LONGITUDINAL CHANGES IN INSULIN SENSITIVITY, INSULIN SECRETION, AND β-CELL FUNCTION DURING PUBERTY

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Objective To determine longitudinal changes in insulin sensitivity (SI), insulin secretion, and β-cell function during puberty in white and black youth.

Study design The tolbutamide-modified frequently sampled intravenous glucose tolerance test and minimal modeling were used to measure SI, the acute insulin response to glucose (AIRg), and β-cell function (disposition index, DI) in white (n = 46) and black (n = 46) children (mean [±SD] age at baseline = 10.2 ± 1.7 years). Growth curve models (including 272 observations) with SI, AIRg, and DI regressed on Tanner stage were run after adjusting for covariates.

Results After adjusting for covariates, growth curve models revealed that SI decreased and subsequently recovered by the end of puberty in whites and blacks (both $p < .05$), AIRg decreased linearly across Tanner stages in both races (both $p < .001$), and DI decreased across puberty in blacks ($p = .001$) but not in whites ($p = .2$).

Conclusions White and black youth exhibited transient insulin resistance and diminished AIRg during puberty. The progressive decline in DI among blacks versus whites may reflect a unique effect of puberty on β-cell compensation in blacks. Future studies are needed to identify whether this difference contributes to the increased risk of type II diabetes in young blacks. *(J Pediatr 2006;148:16-22)*

See editorial, p 3, and related article, p 23.

Puberty is associated with a number of metabolic, hormonal, and body composition changes that can influence risk factors for chronic diseases such as type II diabetes.[1] Historically, type II diabetes has been a condition of adult onset, but in recent years, the disease has increased at an alarming rate in youth.[2,3] The diagnosis of type II diabetes most often occurs during late childhood or adolescence suggesting that physiological changes during puberty may be related to diabetes risk.

Insulin resistance is higher during mid-puberty in relation to its pre- and post-pubertal counterparts.[4] Insulin sensitivity (SI) appears to be highest before the onset of puberty, reaches its nadir midway through maturation, and approaches near pre-pubertal levels at the end of maturation.[5] Increased insulin secretion compensates for the transient decrease in SI during adolescence.[6] It is possible that the influence of puberty on SI, insulin secretion, and pancreatic β-cell function may be population specific, but this has yet to be widely examined in ethnically diverse populations. The implications for this research are relevant and timely because puberty may represent a critical period in the development of type II diabetes in higher-risk populations.[7]

Numerous reports have been published on pubertal insulin resistance; however, many studies have employed indirect and unsophisticated approaches to assess body composition[5,8-10] and insulin resistance.[8,11,12] In addition, small sample sizes in total and at individual pubertal stages[6,9,10,13] as well as a lack of non-white groups[9,10,12,13] limit the ability to generalize findings, especially with respect to populations at increased risk of type II diabetes (ie, blacks and Hispanics). Finally, data regarding pubertal insulin resistance have primarily been derived from cross-sectional reports. In a longitudinal investigation of SI

AIRg	Acute insulin response to glucose	DI	Disposition index
BMI	Body mass index	GCRC	General Clinical Research Center
CV	Coefficient of variation	SI	Insulin sensitivity

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during puberty, we noted that transition from Tanner growth stage I to III was associated with a 32% reduction in insulin sensitivity in both white and blacks.[14] Therefore, we sought to extend our earlier findings by applying growth curve models to examine longitudinal changes in SI, insulin secretion, and pancreatic β-cell function in boys and girls across the continuum of puberty.

METHODS

Subjects

Study participants were part of an ongoing longitudinal study of body composition, energy expenditure, and risk factors for type II diabetes and cardiovascular disease. Findings from this cohort have been published previously.[14-17] Children were recruited for this study through local advertisements and word of mouth. No child was taking medication(s) known to affect body composition, SI, or insulin secretion, and none were diagnosed (at any time since birth) with a disease or syndrome known to influence body composition, SI, or insulin secretion. There were no inclusion criteria with respect to stage of development, but participants were 4 to12 years of age at study entry. This investigation was approved by the Institutional Review Board of the University of Alabama at Birmingham, and parents provided informed consent before testing.

