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Longitudinal Study of Physiologic Insulin Resistance and Metabolic Changes of Puberty

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ABSTRACT: Cross-sectional studies have shown that 1) adolescents are insulin resistant compared with prepubertal children and adults, 2) pubertal insulin resistance is likely mediated by growth hormone (GH), and 3) pubertal insulin resistance is associated with increased fat oxidation and decreased glucose oxidation. The aim of this study was to assess the validity of these cross-sectional observations by performing a longitudinal study in normal children during the prepubertal and pubertal periods. Nine healthy, normal weight, prepubertal children underwent hyperinsulinemic-euglycemic and hyperglycemic clamp studies for evaluation of insulin sensitivity and insulin secretion. Children had repeat evaluations during puberty. Consistent with cross-sectional observations, this longitudinal study demonstrated that during puberty: 1) insulin sensitivity decreased by ~50%, 2) the decrease in insulin sensitivity was compensated by a doubling in insulin secretion, and 3) the decrease in insulin sensitivity was independent of changes in percentage of body fat. Puberty was associated with increased total body lipolysis and decreased glucose oxidation. A novel observation is the demonstration of ~50% decrease in adiponectin levels at the pubertal time point. These metabolic changes are proposed to be partially mediated by increased GH secretion and are consistent with the Randle cycle of competition between glucose and fat oxidation. **(*Pediatr Res* 60: 759–763, 2006)**

Cross-sectional studies examining insulin resistance during puberty have revealed that 1) pubertal insulin resistance is physiologic, occurring with pubertal progression and resolving by the end of puberty (1); 2) measures of adiposity do not completely explain physiologic pubertal insulin resistance (2); and 3) pubertal insulin resistance is associated with decreased peripheral insulin sensitivity and increased insulin secretion (3–6). We and others have shown that the pubertal increase in GH/insulin-like growth factor I (IGF-I) contributes to pubertal insulin resistance (7–9). The metabolic characteristics of pubertal insulin resistance are decreased glucose oxidation and decreased insulin-suppression of free fatty acid (FFA) oxidation (3,10). According to the Randle cycle, increased fat oxidation competes with glucose oxidation, contributing to decreased glucose uptake and insulin resistance (11–13). Our previous cross-sectional studies of the metabolic pathways responsible for pubertal insulin resistance are in agreement with the Randle theory (3).

Longitudinal studies of pubertal insulin resistance are scarce. Three longitudinal studies have reported on *in vivo* insulin sensitivity, using the frequently sampled i.v. glucose tolerance test, without information on the metabolism of insulin-sensitive fuels during the transition from prepuberty to puberty (14–16). Thus, the aim of this study was to investigate the longitudinal changes in *in vivo* insulin action and secretion, glucose and fat oxidation, total body lipolysis, and physical and hormonal characteristics in normal children during the prepubertal and pubertal periods. We hypothesized that puberty is associated with 1) decreased insulin sensitivity, with maintenance of glucose homeostasis *via* increased insulin secretion, and 2) an increase in the ratio of fat to glucose oxidation, mediated by increased GH/IGF-I. We further theorized that the decrease in insulin sensitivity during puberty correlates with the increase in GH/IGF-I and the ratio of fat to glucose oxidation.

METHODS

Study subjects. The studies were approved by the Human Rights Committee of Children's Hospital of Pittsburgh/Institutional Review Board, University of Pittsburgh, and parental informed consent and child assent were obtained for all subjects. Healthy, prepubertal participants were recruited from the surrounding community through local advertisements. Nine [body mass index (BMI) <85th percentile] prepubertal children [six white girls, Tanner stage I for breast development and pubic hair, estradiol levels 0–5 pg/mL; three boys (one black, two white), Tanner stage I for genital development and pubic hair, testosterone levels 7–14 ng/dL] were studied in the General Clinical Research Center (GCRC) at Children's Hospital of Pittsburgh. None of the participants were taking chronic medications, including contraceptive pills or had a chronic disease known to influence body composition or insulin action. All nine participants underwent all study evaluations twice, once while prepubertal and again during puberty. All subjects were in good health during both study periods as assessed by medical history, physical examination, normal glycosylated hemoglobin (HbA1C) values, and routine hematologic and biochemical tests. The mean interval between the prepubertal and pubertal studies for participants was 5.4 ± 1.2 y (range, 3–7 y). Pubertal development was assessed according to the criteria of Tanner by a single pediatric endocrinologist (Tanner stage IV–V for breast development and pubic hair in females, range of estradiol levels 18–159 pg/mL; Tanner stage III–V for genital development and pubic hair in males, range of

