantly higher second-phase insulin secretion in the African-American group. However, we did observe significantly higher circulating insulin levels in the early phase of the response (as indicated by the higher acute insulin response), and this is consistent with our previous report in an independent sample of children (9) as well as with previous studies in adults (20). The higher acute insulin response in African-Americans compared with Hispanics at the same degree of insulin resistance suggests that this may be a specific response to insulin resistance in African-Americans.

Only a few previous studies have compared insulin action and secretion in Hispanics and Caucasians. Haffner et al. (13) compared 10 nonobese, normoglycemic Mexican-American adults with age-, sex-, and BMI-matched Caucasians. This study showed lower insulin sensitivity, higher first-phase insulin secretion, and decreased insulin clearance in Mexican-Americans. In the Insulin Resistance Atherosclerosis Study (IRAS) study (a large, multisite study of insulin resistance and atherosclerosis in adults), it was also shown that Hispanics were more insulin resistant than Caucasians, but this difference did not persist after controlling for BMI and waist-to-hip ratio (13). Few studies have assessed insulin action and secretion in Hispanics and have also incorporated detailed measures of body composition. The current study is the first to show that greater insulin resistance in Hispanics is not explained by differences in body fat content.

In response to the same degree of insulin resistance, we observed marked differences between Hispanic and African-American children in several important parameters associated with insulin action and secretion. Hispanic children had a higher first-phase insulin secretion (this did not reach statistical significance) and a statistically significant higher second-phase insulin secretion, whereas African-American children had similar insulin secretion rates to Caucasians but higher acute insulin response, higher fasting and postchallenge insulin levels, and lower hepatic extraction of insulin. In a larger sample, we have previously shown (12) that the higher acute insulin response to glucose in African-American children compared with Caucasian children is due, in part, to both increased first-phase secretion and lower hepatic insulin extraction. The current study partly supports that finding, at least in terms of the lower hepatic insulin extraction (Table 2). Animal studies (22) have also provided evidence that change in hepatic insulin extraction may play an early role in the response to insulin resistance. A reduction in the amount of insulin extracted by the liver provides an alternative compensatory response to insulin sensitivity that raises peripheral insulin levels without a need to increase insulin secretion. This response may be a mechanism to conserve β-cell function and seems specific to African-Americans and not Hispanics.

Insulin secretion adjusted for insulin sensitivity was significantly lower in African-American children than in to Hispanic children and tended to be lower in African-American children than in Caucasian children (Table 2). Based on assessment of acute insulin response without assessment of insulin secretion, we had previously concluded that the greater acute insulin response in African-Americans was due to oversecretion of insulin by β-cells and that such a response could increase the risk of type 2 diabetes because of the potential for β-cell exhaustion (9). However, the new data from the current study, which combined measures of insulin sensitivity, acute insulin response to glucose, and insulin secretion, seem to suggest the opposite. In fact, our collective interpretation of all data suggests that in African-Americans, there may be a conservation of the need to increase insulin secretion in response to lower insulin sensitivity by the adaptive reduction of hepatic insulin extraction. This modification provides a means to increase peripheral insulin levels without the need to increase secretion. Therefore, in this situation, acute insulin response may not be indicative of insulin secretion. On the other hand, in Hispanic children, insulin secretion is increased to maintain low insulin sensitivity, and in this situation, it is possible that the requirement to increase insulin secretion to maintain the low level of insulin sensitivity may eventually be a contributing factor to β-cell exhaustion and eventual β-cell failure.

The disposition index, usually calculated as the product of insulin sensitivity and insulin secretion, has been proposed as a measure of the overall compensatory response of β-cells to insulin resistance (23). Within a group of subjects, a higher disposition index represents overcompensation (high insulin secretion relative to the degree of insulin resistance), whereas lower levels represent an inability of the pancreas to secrete enough insulin at that level of insulin resistance. In the current study, we calculated the disposition index based on the product of insulin sensitivity and either acute insulin response or insulin secretion rates derived from C-peptide modeling. We have previously shown (11) that disposition index based on acute insulin response is significantly higher in African-American children than in Caucasian children, but we did not detect any significant ethnic differences in the current study (Table 2), although the values tended to be higher in African-Americans than in Caucasians and marginally higher in Hispanics than in Caucasians. These differences did not reach statistical significance because of the greater variances in this variable compared with others that were investigated in this study (see Table 2). Using the values shown in Table 2, we estimate that a sample of 45 subjects would be required to detect a significant difference in disposition index between Caucasians and African-Americans and that a sample of 100 subjects would be required for the comparison of Hispanic and African-American children. Calculation of the disposition index using secretion rates, however, resulted in a much clearer pattern of ethnic differences, with similar values in Caucasians and Hispanics and significantly lower values in African-Americans (Table 2). Therefore, it is important to recognize that different calculations of disposition index may lead to different interpretations. In the current study, the preserved disposition index in the Hispanic children is likely due to β-cell compensation, whereas the nonsignificant but higher disposition index in African-American children (calculated from the acute insulin response to glucose) is likely explained by decreased hepatic insulin extraction rather than β-cell compensation.

