Insulin Resistance During Puberty

Results From Clamp Studies in 357 Children

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Insulin resistance may be an important cause of a constellation of cardiovascular risk factors in adults, and onset of this syndrome may occur in childhood. However, children normally experience transient insulin resistance at puberty. There were 357 normal children (159 girls, 198 boys) age 10–14 years who underwent euglycemic clamp studies to assess the effects of Tanner stage (T), sex, ethnicity, and BMI on insulin resistance. Insulin resistance increased immediately at the onset of puberty (T2), but returned to near prepubertal levels by the end of puberty (T5). Its peak occurred at T3 in both sexes, and girls were more insulin resistant than boys at all T stages. White boys appeared to be more insulin resistant than black boys; no difference was seen between white and black girls. Insulin resistance was strongly related to BMI, triceps skinfold thickness, and waist circumference, and this relationship was independent of Tanner stage or sex. Differences in BMI and adiposity did not, however, entirely explain the insulin resistance of puberty. These results demonstrate that *1*) significant differences in insulin resistance are present between boys and girls; *2*) insulin resistance increases significantly at T2, T3, and T4, but decreases to near prepubertal levels at T5; and *3*) while insulin resistance is related to BMI and anthropometric measures of fatness, these factors do not completely explain the insulin resistance that occurs during the Tanner stages of puberty. *Diabetes* 48:2039–2044, 1999

The pattern of changes in insulin resistance during puberty and the factors influencing these changes have not been completely defined. All children become more insulin resistant at the time of puberty. While prepubertal children and postpubertal young adults are equally sensitive to insulin, adolescents are insulin resistant compared with either of these groups (1,2). Thus, insulin resistance appears to be a transient physiological stage of normal development.

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M, glucose uptake during insulin clamp; T, Tanner stage.

Insulin resistance in adults is associated with obesity, glucose intolerance or diabetes, hypertension, dyslipidemia, and cardiovascular disease. Although the relationship among these conditions is complex, insulin resistance may be the primary initiating factor (3–5). There is increasing evidence that the onset of the insulin resistance syndrome may occur in childhood or adolescence (6,7). Before an etiologic association between insulin resistance and other cardiovascular risk factors can be considered in this age-group, a clear definition is necessary of the normal physiologic changes in insulin resistance that occur during puberty.

Pubertal insulin resistance occurs during a time of profound change in body composition and hormone levels. During puberty, BMI slowly increases (8). Lean body mass and fat mass increase in both sexes, but, by the end of puberty, fat accounts for a greater percentage of total body weight in girls than boys. Increased body fat and BMI correlate strongly with insulin resistance and have been proposed as potential mediators of the pubertal changes in insulin resistance (2,6,9,10). However, insulin resistance can occur during puberty in the absence of changes in BMI (9). Moreover, young adult women are more sensitive to insulin than pubertal girls, despite presumably having a greater percentage of body fat (1,2). It appears, therefore, that factors other than changes in body composition may be more important in the onset of pubertal insulin resistance.

Other studies have compared insulin resistance in adolescents to prepubertal children and adults (1,2,6,9–12). However, no study has had a sufficient number of subjects to characterize insulin resistance at each of the five Tanner stages of puberty or to define the relation within Tanner stages to sex, body size, or body fatness. The present study, in which euglycemic insulin clamps were performed on 357 normal children age 10–14 years, clarifies these relations. It represents the largest cross-sectional study to date that examines insulin resistance in the pediatric population.

RESEARCH DESIGN AND METHODS

Subjects. This study was approved by the University of Minnesota Committee for the Use of Human Subjects in Research. Informed consent was obtained from parents and informed assent from the children.