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Abbreviations: GCRC, General Clinical Research Center; **R_a,** rate of appearance

Table 1. *Physical, hormonal, and metabolic characteristics of subjects at baseline (prepuberty) and at puberty*

	Prepuberty ($n = 9$)	Puberty ($n = 9$)
Age, y‡	9.8 ± 0.4	15.3 ± 0.4
Weight, kg‡	31.8 ± 1.3	62.7 ± 3.1
Height, cm‡	137.8 ± 2.6	167.2 ± 3.0
BMI percentile	47.8 ± 7.0	62.2 ± 10.4
Fat-free mass, kg‡	23.7 ± 0.9	42.5 ± 2.2
Fat mass, kg*	6.0 ± 0.7	17.1 ± 4.1
% Body fat	19.2 ± 2.0	26.1 ± 5.2
Visceral adipose tissue, cm^2*	10.8 ± 0.9	31.8 ± 6.2
IGF-I, ng/mL†	201.3 ± 14.3	330.7 ± 31.3
Glucose, mg/dL	93.8 ± 1.8	95.4 ± 1.5
Insulin, μU/mL*	12.6 ± 0.9	24.1 ± 4.1
C-peptide, ng/mL*	1.01 ± 0.12	2.28 ± 0.33
Fasting hepatic glucose production, mg/kg/min*	4.6 ± 0.8	2.6 ± 0.3
Leptin, ng/mL*	7.5 ± 1.4	17.9 ± 5.4
Adiponectin, μg/mL†	15.9 ± 2.3	7.5 ± 1.2
Cholesterol, mg/dL*	165 ± 8	146 ± 10
Triglycerides, mg/dL	91 ± 14	81 ± 8
LDL, mg/dL	94 ± 7	88 ± 10
HDL, mg/dL*	53 ± 4	43 ± 2
VLDL, mg/dL	18 ± 3	16 ± 2
LDL/HDL	1.8 ± 0.2	2.2 ± 0.3

* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low density lipoprotein.

testosterone levels 637–781 ng/dL). Baseline characteristics and characteristics at follow-up of the participants are presented in Table 1.

Metabolic studies. All evaluations were performed in the GCRC after a 10- to 12-h overnight fast. At both the prepubertal and pubertal time points, each subject was studied twice (1–3 wk apart), once during a 3-h hyperinsulinemic-euglycemic clamp to assess insulin sensitivity and once during a 2-h hyperglycemic clamp to assess insulin secretion, according to the methods originally described by DeFronzo *et al.* (17). For each study, two i.v. catheters were inserted, one in a forearm vein for administration of stable isotopes, insulin, and glucose, and the second in a dorsal contralateral hand vein for sampling of arterialized venous blood from the warmed hand.

Total-body lipolysis was measured at baseline after overnight fasting by the use of a primed (1.2 μmol/kg) constant rate (0.08 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) infusion of [$^2H_5$]glycerol (Isotec, Miamisburg, OH), which was started 3 h before the clamp (3). Fasting hepatic glucose production was measured simultaneously with a primed (2.8 μmol/kg) constant infusion (0.28 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) of [6,6-$^2H_2$]glucose (18). Insulin sensitivity was assessed during a 3-h 40 $mU \cdot m^{-2} \cdot min^{-1}$ hyperinsulinemic-euglycemic clamp in conjunction with indirect calorimetry (3,19,20). First- and second-phase insulin secretion was assessed during a 2-h hyperglycemic clamp (225 mg/dL) (3,20).

Body composition analysis. Body composition was determined by dual-energy x-ray absorptiometry (DEXA). Visceral adipose tissue (cm^2) was determined using a single-slice computed tomography scan at intervertebral space L4-5, as previously described (20).

