Evaluation of the Insulin Resistance Syndrome in 5- to 10-Year-Old Overweight/Obese African-American Children

Deborah Young-Hyman, phd[1]
David G. Schlundt, phd[2]
Leanna Herman, ma[1]

Francesco De Luca, md[1]
Debra Counts, md[1]

OBJECTIVE — To characterize the insulin sensitivity of overweight and obese 5- to 10-year-old (Tanner stage 1–3) African-American children screened for participation in a diabetes prevention study and to identify the association of insulin sensitivity with obesity, hyperlipidemia, and hypertension.

RESEARCH DESIGN AND METHODS — Measures of insulin resistance (homeostasis model assessment) and insulin sensitivity (Matsuda and DeFronzo's whole-body insulin sensitivity) were calculated from a 2-h oral glucose tolerance test in 137 African-American children recruited into a diabetes prevention study. Measures of lipids (LDL, HDL, total cholesterol, and triglycerides), blood pressure, and body composition were obtained for a subset of the children.

RESULTS — In response to a glucose challenge, girls and older and heavier children produced significantly more insulin. As BMI increased, there was a statistically significant decrease in insulin sensitivity, particularly in girls. Insulin sensitivity was inversely correlated with increases in blood pressure, triglycerides, subcutaneous fat, the percentage of total body fat, and Tanner stage, but it was not correlated with LDL and HDL.

CONCLUSIONS — Reduced insulin sensitivity and the cluster of risk factors known as the insulin resistance syndrome (IRS) are already apparent in these overweight African-American children. Young African-American girls, in particular, already show evidence of hyperinsulinemia in response to a glucose load, suggesting that the early stages of metabolic decompensation that lead to type 2 diabetes are already occurring. Monitoring of those risk factors known to be part of IRS should become part of routine medical care for overweight or obese African-American children.

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T he prevalence of overweight/obesity is increasing in children, as is the diagnosis of type 2 diabetes (1–3). Obesity and insulin resistance are known risk factors for the development of type 2 diabetes in adults (4). For adults, type 2 diabetes and obesity are more prevalent in the African-American population than in European-Americans, especially among African-American women (5). Minority populations have also seen the greatest increase in childhood and adolescent diagnoses of type 2 diabetes (6).

Studies in adults have consistently shown insulin resistance and hyperinsulinemia to be strong predictors of the development of type 2 diabetes (7). In addition to insulin resistance and β-cell dysfunction, obesity (specifically central adiposity [8]), dyslipidemia (9–10), and genetic predisposition (11) are risk factors for the development of impaired glucose tolerance and type 2 diabetes in adults.

The clustering of insulin resistance, obesity, hypertension, dyslipidemia, and atherosclerosis has been referred to as the insulin resistance syndrome (IRS), the metabolic syndrome, or syndrome X (12). Increasing rates of type 2 diabetes in the pediatric population suggest the need to explore the development of insulin resistance and other risk factors (13) for type 2 diabetes in childhood (14).

A number of studies (15–21) suggest that overweight status in African-American children and adolescents is associated with insulin resistance and that children may be developing IRS early in life. Establishing the relation between obesity and the risk factors of IRS and insulin resistance in young children <10 years of age will aid in understanding the disease course of the development of type 2 diabetes.

We wished to further examine the relation between insulin sensitivity and age, pubertal status, family history, and obesity in overweight African-American children. We also examined the clustering of blood pressure, lipids, and insulin sensitivity in these children. Our predictions were that *1*) insulin sensitivity will decrease with age, *2*) insulin sensitivity will be inversely correlated with weight, *3*) girls will be more insulin resistant and will have a more exaggerated insulin response to a glucose load than boys, *4*) children with a family history of diabetes will be less insulin sensitive, and *5*) insulin resistance will be associated with increased adiposity, elevated lipid profiles, and increased blood pressure.