The subjects were participants in a longitudinal study of the relation between insulin resistance and cardiovascular risk factors in children. They were randomly selected after blood pressure screening of 12,043 fifth through eighth grade children in the Minneapolis public school system in 1996 and stratified according to sex, ethnicity (black and non-Hispanic white), and blood pressure percentile (50% from the upper 25th percentiles and 50% from the lower 75th percentiles) to increase the percentage of children at potential cardiovascular risk. The percentage of children of each race, sex, and Tanner stage was relatively evenly distributed between the two blood pressure groups. Informed consent was obtained

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TABLE 1
Subject characteristics for girls

	Tanner stage				
	T1	T2	T3	T4	T5
n	3	18	41	45	52
Race					
Black	1	3	5	5	9
White	2	15	36	40	43
Age (years)	11.7 ± 1.2	11.7 ± 1.0	12.2 ± 0.9	13.0 ± 1.1	13.8 ± 0.9
Height (cm)	148.7 ± 7.3	153.3 ± 9.9	157.7 ± 7.1	161.7 ± 5.5	163.9 ± 6.3
Weight (kg)	34.9 ± 5.4	49.0 ± 9.7	57.0 ± 16.3	55.7 ± 18.5	64.8 ± 12.6
BMI (kg/m^2)	15.9 ± 3.1	20.8 ± 3.7	22.7 ± 5.5	21.3 ± 3.1	24.0 ± 4.4
Triceps (cm)	20.2 ± 5.8	23.5 ± 8.8	26.4 ± 9.9	22.0 ± 6.4	26.0 ± 8.9
Subscapular (cm)	7.0 ± 1.8	14.2 ± 9.0	15.9 ± 7.8	13.5 ± 5.2	16.3 ± 7.0
Waist (cm)	61.9 ± 5.1	72.9 ± 9.3	77.4 ± 13.2	73.0 ± 8.7	78.8 ± 10.5
Hips (cm)	77.1 ± 9.3	87.4 ± 8.9	95.2 ± 11.8	94.2 ± 6.5	100.7 ± 10.3

Data are means ± SD. n = 159.

from 401 individuals; 33 subsequently refused the clamp studies and an additional 11 children did not have the clamp performed because of technical problems with catheter placement. Insulin clamps were completed in 357 participants who form the cohort for this study.

Body composition measurements. All participants attended a clinic dedicated to this study, where history and physical examination were performed by board-certified pediatricians. Children were divided into Tanner stages according to pubic hair development in boys and breast and pubic hair development in girls. In girls, the greater of the two values was used for statistical analysis so that we would not underestimate pubertal maturation. Body composition measurements were obtained by trained research personnel. Height was measured using a wall-mounted stadiometer, and weight was determined using a balance scale. BMI was calculated as the weight (kg) divided by the height (meters) squared. Thickness of triceps and subscapular skinfold was measured in duplicate to the nearest millimeter with Lange calipers, and the mean value was used in these analyses.

Euglycemic clamps. Participants were admitted to the University of Minnesota Clinical Research Center after a 10- to 12-h overnight fast. Two intravenous catheters were inserted 1 h before the clamp studies. An arm vein was cannulated for infusion of potassium phosphate, insulin, and dextrose. A contralateral vein was cannulated for blood sampling, and the hand was placed in a heated box (65°C) to arterialize venous blood. Insulin resistance was determined by the euglycemic insulin clamp method in which insulin was infused at a rate of 1 mU · kg^{-1} · min^{-1} for 3 h. A variable infusion of 20% dextrose was used to maintain the serum glucose level at 100 mg/dl with plasma glucose levels determined every 5 min. Insulin levels were drawn at baseline (–15, –10, and –5 min before the beginning of the infusion) and at steady state (140, 160, and 180 min after starting the infusion).

Analytical methods and calculations. Plasma glucose was measured immediately at the bedside with a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Insulin samples were collected on ice and centrifuged within 20 min. Serum insulin levels were determined by radioimmunoassay using a double antibody method. Basal levels of glucose and insulin were calculated by averaging the values of the samples obtained before beginning the insulin infusion. Insulin sensitivity (glucose uptake during insulin clamp [*M*]) was calculated as the average amount of glucose (mg · kg^{-1} · min^{-1}) required to maintain euglycemia during the last 40 min of the clamp. A lower *M* value represents greater insulin resistance.