Protocol

On an annual basis, children were admitted to the General Clinical Research Center (GCRC) in the afternoon for an overnight visit. Anthropometric measurements and a physical exam were conducted upon arrival. A pediatrician determined Tanner stage based on breast stage and pubic hair development in girls and genitalia development in boys using the guidelines of Marshall and Tanner.[18,19] Boys and girls were then served dinner (a mixed meal consisting of 55% carbohydrate, 15% protein, and 30% fat) and an evening snack; all food was consumed before 2000 hours. Only water or noncaloric, noncaffeinated beverages were consumed between 2000 hours and testing the following morning. Children returned to the GCRC approximately 2 weeks later to undergo body composition measurements.

Tolbutamide-modified Frequently Sampled Intravenous Glucose Tolerance Test

At 0600 hours on the morning after the GCRC admission, a topical anesthetic (EMLA cream, AstraZeneca Pharmaceuticals, Wilmington, Del) was applied to the antecubital region of both arms; flexible intravenous catheters were placed at ~0700 hours. Three fasting blood samples were drawn for determination of basal glucose and insulin. At time 0, glucose (25% dextrose provided at 11.4 g/m^2) was administered intravenously. Blood samples (2.0 mL) were then collected at the following times relative to glucose administration at 0 minutes: 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 minutes. Tolbutamide (125 mg/m^2) was injected intravenously at 20 minutes. Sera were analyzed for glucose (using the Ektachem DT II System; Johnson and Johnson Clinical Diagnostics, Raritan, NJ) and insulin (using radioimmunoassay; Diagnostic Products, Los Angeles, Calif). In our laboratory, the glucose analysis has a mean intra-assay coefficient of variation (CV) of 0.61% and a mean inter-assay CV of 1.45%. According to the supplier, cross-reactivity of the insulin assay with proinsulin is 40% at midcurve; C-peptide was not detected. In our laboratory, we observed a mean intra-assay CV of 5% and a mean inter-assay of 6%. Values were entered into the MINMOD Millenium 2003 computer program (version 5.16) to determine SI, the acute insulin response to glucose (AIRg), and the disposition index (SI × AIRg).[20]

Anthropometry and Body Composition

Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer, and weight was determined to the nearest 0.1 kg using a medical balance-beam scale; body mass index (BMI) was subsequently calculated. BMI percentiles were generated based on the Centers for Disease Control and Prevention Growth Charts using EpiInfo^{TM} (2003, Centers for Disease Control and Prevention; Atlanta, Ga). Fat mass and soft lean tissue mass (total lean tissue mass – bone mineral content) were assessed by dual-energy X-ray absorptiometry using a Lunar DPX-L densitometer that included pediatric software version 1.5e (LUNAR Radiation, Madison, WI).

Statistics

Children with at least 2 years of complete data and who progressed by at least one Tanner stage over their period of study participation were included in these analyses. This sample included 92 children (46 white, 46 black; 57 girls) and a total of 272 clinical observations. Multiple visits with clinical measurements corresponding to the same Tanner stage within each person were averaged to create a mean score for that Tanner stage. The averaging of data from multiple visits was done in favor of arbitrarily selecting an exam visit that corresponded to a specific Tanner stage.

At baseline, descriptive differences in anthropometry, body composition, and insulin/glucose measures in whites and blacks, and in boys and girls, were examined using independent samples *t* tests. Proportions of whites/blacks and boys/girls at baseline were compared across Tanner stages using χ^2 tests. For longitudinal analyses, mixed models regression (growth curve models) was performed with the dependent variables (SI, AIRg, and DI) being regressed on Tanner stage (ie, time variable), and these data did not deviate substantially from normality. Our research group has previously published longitudinal studies of changes in body fat and body fat distribution in youth[21,22] where growth curves were used to regress body composition over time.