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RESEARCH DESIGN AND METHODS — The data reported in this study were part of a baseline screening of children for entrance into a diabetes

prevention study. The goal of the study was to recruit overweight children (>90th percentile of BMI for age and sex) into a randomized clinical trial of interventions for weight modification. Informed consent was obtained from the parents of the participants. Several methods were used to recruit families. Chart reviews were conducted at University of Maryland Medical System–affiliated primary care sites to identify African-American children between 5 and 10 years of age who were above the 90th percentile of weight for height at their last well-child visit within the previous year. Families with potentially eligible children were sent a letter describing the diabetes prevention study. Radio, television, print, and internet media were also used to advertise the program. Regardless of the recruitment source, initial screening took place over the phone and consisted of questions designed to determine whether the child was believed to be overweight, whether the child had any conditions that would affect his or her ability to benefit from a weight management program, and whether a primary caregiver was available to participate in the program.

Initially, an oral glucose tolerance test (OGTT) was conducted during the first clinic visit, and the physical examination, which included anthropometric measures, was conducted during the second visit. Many of these children were determined to be ineligible to participate for a variety of reasons, and the protocol was changed such that the OGTT took place during visit number 2 and the physical examination took place during visit number 1. As a result, not all of the children in this analysis have all measures. The data set for this analysis includes children who received an OGTT at any time during their screening.

Laboratory and anthropometric evaluations

OGTT. A standard 2-h OGTT was performed after a 12-h fast. Children ingested 75 g of carbohydrate in the form of glucola. Before ingestion of carbohydrates, blood was drawn for determining the fasting glucose value and insulin level. Repeat samples for both insulin and glucose were taken at 30, 60, 90, and 120 min post–carbohydrate load (22). Insulin concentrations were determined using the Coat-A-Count radioimmunoassay (Diagnostic Product, Los Angeles, CA).

Two approaches were used to characterize insulin sensitivity: homeostasis model assessment (HOMA; $n = 137$) (23) and the whole-body insulin sensitivity (WBIS) index (equation 4) of Matsuda and DeFronzo (24) ($n = 111$). Because the distribution of the HOMA resistance values was skewed, the values were transformed by taking the natural logarithm (Ln-[HOMA]). HOMA is based only on the fasting insulin and glucose values, whereas the WBIS index is based on values from all five time points of the OGTT.

Physical exam. A standardized physical examination was conducted by a physician, and the following characteristics were assessed: height, weight, blood pressure (children were seated and blood pressure was measured using a Dinamap model 1846SKP cuff [Critikon, Tampa FL]), and pubertal status (assessed by a physician using Tanner staging [25–26]). Of the children examined, 51% showed no evidence of pubertal development (Tanner stage 1), 40% showed very early signs of pubertal development (Tanner stage 2), and 9% of the children were determined to be Tanner stage 3.

Skinfold thickness, a measure of subcutaneous body fat, was measured using calipers in the tricep and subscapular regions by either the study nurse or physician. Personnel received training in skinfold measurements and followed the protocol described by Lohman (27) for locating skinfold sites and taking measurements. An average for each site was calculated from three measurements (22).

Lipids, fasting glucose, and insulin were obtained either from the fasting blood draw of the OGTT or a fasting blood draw during screening visits. Lipids were analyzed using a Vitros 900 analyzer (Ortho Clinical Diagnostics, Raritan, NJ). Total body fat percentage was estimated using bioelectrical impedance analysis (BIA) (RJL Systems, Mt. Clemens, MI) (28). BIA measures were taken in a nonfasting state, and children had not recently engaged in any vigorous physical activity.

Because normative values of BMI differ by sex and change as children grow older, we computed an age- and sex-adjusted BMI. We took normative means and standard deviations for BMI for each age (5–10 years) and sex group (29) and used these values to calculate a z-score (z-BMI) for each child's BMI, representing the number of standard deviation units above or below their age-sex mean.

Family history of type 2 diabetes was assessed on two different occasions as part of a health history interview conducted with the child's caregiver and during the child's physical exam. Caregivers were asked if any members of the child's immediate or extended family (second degree relatives) had diabetes that occurred as a result of being overweight, diabetes that was controlled with pills or "sugar," or diabetes for which the respondent otherwise indicated that disease onset was during adulthood and was weight related. This variable was coded yes ($n = 81$) if one or more relatives were reported to have diabetes and no ($n = 36$) if the caregiver did not identify any of the child's relatives as having diabetes.