Data analysis. We hypothesized in both boys and girls that there is a reduction and a recovery in *M* during puberty, and that *M* is inversely associated with BMI, independent of pubertal stage. The following analyses were performed. *1*) *M* was estimated within Tanner stages using a general linear regression model with Tanner stage categories as indicator variables. Covariates were sex, race, and BMI in the following six BMI categories (cutpoints selected to have approximately the same number of subjects in each category): <18, 18–19.9, 20–20.9, 21–22.9, 23–26.9, and ≥27 kg/m^2. We examined each of the 10 pairwise comparisons between Tanner stages without adjustment for multiple comparisons. *2*) To further examine the pattern of *M* during puberty without significance testing, we repeated these regression analyses stratifying by sex to get sex-specific mean levels of *M* within Tanner stages. *3*) The association of *M* with BMI was estimated within sex by regressing *M* on a linear continuous variable for BMI. Covariates were the indicator variables for the Tanner stages and race. We also ran this analysis further stratified by Tanner stage. To assess goodness of fit of these linear regression analyses, we estimated *M* within the six BMI categories by regressing *M* on indicator variables for the six BMI categories, and with the same covariates, we inspected plots of linear fits and predicted means. *4*) To assess whether steady-state insulin levels were an important covariate, we reran all analyses with steady-state insulin as an additional covariate. We do not present these analyses, because findings were not substantially different from those in which steady-state insulin was not a covariate. *P* values <0.05 were considered to be statistically significant.

RESULTS

Body composition. Subject characteristics are presented in Table 1 (girls) and Table 2 (boys). Participants included 159 girls (136 white, 23 black) and 198 boys (148 white, 50 black), age 10–14 years. Weight and height increased with Tanner stage (T), with the greatest increment in height occurring from T1 to T2 in girls and T2 to T3 in boys. Waist and hip circumference gradually increased from T1 to T5 in both sexes. Triceps and subscapular skinfold thickness increased during puberty in girls, but relatively little change was noted in boys.

BMI increased steadily throughout puberty and was significantly greater at T5 than at T1 in both sexes (P = 0.01). Although a larger increase was noted in girls, there was no significant difference in BMI between boys and girls at any Tanner stage. BMI strongly correlated with measures of adiposity including waist circumference (girls: r = 0.84, P < 0.0001; boys: r = 0.89, P < 0.0001), triceps skinfold measurement (girls: r = 0.75, P < 0.0001; boys: r = 0.65, P < 0.0001), and subscapular skinfold measurement (girls: r = 0.86, P < 0.0001; boys: r = 0.88, P < 0.0001). BMI was less strongly correlated with waist-to-hip ratio (girls: r = 0.20, P < 0.0001; boys: r = 0.26, P < 0.0099). For T2–T5 and for each of the six BMI categories, girls had greater triceps and subscapular skinfold thickness than boys.

Insulin resistance. Insulin sensitivity decreased significantly with the onset of puberty from T1 to T2 (P = 0.015), remained relatively unchanged from T2 to T4 (P < 0.44), and at T5, had returned almost to the prepubertal level, although the T5 *M* value was slightly but significantly lower than the value at T1 (P = 0.045) (Fig. 1). Insulin sensitivity was lowest at T3 in both sexes; *M* was 18% lower at T3 than at T1 in girls and 22% lower in boys.

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TABLE 2
Subject characteristics for boys

	Tanner stage				
	T1	T2	T3	T4	T5
n	25	44	31	60	38
Race					
Black	3	6	9	21	11
White	22	38	22	39	27
Age (years)	11.8 ± 0.7	12.2 ± 0.8	13.0 ± 0.9	13.4 ± 1.1	14.3 ± 0.8
Height (cm)	152.9 ± 6.6	155.5 ± 8.2	164.2 ± 6.8	167.2 ± 7.4	173.1 ± 9.6
Weight (kg)	48.5 ± 13.1	50.0 ± 12.0	58.1 ± 15.1	60.9 ± 12.0	70.8 ± 17.3
BMI (kg/m^2)	20.6 ± 4.8	20.5 ± 4.1	21.5 ± 5.2	21.7 ± 3.9	22.0 ± 5.0
Triceps (cm)	21.1 ± 8.1	20.5 ± 9.2	18.4 ± 12.7	20.7 ± 10.8	19.3 ± 9.8
Subscapular (cm)	11.2 ± 6.8	10.3 ± 5.3	11.6 ± 8.3	11.1 ± 5.9	13.1 ± 7.9
Waist (cm)	74.3 ± 11.9	75.4 ± 9.0	79.2 ± 12.4	78.7 ± 9.6	84.3 ± 13.1
Hips (cm)	87.7 ± 8.7	86.9 ± 10.2	91.9 ± 11.0	93.6 ± 8.4	98.4 ± 11.6

Data are means ± SD. n = 198.