In the present study, both the intercept and Tanner stage were treated as random factors with an unconstrained covariance structure. The β-coefficient for Tanner stage represents the unit change of SI, AIRg, and DI per one Tanner stage change. Stratified mixed models for SI, AIRg, and DI

Table 1. Descriptive characteristics of sample at initial clinic visit

	White (n = 46)	Black (n = 46)	Boys (n = 35)	Girls (n = 57)
Gender (boy/girl)	13/33	22/24	-	-
Tanner stage (range: 1-5)	1.5 ± 0.7	1.4 ± 0.9	1.1 ± 0.4	1.7 ± 0.9**
Age (y)	10.8 ± 1.5	9.5 ± 1.7*	9.6 ± 1.5	10.5 ± 1.8*
Height (cm)	145.6 ± 9.9	141.7 ± 10.4	141.9 ± 10.2	144.7 ± 10.3
Weight (kg)	44.4 ± 12.2	42.9 ± 13.7	43.1 ± 12.8	43.9 ± 13.1
BMI (kg/m^2)	20.7 ± 4.2	21.0 ± 4.7	21.0 ± 4.2	20.7 ± 4.6
BMI percentile	69.5 ± 27.7	79.3 ± 22.1	80.8 ± 22.9	70.4 ± 26.2
Fat mass (kg)	13.5 ± 7.8	12.8 ± 9.1	12.7 ± 8.7	13.4 ± 8.4
Lean tissue mass (kg)	28.1 ± 5.5	28.1 ± 5.4	28.2 ± 4.6	28.1 ± 5.9
SI ($\times 10^{-4}/min^{-1}/\mu IU/ml$)	5.84 ± 4.15	4.16 ± 2.33*	5.15 ± 3.37	4.91 ± 3.52
AIRg (μIU/ml)	730 ± 440	1777 ± 1244**	1474 ± 1500	1119 ± 660
DI ($\times 10^{-4}/min^{-1}$)	3342 ± 1754	6453 ± 3921**	5814 ± 4049	4335 ± 2829
Fasting insulin (μIU/ml)	13.2 ± 6.4	13.9 ± 7.0	13.4 ± 7.2	13.6 ± 6.4
Fasting glucose (mg/dl)	93.5 ± 4.7	94.1 ± 4.9	93.7 ± 4.8	93.8 ± 4.8

Values shown are means ± SD.
BMI (body mass index), *SI* (insulin sensitivity), *AIRg* (acute insulin response to glucose), *DI* (disposition index).
*p < 0.05 (Blacks < Whites; boys < girls).
**p < 0.01 (Blacks > Whites; boys < girls).

were run for whites and blacks separately because black children are known to have lower SI and higher insulin secretion compared with white children.[16,23,24] Both linear and quadratic models were fitted for SI variables because a curvilinear U-shape was expected based on earlier cross-sectional reports in which SI was lowest at Tanner stage III versus Tanner stage I (pre-puberty) and Tanner stage V (post-puberty).[5] Linear models were fitted for AIRg and DI. To estimate least square means of SI, AIRg, and DI, both race and Tanner stage were entered as categorical variables in separate mixed models for SI, AIRg, and DI.

In all adjusted models, fat mass (time-variant), sex, and baseline age (to account for the range of ages when children entered the study) were included as covariates. We did not simultaneously include both fat mass and soft lean tissue mass as covariates because they were highly and positively correlated, and because fat mass is a stronger correlate of insulin dynamics than soft lean tissue mass.[25,26] All statistical analyses were performed using Statistical Analysis Systems (*v*8.2, SAS Institute Inc., Cary, NC). Growth curve models were performed using the Mixed Procedure, and the type I error was set at $p < .05$.

RESULTS

Baseline Characteristics

Chi-square tests revealed that the distribution of whites and blacks across Tanner stages did not differ at baseline (χ^2 statistic = 6.9, $p = .10$), but there were more girls at later pubertal stages than boys (χ^2 statistic = 11.0, $p = .01$). Independent samples *t* tests showed that white children were older ($p < .05$), and, as expected from previous studies, had higher SI ($p < .05$) and lower AIRg and DI (both $p < .01$) compared with their black peers at baseline (Table I). No racial differences in anthropometry or body composition were observed. Boys and girls were not significantly different from one another with respect to any measures of anthropometry, body composition, or insulin/glucose measures, although boys were younger than girls at baseline ($p < .05$).

Number of Repeated Observations Across Sample

In these analyses, 34 children had two repeated observations, 33 children had three repeated observations, 20 had four repeated observations, and 5 had five repeated observations for a total of 92 children. Table II (available at www.jpeds.com) shows the sample size per number of repeated visits separated by sex and race. The total number of observations at each Tanner stage is shown in Table III (available at www.jpeds.com).