Statistical methods. The OGTT data were analyzed using repeated measures analysis of variance. Time (baseline, 30, 60, 90, and 120 min) was treated as a repeated measures factor, and sex was used as a between-subjects factor. Age and z-BMI were used as covariates. Measures that summarized insulin resistance were analyzed with hierarchical linear regression, analysis of variance, and analysis of covariance, depending on whether the independent variables were continuous, categorical, or mixed. Other analyses were conducted using χ^2 tests of association (when variables were categorical) and Pearson correlation coefficients (when variables were continuous).

RESULTS

Subject characteristics

Data were analyzed for 137 children (51% female) who started the OGTT and at least had a fasting insulin and glucose measurement taken. Boys ($n = 67$) and girls ($n = 70$) did not differ (means ± SD) in terms of height (135.9 ± 11.1 vs. 133.9 ± 11.4 cm), weight (45.6 ± 15.6 vs. 45.7 ± 13.9 kg), or z-BMI (3.7 ± 1.7 vs. 3.8 ± 1.3). Girls (7.9 ± 1.4 years) were significantly ($P < 0.05$) younger than boys (8.5 ± 1.3 years).

Missing data

For various reasons (e.g., difficulty maintaining venous access), 26 children did not have complete data for the OGTT (14 boys and 12 girls). The children who did and did not complete the OGTT were compared with regard to age (8.2 ± 1.3 vs. 7.8 ± 1.6), sex, Tanner stage, and z-BMI (3.7 ± 1.5 vs. 4.0 ± 1.6), and did not
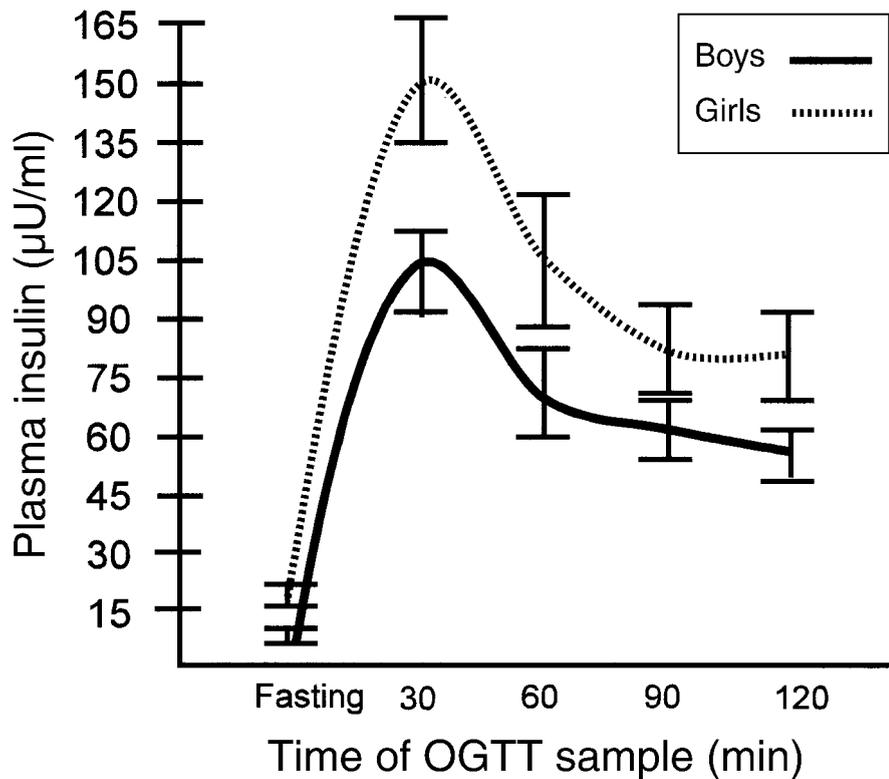
Figure 1—*Plasma insulin concentrations (means ± SEM) for boys and girls during a 2-h OGTT.*

differ significantly. A number of children assessed with the OGTT did not meet eligibility requirements, and therefore anthropometric and lipid data were not collected.