The cohort of 159 girls was significantly more insulin resistant than the cohort of 198 boys (girls: M = 8.1 ± 0.2, boys: M = 9.9 ± 0.3 mg · kg^{-1} · min^{-1}, P < 0.0001) (Fig. 2). Half of the sex-related difference in insulin resistance could be explained by differences in adiposity as measured by adjustment for triceps skinfold thickness (girls: M = 8.6 ± 0.3, boys: M = 9.5 ± 0.2 mg · kg^{-1} · min^{-1}, P < 0.01) or subscapular skinfold thickness (girls: M = 8.7 ± 0.2, boys: M = 9.4 ± 0.3 mg · kg^{-1} · min^{-1}, P < 0.02), but there was still a significant difference in insulin resistance between the sexes when adjustment for these factors was made. Adjustment for BMI, waist circumference, or hip circumference had little effect on sex differences in M (BMI adjustment: girls: M = 8.3 ± 0.2, boys: M = 9.7 ± 0.2 mg · kg^{-1} · min^{-1}, P < 0.0001). Although M was greater in boys than girls at each Tanner stage, the difference was statistically significant only at T4 (P < 0.01).

Although M was significantly associated with the fasting insulin level (r = 0.48, P < 0.0001), the fasting insulin level did not significantly differ between any of the Tanner stages, between boys and girls, or between the races. Steady-state insulin levels achieved during the final 40 min of the clamp differed between the sexes (girls: 88 ± 2, boys: 74 ± 2 µU/ml, P = 0.0001), although the standard deviation was fairly large (girls 33, boys 22). This difference persisted when adjusted for BMI, skinfold thickness, or blood pressure group. Adjustment of M for steady-state insulin levels did not alter the pattern of Tanner stage changes in insulin resistance or the sex difference.

We evaluated the racial difference in insulin resistance between the 284 white children and 73 black children (Fig. 3). In children of both races, the sex and Tanner stage differences in M were the same as the differences noted above for the entire cohort. Sample size did not allow separate analysis by race at each Tanner stage. The cohort of white boys was more insulin resistant than the cohort of black boys (P < 0.02, average difference in M values 1.1 mg · kg^{-1} · min^{-1}), but

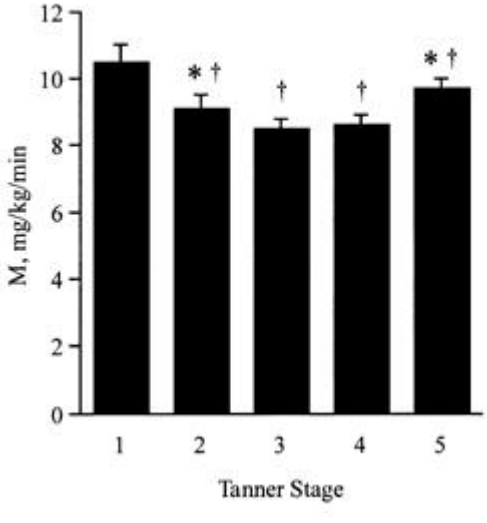

FIG. 1. Insulin resistance (M) by Tanner stage, adjusted for sex and BMI. A lower M value represents greater insulin resistance. Data are expressed as means ± SE. *P < 0.05 compared with preceding Tanner stage, †P < 0.05 compared with T1.

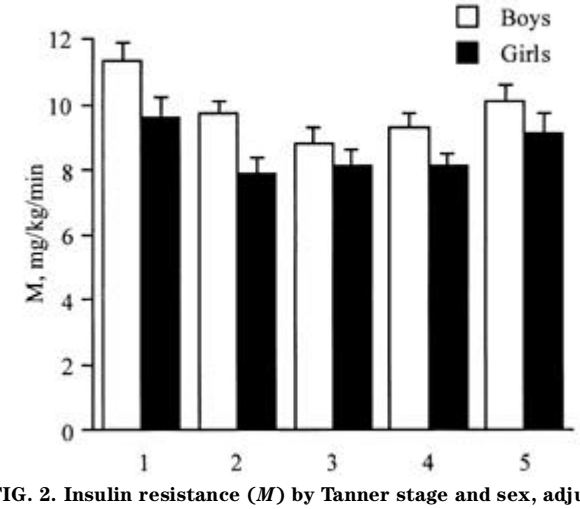

FIG. 2. Insulin resistance (M) by Tanner stage and sex, adjusted for BMI. The cohort of 159 girls was more insulin resistant than the cohort of 198 boys (P < 0.0001). Girls appeared to be more insulin resistant than boys at each Tanner stage, but statistical significance was only achieved for T4 (P < 0.01).