Changes in SI, AIRg and DI During Puberty

For SI, the effect of Tanner stage (quadratic) was significant in unadjusted models for both whites ($p = .003$) (Table IV, model 1) and blacks ($p = .002$) (Table IV, model 3). In both races, the change in SI across Tanner stages (quadratic) remained significant after adjusting for fat mass, sex, and baseline age (Table IV, model 2 and Table IV, model 4). As shown in Figure 1, SI decreased from Tanner stage I to II in both races, remained relatively stable between stages II and III, and showed a trend toward recovery by Tanner stage V to levels slightly above those at Tanner stage I. SI was higher in whites versus blacks at all points of sexual development (all $p < .001$). In addition, fat mass was inversely correlated with SI in both whites ($p = .0002$) and blacks ($p < .0001$).

Table IV. Unadjusted and adjusted mixed model regression of insulin sensitivity (SI) during puberty in whites and blacks

Dependent Variable	Effect	β ± SE	p-value
Whites (n = 46)			
Model 1:	Intercept	6.40 ± 0.66	<0.0001
SI (unadjusted)	Tanner stage (linear)	−1.65 ± 0.52	0.003
	Tanner stage (quadratic)	0.44 ± 0.14	0.003
Model 2:	Intercept	7.42 ± 2.63	0.007
SI (adjusted)	Tanner stage (linear)	−1.00 ± 0.55	0.08
	Tanner stage (quadratic)	0.35 ± 0.14	0.02
	Baseline age (y)	0.07 ± 0.23	0.8
	Gender[1]	−0.26 ± 0.75	0.7
	Fat mass (kg)	−0.14 ± 0.03	0.0002
Blacks (n = 46)			
Model 3:	Intercept	4.41 ± 0.36	<0.0001
SI (unadjusted)	Tanner stage (linear)	−1.17 ± 0.29	0.0002
	Tanner stage (quadratic)	0.25 ± 0.07	0.002
Model 4:	Intercept	6.17 ± 1.24	<0.0001
SI (adjusted)	Tanner stage (linear)	−0.76 ± 0.3	0.01
	Tanner stage (quadratic)	0.2 ± 0.08	0.009
	Baseline age (y)	−0.07 ± 0.13	0.6
	Gender[1]	−0.42 ± 0.39	0.3
	Fat mass (kg)	−0.08 ± 0.02	<0.0001

[1]Coded: Boy = 1, Girl = 0.

In unadjusted analyses, AIRg decreased linearly across Tanner stages in whites (p = .0007; Table V, model 1) and blacks (p = .01; Table V, model 3). After controlling for fat mass, sex, and baseline age, the effect of Tanner stage remained significant for both whites (Table V, model 2) and blacks (Table V, model 4). AIRg was higher in blacks versus whites at all Tanner stages (all p < .001; Figure 2). Although models were run separately by race, the β-coefficient for Tanner stage was twice the magnitude in blacks compared with whites suggesting a steeper drop in AIRg within the black group. As well, fat mass was positively related to AIRg in blacks (p = .001), but was borderline significant for whites (p < .06).

DI declined across increasing Tanner stages in the unadjusted models for both whites (p = .008; Table VI, model 1) and blacks (p = .0001; Table VI, model 3). After controlling for fat mass, sex, and baseline age, the only significant predictor of DI in whites was fat mass (p = .007; Table VI, model 2), whereas the effect of Tanner stage remained significant and negative in blacks (p = .001; Table VI, model 4) indicating an independent influence of Tanner stage on DI as shown in Figure 3. From Tanner stage I to V, DI decreased 21.8% in whites and 35.6% in blacks. Overall, we did not find that sex was a significant predictor of SI, AIRg, or DI in any of the adjusted models.