To evaluate whether missing data created a bias in the sample, we compared those children with and without lipid ($n = 81$), blood pressure ($n = 61$), and skinfold ($n = 81$) data. Children missing lipid data were significantly more overweight by ~2 SD ($P < 0.02$) but did not differ in terms of age, sex, or insulin resistance. Children missing blood pressure data were more likely to be boys ($P < 0.004$), less overweight ($P < 0.0001$), younger ($P < 0.007$), more insulin-sensitive (WBIS; $P < 0.003$), and less insulin resistant, with Ln(HOMA) P values of <0.003. Children missing skinfold data were more likely to be less overweight ($P < 0.0001$), younger ($P < 0.001$), more insulin sensitive (WBIS, $P < 0.005$), and less insulin resistant, with Ln-(HOMA) P values of <0.0001. These data reflect the fact that a greater number boys were eliminated early in the protocol because they did not qualify for the study based on weight. These differences would tend to reduce the range of variables and

attenuate the size of correlation and regression coefficients.

Results of the OGTT
Results of the OGTT for the 111 children with data at all time points are summarized for insulin (Fig. 1) and blood glucose (Fig. 2). For insulin, there was a main effect for time ($P < 0.0001$), and there were interaction effects for time by age ($P < 0.0001$), for time by z-BMI ($P < 0.005$), and for time by sex ($P < 0.0001$). During the OGTT, insulin values rose significantly then fell. Insulin levels were positively associated with z-BMI and age. Thus, older and heavier children produced more insulin in response to the glucose load. In addition to variance accounted for by changes over time (6%), an additional 21% of the variance in insulin response was accounted for by age (11%), z-BMI (4%), and sex (6%).

Glucose values changed significantly over time ($P < 0.05$), rising from 0 to 30 min and then falling from 30 to 60 min (Fig. 2). The profile of glucose values did not change as a function of age ($P < 0.71$), z-BMI ($P < 0.18$), or sex ($P < 0.75$), and on average glucose values remained within normal limits for the duration of

the test. One child met the criteria for impaired fasting glucose (fasting glucose ≥110 and <126 mg/dl). Six children met the criteria for impaired glucose tolerance (120-min glucose ≥140 and <200 mg/dl). None of the children were diagnosed as diabetic as a result of the OGTT (30).

Insulin resistance and insulin sensitivity
The correlation between Ln(HOMA) and WBIS was $r = -0.80$ ($P < 0.0001$). Both measures were strongly correlated with fasting insulin, with $r = 0.89$ ($P < 0.0001$) and $r = -0.62$ ($P < 0.0001$) for Ln(HOMA) and WBIS, respectively. Using hierarchical linear regression, age, sex, and z-BMI accounted for 41% of the variance in Ln(HOMA), with each variable making a significant independent contribution. Age, sex, and z-BMI accounted for 39% of the variance in WBIS with each variable, making a significant independent contribution. Girls were more insulin resistant than boys, older children more resistant than younger children, and children who were more overweight were more insulin resistant than those children who were less overweight.

Correlates of insulin sensitivity
To evaluate the degree to which children are showing early signs of developing the cluster of risk factors described as IRS (10), we calculated the Pearson correlations of Ln(HOMA) and WBIS with total cholesterol, LDL cholesterol, HDL cholesterol, fasting triglycerides, systolic and diastolic blood pressure, tricep and subscapular skinfold thicknesses, and percentage body fat measured using bioelectrical impedance. The correlation coefficients are presented in Table 1, along with means and standard deviations. Both measures of insulin sensitivity (Ln [HOMA] and WBIS) were significantly correlated with triglycerides, systolic and diastolic blood pressure, tricep and subscapular skinfold thickness, and body fat percentage. LDL and HDL were not significantly correlated with insulin sensitivity; however, total cholesterol was inversely correlated with WBIS.