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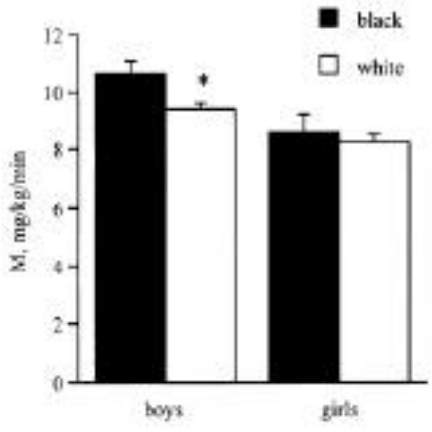

FIG. 3. Insulin resistance (*M*) by race and sex, adjusted for Tanner stage and BMI. **P* < 0.002 for white boys compared with black boys; no ethnic difference in insulin resistance was found between white and black girls (*P* = 0.48).

there was no significant racial difference in insulin resistance in girls (average difference 0.2 mg · kg^{-1} · min^{-1}). These relationships persisted when adjustment was made for BMI, blood pressure group, or measures of adiposity. Black children achieved somewhat higher steady-state insulin levels than white children (black girls: 91 ± 5 vs. white girls: 86 ± 2, *P* = 0.32; black boys: 82 ± 3 vs. white boys: 72 ± 1, *P* = 0.02). Adjustment for steady-state insulin levels did not, however, change the effect of race on insulin resistance.

There was a strong correlation between insulin resistance and BMI for both sexes (*P* < 0.0001, Fig. 4). For a given BMI, insulin resistance was significantly greater in girls than boys in BMI categories <27 kg/m^2, but the sex difference was not present in the BMI category ≥27 kg/m^2. The relationship between insulin resistance and BMI was similar across Tanner stages (*P* = 0.26, Fig. 5). Insulin resistance was similarly related to triceps skinfold thickness and waist circumference for both sexes and all Tanner stages.

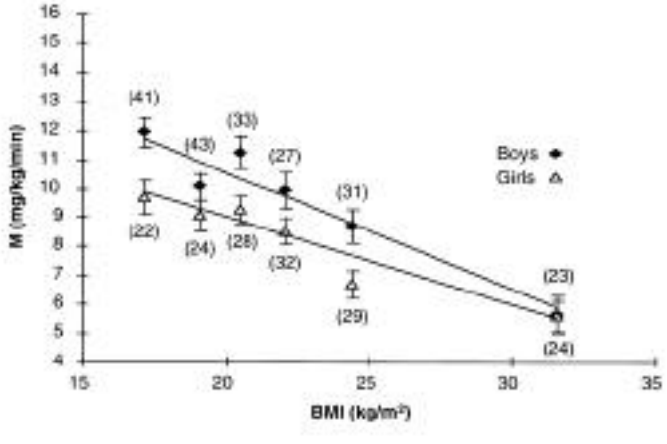

FIG. 4. Regression of *M* on BMI by sex, adjusted for ethnicity and Tanner scale. For the BMI categories, subjects were divided into sextiles as follows: <18, 19–19.9, 20–20.9, 21–22.9, 23–26.9, and ≥27 kg/m^2. Number of individuals in each BMI category is given in parentheses. Formulas for the fitted line are as follows: boys, *M* = 18.18 – 0.42 × BMI; girls, *M* = 14.49 – 0.31 × BMI. The slopes of the two lines were not significantly different from each other (*P* = 0.12).