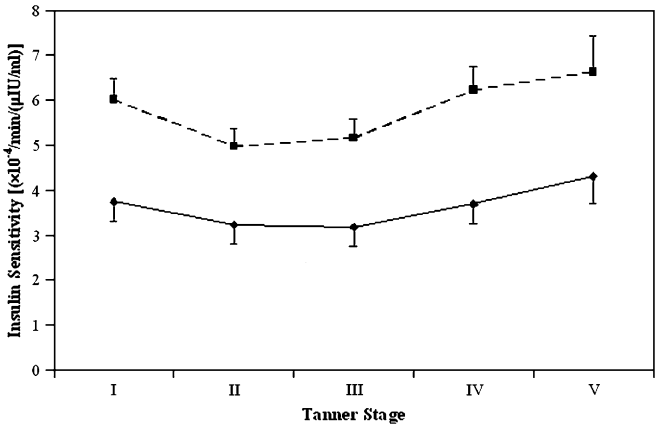

Figure 1. Plot of least square means (±SE) for insulin sensitivity across all five Tanner stages after adjusting for fat mass, sex, and baseline age. Dashed line, black squares represent white, whereas solid line, black diamonds represent black.

DISCUSSION

We report the longitudinal investigation of SI, insulin response, and DI during pubertal progression. Goran and Gower previously established that SI decreased as children matured from Tanner stage I to III.[14] Our present analyses revealed a curvilinear pattern of change in SI with levels decreasing at onset and subsequently recovering at the end of puberty. AIRg decreased linearly across Tanner stages in both racial groups, and increasing fat mass was also associated with increasing insulin secretion. Changes in DI differed between the two racial groups. In whites, DI was significantly related to fat mass but not Tanner stage; in blacks, DI declined linearly across increasing Tanner stages before and after adjusting for covariates. These data demonstrate that puberty may have a unique effect on β-cell compensation to insulin resistance in black children.

Insulin Sensitivity

This longitudinal study provides strong evidence confirming reports that SI decreases with onset of puberty and subsequently recovers by the end of puberty. Using the euglycemic-hyperinsulinemic clamp, Moran and coworkers[5] showed cross-sectionally in a large sample of black and white boys and girls (n = 357) that insulin resistance was increased in the Tanner stage II group versus Tanner stage I, remained relatively stable in the Tanner stage III and IV groups, and was decreased in the Tanner stage V group to similar levels as those at Tanner stage I. Although groups were not subdivided by Tanner stage, Caprio and colleagues[6] compared insulin

Table V. Unadjusted and adjusted mixed model regression of the acute insulin response to glucose (AIRg) during puberty in whites and blacks

Dependent Variable	Effect	β ± SE	p-value
Whites (n = 46)			
Model 1:	Intercept	767.28 ± 71.56	<0.0001
AIRg (unadjusted)	Tanner stage (linear)	−74.91 ± 20.61	0.0007
Model 2:	Intercept	922.58 ± 370.33	0.02
AIRg (adjusted)	Tanner stage (linear)	−93.15 ± 25.11	0.0006
	Baseline age (y)	−23.42 ± 32.62	0.5
	Gender[1]	−3.87 ± 106.87	0.9
	Fat mass (kg)	7.86 ± 4.05	0.06
Blacks (n = 46)			
Model 3:	Intercept	1872.09 ± 184.63	<0.0001
AIRg (unadjusted)	Tanner stage (linear)	−110.29 ± 42.59	0.01
Model 4:	Intercept	1494.06 ± 882.23	0.1
AIRg (adjusted)	Tanner stage (linear)	−187.71 ± 49.46	0.0004
	Baseline age (y)	18.26 ± 93.55	0.8
	Gender[1]	−367.10 ± 301.93	0.2
	Fat mass (kg)	31.46 ± 9.01	0.001

[1]Coded: Boy = 1, Girl = 0.

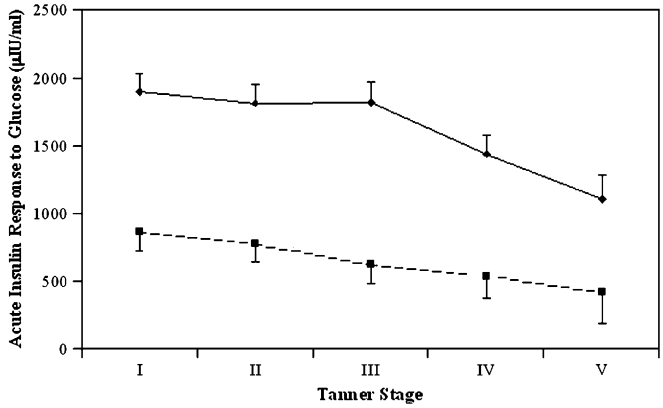

Figure 2. Plot of least square means (±SE) for the acute insulin response to glucose across all five Tanner stages after adjusting for fat mass, sex, and baseline age. Dashed line, black squares represent white, whereas solid line, black diamonds represent black.