The National Cholesterol Education Program guidelines (31) for lipids in children were used to evaluate the level of risk represented by the lipid data, and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of
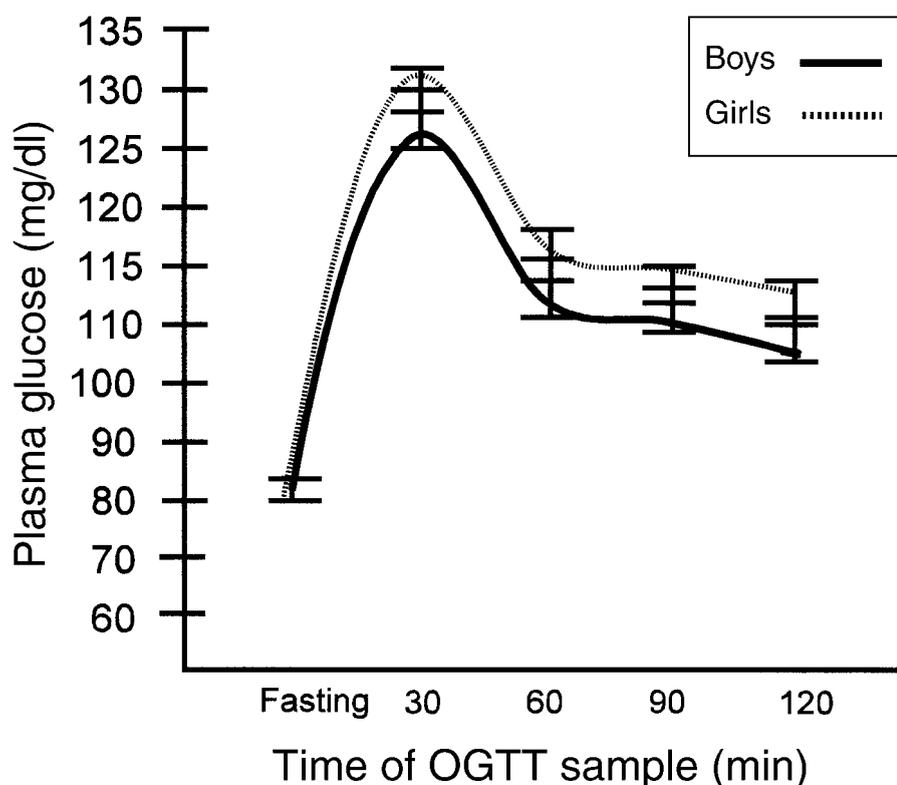
Figure 2—*Plasma glucose concentrations (means ± SEM) for boys and girls during a 2-h OGTT.*

High Blood Pressure guidelines for children (32) were used to evaluate the level of risk represented by the blood pressure data. Using child-specific norms, the percentage of children who exceeded the levels for borderline or high lipid values was 36 and 27% for total and LDL cholesterol, respectively. For HDL cholesterol, 66% of the children were below the cutoff for borderline or low values. In addition, 8% of the children were borderline or high for systolic blood pressure, and 2% were borderline or high for diastolic blood pressure.

A t test was used to compare children with and without a family history of type 2 diabetes. There was no difference for Ln(HOMA) ($t = 1.24$, df = 115, $P < 0.28$), and there was a marginally significant difference for WBIS ($t = -1.93$, df = 94, $P < 0.056$). The one child with impaired fasting glucose and five of the six children with impaired glucose tolerance had a family history of diabetes.

A one-way analysis of variance was used to compare children at each of the three Tanner stages. There was a significant increase in Ln(HOMA) as the Tanner stage increased ($P < 0.004$). WBIS appeared to decrease as the Tanner stage increased, but the effect did not reach statistical significance ($P < 0.13$). A hierarchical linear regression, first controlling for age and sex, showed that Tanner stage did not significantly add to the prediction of Ln(HOMA) ($P < 0.16$) or WBIS ($P < 0.82$).

CONCLUSIONS — These data present the relation among age, sex, weight, pubertal status, insulin response to a glucose challenge, insulin sensitivity, and the risk factors of IRS. Girls produced more insulin at all time points, and values for insulin increased with age and weight, regardless of sex. We found that 27% of the variance in insulin response was attributable to age, z-BMI, and sex, all of which made significant independent contributions. The mean glucose value profiles for boys and girls remained within normal limits; however, one girl met the criterion of impaired fasting glucose and six—all girls—showed evidence of impaired glucose tolerance. Age, sex, and degree of overweight accounted for 41 and 39% of the variance in Ln(HOMA) and WBIS, respectively. Girls and those children who were older and more overweight were more insulin resistant.