DISCUSSION

This cross-sectional analysis of 357 normal children and adolescents represents the largest examination to date of the relation of insulin resistance to Tanner stage, sex, and ethnicity. Previous studies have documented the increase in insulin resistance associated with puberty (1,2,6,9–11), but none has had a large enough sample size to permit analyses of all five Tanner stages. Bergman's minimal model was used to compare two stages of puberty (T2 and T3) in 96 children (10). For a given BMI, insulin resistance was greater in T3 than T2 and greater in girls compared with boys. The minimal model also was used in a mixed-sex group of 58 girls and boys (9); a sharp increase in insulin resistance was noted from T1 to T2, and a gradual but nonsignificant further increase from T2 to T5. Data from the present study clearly show that insulin resistance increases significantly by T2, remains constant between T2 and T4, and returns almost to T1 levels by the end of puberty (T5). These changes do not correlate with changes in BMI or triceps skinfold thickness, suggesting that changes in body composition are not the driving force behind the insulin resistance of puberty.

The Tanner staging method has been the standard for assessing the degree of pubertal development for >30 years (13–15), and it is the method used in previous studies of insulin resistance during puberty (1,2,6,9–11). Inherent in this method is a discordance between pubic hair growth and breast development in girls (14). We scored both pubic hair and breast development in girls and used the greater of the two values for statistical analysis so that pubertal maturation would not be underestimated. Identical patterns of insulin resistance were seen, however, when these data were examined using either breast development or pubic hair score as the single measure of Tanner stage. Other methods of assessing puberty were not felt to be appropriate for the present study. Sex hormone levels rise throughout puberty, but there is considerable overlap between Tanner stages; therefore, these levels cannot be used to assign an individual subject to a specific Tanner stage or to determine when puberty has begun (16). Measurement of testicular size is clinically useful in the evaluation of boys with delayed onset of puberty, because enlargement suggests that the pubertal hypothalamic-pituitary-gonadal axis has been activated and that development of pubic hair is likely to begin within 1 year (17). However, it would not be appropriate to use testicular size in a study comparing differences between boys and girls unless the analogous indicator of the earliest pubertal development in girls, i.e., ovarian size measured by ultrasound, was also used.

It has been postulated that hormonal changes in the growth hormone/IGF-1 axis are the primary cause of pubertal insulin resistance (1,9,12). Serum levels of these hormones are higher during puberty than in the prepubertal or adult years (18), and insulin resistance in adolescents has been shown to positively correlate with serum IGF-1 levels (1,9,12) and mean 24 h serum growth hormone levels (1). Our data support this theory, since peak insulin resistance in our patients was temporally related to the pubertal growth spurt in each sex. Although sex hormone levels change dramatically during puberty, neither testosterone nor estradiol has been shown to be associated with insulin resistance (10).

Girls were more insulin resistant than boys. Although this difference was noted at all Tanner stages, it was statistically

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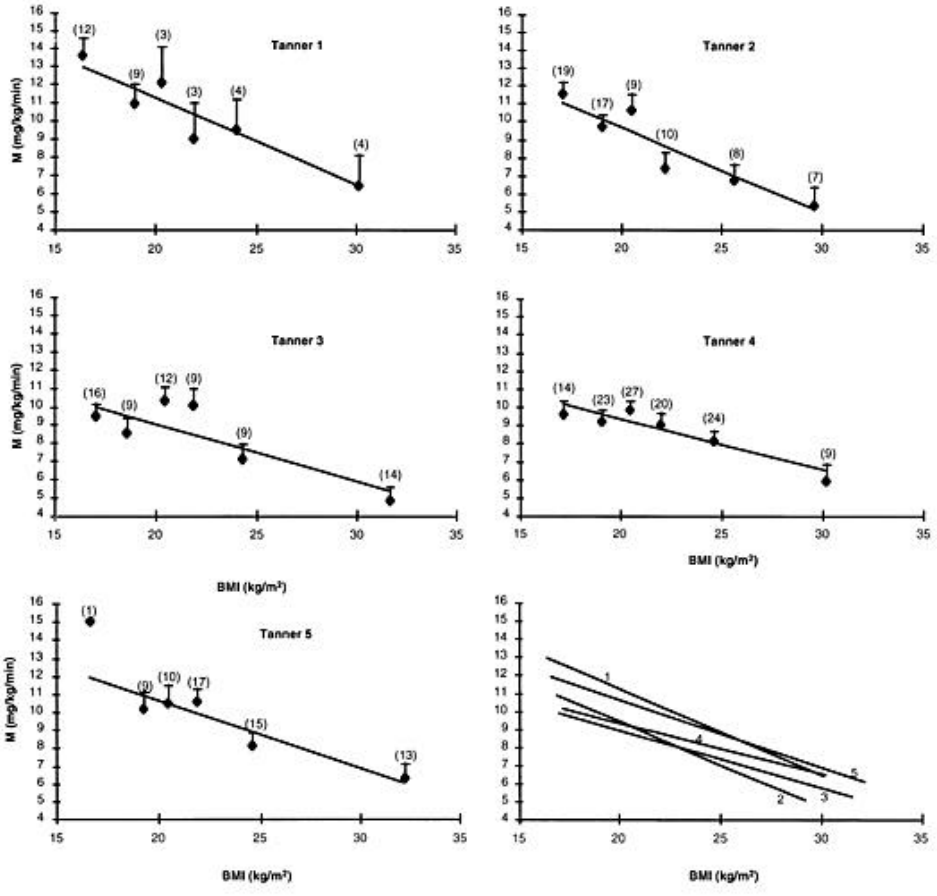