Our results also provide some evidence of ethnic differences in the relationships between free fatty acids and insulin

secretion and insulin sensitivity, showing significant relationships in African-Americans but no significant relationships in Caucasians or Hispanics. A previous study in adolescents (24) has shown lower fasting free fatty acids in African-Americans, probably explained by higher insulin levels, but this is not a consistent finding (values in the current study tended to be nonsignificantly higher in both African-American and Hispanic children compared with Caucasian children). We have also previously shown (25) that elevated insulin levels in response to glucose contribute to lower postchallenge free fatty acids in African-American children and that this effect may contribute to the lower triglyceride levels seen in African-Americans. However, we are not aware of other studies that have examined the relationships between free fatty acid levels and insulin action and secretion. More detailed studies incorporating postchallenge free fatty acid levels are warranted, because these may be more meaningful than fasting levels.

Our studies have focused on examination of insulin resistance and adiposity in the pediatric population to address risk factors for development of type 2 diabetes during adolescence. Studies in the adolescent population are important to establish whether the pathophysiology and natural history for the development of type 2 diabetes is the same as in adults. However, studies in children are also useful for examining ethnic differences across the population, because any ethnic differences evident early in life may be representative of underlying physiological differences. Also, results are easier to interpret, especially in prepubertal children, because they are less likely to be confounded by factors that may exist in adults, such as smoking, menstrual cycle, alcohol intake, and glucose intolerance.

Our findings also have several important implications relating to treatment and prevention of type 2 diabetes across different ethnic groups at increased risk for the disease. Intervention studies are needed to examine the influence of various potential factors (diet, physical activity, weight loss, pharmacotherapy) on insulin resistance and body fat across different ethnic groups. In addition, these interventions should be examined for their effects not only on insulin response but also on associated compensatory factors such as insulin secretion and insulin extraction. Because the compensatory response to insulin resistance is different across ethnic groups, it is likely that different treatments and interventions may have varying effects in different ethnic groups. Further studies are needed to examine these ethnic differences in more detail so that specific treatments and interventions can be tailored toward specific subgroups of the population at higher risk for type 2 diabetes.

Several limitations of our study should be noted. First, we did not assess glucose tolerance in the children enrolled in our study. It is possible that the insulin sensitivity and compensatory responses we observed could be different in glucose-tolerant versus glucose-intolerant children, which may explain some of the ethnic differences. Therefore, future studies should focus on examining ethnic differences in glucose-tolerant and glucose-intolerant children. Second, the Combined Model method has not been specifically validated in children. However, we are not aware of any age or maturation factors that would influence insulin or C-peptide kinetics; therefore, we have no reason to believe that the models would not be valid in these groups. Third, it is possible that there may be ethnicity-related differences in β-cell sensitivity to tolbutamide, which could explain some of our findings. We are unaware of any data that have examined β-cell sensitivity to tolbutamide across ethnic groups. Future studies may avoid this concern by switching to the insulin-modified intravenous glucose tolerance test. Finally, we have not been able to examine associations between insulin sensitivity and indexes of β-cell function because of multicolinearity issues (the parameter estimates are derived from similar data and are therefore interdependent).

In summary, our data suggest that African-American and Hispanic children are more insulin resistant than Caucasian children, and this difference is independent of body fat content. However, this study also shows that the compensatory response to the same degree of insulin resistance is different in African-American children than in Hispanic children. African-American children compensated with a higher acute insulin response to glucose, which is achieved by, or results from, a lower hepatic insulin extraction that spares the need of β-cells to increase insulin secretion. Hispanic children compensated to the same degree of insulin resistance with a higher second-phase insulin secretion. These differences suggest that the underlying disease pathology may vary in subgroups of the population at increased risk and may have important implications for developing optimal strategies for the treatment and prevention of type 2 diabetes across subgroups of the population at greater risk.

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