Both measures of insulin sensitivity were significantly correlated with increases in blood pressure, triglycerides, subcutaneous fat, and percentage of total body fat, but there was no correlation with LDL and HDL. Total cholesterol was inversely related to WBIS. These associations suggest that a clustering of risk factors is present in these children, although the magnitude of the correlations is modest. Because this analysis is cross-sectional, the clinical significance of these findings can only be determined by prospective evaluation of these potential risk factors, which is planned as part of the larger study from which these data were derived. Although none of the children had completed pubertal development, there was a significant increase in fasting insulin production with increasing Tanner stages (up to 3); however, pubertal status was not associated with WBIS.

Table 1—*Correlations of cardiovascular risk factors with insulin sensitivity in 5- to 10-year-old African-American children*

Variable	Mean	SD	Correlation (r) with Ln(HOMA)	Correlation (r) with WBIS
Total cholesterol (mg/dl)	163.7	32.0	0.19	−0.25*
LDL cholesterol (mg/dl)	104.1	31.2	0.17	−0.22
HDL cholesterol (mg/dl)	42.3	10.4	−0.13	0.15
Triglycerides (mg/dl)	87.6	43.4	0.25*	−0.36*
Systolic blood pressure (mmHg)	110.3	13.5	0.45†	−0.37†
Diastolic blood pressure (mmHg)	62.2	7.3	0.23*	−0.23*
Triceps skinfold (mm)	28.18	8.1	0.35*	−0.45†
Suscapular skinfold (mm)	27.2	9.7	0.35*	−0.53†
Percent body fat (BIA)	34.9	6.1	0.31*	−0.56†

*Correlation is significant, $P < 0.05$; †Correlation is significant, $P < 0.01$.

These data show that in 5- to 10-year-old African-American children who are not fully pubertal, overweight status is associated with increased risk of insulin resistance and increased subcutaneous fat and elevations in lipid and blood pressure profiles. Young African-American girls were more insulin resistant than their male counterparts, regardless of weight status, and they produced more insulin in response to a glucose load. HOMA and WBIS measures of insulin sensitivity have been developed and validated in adults. In this sample of overweight/obese children, both measures were strongly correlated with fasting insulin concentrations, suggesting that we have valid measures of hyperinsulinemia for children. Further research is needed to more clearly establish the applicability of HOMA and WBIS for children.

Our study results confirm previous findings showing that African-American girls are more insulin resistant than boys and that increasing weight is associated with both decreased insulin sensitivity and risk factors identified in the IRS (14–16,19–21). Our findings extend this work by establishing the relations among obesity, insulin resistance, and cardiovascular risk factors in very young (5- to 10-year-old) overweight African-American children.

A lack of significant associations (e.g., between measures of resistance and lipids) and restrictions in the range of insulin sensitivity values may both be attributable to small sample sizes resulting from the ineligibility of some of the children screened for the study. Despite these limitations, it is clear that overweight status is associated with early signs of IRS in African-American children under the age of 10 years. Future research needs to examine these risk factors in relationship to obesity in other ethnic groups and in samples that include more normal-weight children.

These results provide compelling evidence that overweight African-American children should be monitored for insulin resistance and cardiovascular risk factors early in life, and that this monitoring should occur as part of their ongoing medical care. Girls in particular are at increased risk for the development of insulin resistance at an early age, and they mirror the increased prevalence found in minority women. Although the cross-sectional nature of these analyses do not allow an assessment of the time-course of the development of type 2 diabetes in this population, baseline assessment suggests that intervention needs to begin at an early age, when signs of disease are preclinical. Follow-up evaluation is planned for this cohort; this will allow us to assess the relation between weight change and insulin sensitivity, the related IRS risk factors, and the development of impaired glucose tolerance and type 2 diabetes.

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