FIG. 5. Regression of *M* on BMI by Tanner scale adjusted for sex and ethnicity. BMI categories are as in Fig. 4. Number of individuals in each BMI category is given in parentheses. Formulas for the fitted lines are Tanner 1, $M = 20.63 - 0.47 \times BMI$; Tanner 2, $M = 19.1 - 0.47 \times BMI$; Tanner 3, $M = 15.34 - 0.31 \times BMI$; Tanner 4, $M = 15.0 - 0.28 \times BMI$; Tanner 5, $M = 18.4 - 0.38 \times BMI$.

significant only at T4, probably because of a lack of statistical power due to sample size. The sex difference was partially, but not completely, explained by differences in adiposity as measured by skinfold thickness. For a given BMI, girls had greater triceps and subscapular skinfold thickness than boys. Adjustment for skinfold thickness narrowed but did not eliminate the significant difference in *M* between the sexes. Interestingly, the sex difference in insulin resistance disappeared in exceptionally obese boys and girls (BMI >27, mean = 31 kg/m^2), even though the difference in triceps skinfold thickness persisted. A BMI level of 30 is well beyond the 95th percentile for children in this age-group (8). In morbid obesity, sex differences in insulin resistance may be obscured by the influence of extreme adiposity.

Insulin resistance has been compared in a small sample of black (n = 14) and white (n = 16) nonobese adolescents using the hyperglycemic clamp (19), and black subjects were found to be more insulin resistant than white subjects. In the present study, which included 73 black subjects, insulin resistance was not significantly different between the cohorts of black and white children. However, when considered separately by sex, black boys were significantly less insulin resistant than white boys, and there was no significant difference between the girl groups. While an explanation for the different outcome in the present study is not evident, it is possible that the substantially larger sample size in this cohort was able to provide a more accurate estimate.

Fasting insulin levels are sometimes used as an index of insulin resistance, and there was a significant correlation between *M* and fasting insulin levels in the present study. However, comparison of fasting insulin did not have the same discriminatory power as *M*, since it did not show the differences between boys and girls or between the Tanner stages. The lack of comparability between *M* and fasting insulin may be explained by the fact that determination of insulin sensitivity (*M*) with the insulin clamp is an experimentally controlled model that isolates insulin resistance, whereas fasting insulin represents an active integrated biological system of which insulin sensitivity is only one variable. Small but statistically significant differences in steady-state insulin levels were observed between girls and boys and black and white subjects. These differences did not appear to be clinically important, however, because adjustment of *M* values for steady-state insulin levels did not change the effect of sex or race on insulin resistance.

In concordance with previous studies (2,6,9,10), insulin resistance strongly correlated with BMI in both prepubertal and pubertal children. Although BMI does not directly measure body fat, it is routinely used to evaluate adiposity in adults and it has recently been recognized as a useful predictor of adiposity in children and adolescents (20,21). A strong correlation was found in this study between BMI and anthropometric measures of body fat, including triceps skinfold thickness, subscapular skinfold thickness, and waist circumference.

In conclusion, normal children experience a stage of physiological insulin resistance beginning at the onset of puberty. This corresponds with the period of rapid growth and development and resolves by the end of puberty. Although insulin resistance is strongly and similarly related to BMI and adi-

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posity in each of the Tanner stages, the results from this study show that these factors do not completely explain the insulin resistance of puberty.

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