resistance and secretion among children, adolescents, and young adults using the hyperglycemic clamp procedure. Plasma insulin and C-peptide concentrations were elevated in adolescents compared with the other groups implying that pubertal insulin resistance (and compensatory insulin secretion) is a transient phenomenon. To date, most studies of insulin resistance during puberty have not specifically examined children at high risk for developing type II diabetes early in life. We have evidence suggesting that puberty does not have an independent effect on SI in overweight Hispanic youth with a family history of type II diabetes after adjusting for the effects of age, sex, and body composition.[27] These data suggest that a high degree of body fat and/or family history of type II diabetes may mask the independent effects of puberty on insulin action and that pubertal changes in insulin resistance may be population specific.

Insulin Secretion

Several reports of pubertal insulin resistance have been published,[4,5,9,13] but few have assessed insulin secretion concurrently.[6,28] Caprio et al showed that both first and second (10–120 minutes) phase insulin secretion were higher in adolescents (Tanner stages II to V) versus children or young adults.[6] Others have shown using the homeostasis model assessment for pancreatic insulin secretion (HOMA β-cell) that insulin secretion did not differ across Tanner stage groups,[8] although this measure is less direct given its derivation from fasting insulin and glucose concentrations only. When we included SI as an additional covariate to control for the degree of insulin resistance, SI was the only significant correlate of AIRg for both races indicating that AIRg varies primarily as a function of SI (data not shown). However, our final models excluded SI as a covariate because we were primarily interested in AIRg variability across Tanner stages irrespective of the degree of insulin resistance.

AIRg decreased linearly as Tanner stage increased in both whites and blacks. However, insulin secretion and extraction are known to differ by race. Gower and colleagues[23] have shown that AIRg is higher in blacks versus whites, and this may be the result of either increased insulin secretion or decreased insulin clearance. The underlying physiology is still unknown, but group differences may relate to lower hepatic tissue mass or a conservation of β-cell function in blacks.[29] It is possible that other measures would be able to provide a more detailed assessment of insulin secretory dynamics. Although our research group has previously characterized differences in insulin secretory measures among whites, blacks, and Hispanics using C-peptide modeling,[23] we were unable to perform similar analyses in the present study. C-peptide modeling would help to identify both insulin secretion and clearance and whether differences in these variables are evident during puberty.

β-cell Function

The reduced DI in black children as they progressed through puberty underscores the potential importance of this developmental period in affecting diabetes risk. Inadequate insulin secretion in response to insulin resistance has been shown to be an important factor in the development of type II diabetes.[30] In our earlier report,[14] the reduced SI did not result in a concomitant increase in AIRg that was able to fully compensate for the degree of insulin resistance as

Table VI. Unadjusted and adjusted mixed model regression of the disposition index (DI) during puberty in whites and blacks

Dependent Variable	Effect	β ± SE	p-value
Whites (n = 46)			
Model 1:	Intercept	3311.73 ± 272.42	<0.0001
DI (unadjusted)	Tanner stage (linear)	−259.33 ± 93.54	0.008
Model 2:	Intercept	4226.17 ± 1547.86	0.009
DI (adjusted)	Tanner stage (linear)	−137.21 ± 102.72	0.2
	Fat mass (kg)	−49.95 ± 17.54	0.007
	Baseline age (y)	−11.02 ± 137.0	0.9
	Gender[1]	−213.02 ± 445.17	0.6
Blacks (n = 46)			
Model 3:	Intercept	6566.41 ± 609.7	<0.0001
DI (unadjusted)	Tanner stage (linear)	−818.01 ± 196.51	0.0001
Model 4:	Intercept	4182.6 ± 2138.47	0.06
DI (adjusted)	Tanner stage (linear)	−764.6 ± 218.62	0.001
	Fat mass (kg)	−37.89 ± 24.44	0.1
	Baseline age (y)	338.69 ± 225.02	0.1
	Gender[1]	−605.68 ± 693.08	0.4

[1]Coded: Boy = 1, Girl = 0.

children progressed from Tanner stage I to III, and a fall in DI was observed. An increased AIRg would be required to maintain a constant DI and reflect a healthy response by the β cell. The present analyses across all five Tanner stages revealed that in blacks, β-cell compensation decreased across increasing Tanner stages, suggesting that there may be conservation of β-cell activity or that β cells may be deteriorating. We did not perform oral glucose tolerance tests to clinically determine the degree of glucose tolerance, so it is unknown whether the declining β-cell function we observed in blacks represented an intermediate stage in the progressive development of impaired glucose tolerance (IGT) and type II diabetes. Despite normal glucose tolerance, β-cell compensation to the increased insulin secretory demand of obesity is reduced in adults with a positive family history of type II diabetes[31] suggesting that a high degree of adiposity combined with familial factors (environmental and/or genetic) may precede IGT or type II diabetes. In overweight Hispanic youth with a family history of type II diabetes,[27] we observed slightly lower β-cell function in later Tanner stages suggesting diminished insulin secretion for the degree of insulin resistance. Our observations in blacks (longitudinal data) and Hispanics (cross-sectional data), but not whites, offer suggestive evidence that declining DI may partly explain the increased risk of type II diabetes in these minority populations.

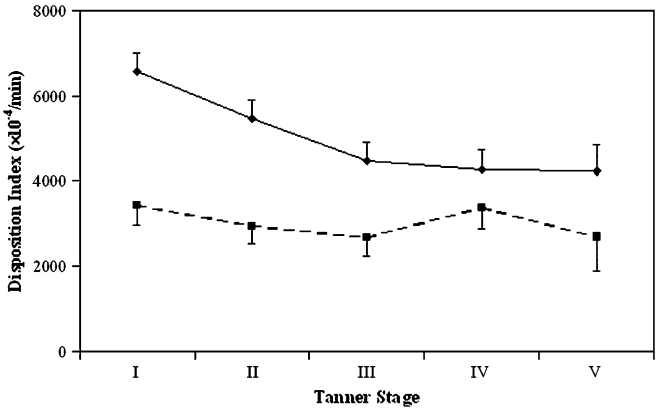

Figure 3. Plot of least square means (±SE) for the disposition index across all five Tanner stages after adjusting for fat mass, sex, and baseline age. Dashed line, black squares represent white, whereas solid line, black diamonds represent black.

Study Strengths and Limitations

The longitudinal design, inclusion of both white and black youth, the wide range of body fatness represented, and objective measures of body composition and insulin/glucose dynamics are clear strengths of this study. The growth curve modeling we employed was a distinct advantage because it took into account intraclass correlations across repeated measures and allowed for missing values in the dependent variables as well as the specification of the intercept and growth slope as random factors. Despite these advantages, several limitations must be acknowledged. There was a relatively small number of clinical observations at Tanner stage V (n = 20), and few individual children went through the whole continuum of pubertal development (n = 5). Future studies should examine changes in insulin and glucose parameters in children who progress through all five Tanner stages to confirm these observations. In addition, AIRg represented a measure of insulin secretion and clearance during the first 2 to 10 minutes of the frequently-sampled intravenous glucose tolerance test (FSIVGTT) only. Measuring insulin secretory dynamics over an extended period, along with C-peptide modeling to examine both secretion and extraction, would be useful to derive a comprehensive assessment of insulin secretion. It is unknown whether proportions of impaired fasting glucose or IGT differed across ethnic groups, or if familial factors such as gestational diabetes or family history of type II diabetes varied across groups because these latter factors may influence insulin action or secretion in offspring.[32] Additional longitudinal investigations that include adequate numbers of children at all Tanner stages and in populations at increased risk of type II diabetes (ie, overweight, Hispanic offspring of mothers with gestational diabetes) and with a focus on underlying mechanisms should provide insight into whether distinctive patterns of change in insulin action and secretion occur during puberty and whether population-specific differences in insulin resistance and β-cell function are evident.

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