Biochemical measurements. Plasma glucose was measured by the glucose oxidase method (Yellow Springs Instrument, Yellow Springs, OH). Plasma insulin concentration was determined by radioimmunoassay (RIA) (20). Plasma FFA levels were quantitated by an enzymatic colorimetric method with the use of the nonesterified fatty acid C test kit (Wako, Osaka, Japan) (10). IGF-I was measured by RIA after acid ethanol extraction (Nichols, San Juan Capistrano, CA). Plasma lipid levels were measured using the standards of the Centers for Disease Control and Prevention as described previously (19). Serum leptin was measured by double-antibody RIA using ^{125}I-labeled human leptin as tracer and rabbit antihuman leptin antibodies (Linco, St. Louis, MO). Adiponectin was measured using a commercially available RIA kit (Linco Research) (21). C-peptide determinations were performed at Esoterix Inc., (Calabasas Hills, CA) by immunochemiluminescent assay. Total and free testosterone, estradiol, and dehydroepiandrosterone sulfate were measured as described previously (18–20,22).

Deuterium enrichment of glucose and glycerol in the plasma were determined on a Hewlett-Packard Co. 5971 mass spectrometer (Palo Alto, CA) coupled to a 5890 series II gas chromatograph as previously reported (10,18). Plasma samples were deproteinized with methanol. Supernatants were dried in a vacuum centrifuge. The aldolnitrile pentaacetate derivative of glucose was analyzed for ^2H enrichment in the electron impact mode. Selective ion monitoring software was used to monitor the mass-to-charge ratio for (*m/z*) 200 and 202, reflecting unlabeled and labeled glucose. Pentafluoropropyl derivatives of glycerol were prepared by adding pentafluoropropionic anhydride and ethyl acetate to the dried samples. Selected ion monitoring software was used to monitor charge-to-mass ratio (*m/z*) 367 for (*M*) and 372 for (*M* + 5), representing unlabeled and $^2H_5$-labeled glycerol. Standard curves of known enrichments were performed with each assay.

Insulin sensitivity and secretion. Glucose turnover at baseline was calculated during the last 30 min of the fasting [6,6-$^2H_2$]glucose infusion period according to steady-state tracer dilution equations as previously reported (18). Insulin-stimulated glucose disposal was calculated during the last 30 min of the euglycemic-hyperinsulinemic clamp to be equal to the rate of exogenous glucose infusion. Peripheral insulin sensitivity was calculated by dividing the glucose disposal rate by the steady-state clamp insulin level and multiplied by 100 ($mg \cdot kg$ fat-free $mass^{-1} \cdot min^{-1}$ per $\mu U \cdot mL^{-1}$). The glucose disposition index was calculated as the product of insulin sensitivity × first-phase insulin secretion (23). During the hyperglycemic clamp, the first-phase insulin concentration was calculated as the mean of five determinations every 2.5 min during the first 15 min of the clamp, and the second-phase concentration was calculated as the mean of eight determinations from 15–120 min (24).

Total-body lipolysis. The rate of appearance (R_a) of endogenous glycerol in plasma was calculated during the last 30 min of the fasting period according to steady-state tracer dilution equations (3).

Glucose and fat oxidation. Basal and insulin-stimulated glucose and fat oxidation rates were calculated from indirect calorimetric data by averaging the data over the 30 min of measurements at baseline and at the end of the 3-h clamp study according to Frayn formulas (10). Glucose storage or nonoxidative glucose disposal during hyperinsulinemia was estimated by subtracting glucose oxidation from total glucose disposal.

Statistical analysis. Statistical analyses were performed using within-subject changes and were assessed by a paired two-tailed *t* test. Spearman correlation analysis was used, where appropriate, to examine bivariate relationships. Data are presented as means ± SEM. A *p* value of ≤0.05 was considered statistically significant.

RESULTS

Physical, hormonal, and lipid profiles. The longitudinal physical, hormonal, and lipid profiles of the participants at the prepubertal to pubertal time points are summarized in Table 1. Fat mass, including visceral fat, and fat-free mass increased during puberty, as expected. Only one subject became overweight (BMI ≥95th percentile) during puberty. Overall, the mean BMI percentiles and percentages of body fat were not significantly different during the prepubertal and pubertal time points, especially after excluding this subject. Moreover, the paired sample correlation for the percentage of body fat at prepubertal and pubertal time points was significant ($r = 0.848$, $p = 0.004$). Fasting hepatic glucose production decreased, fasting insulin levels increased, whereas fasting glucose levels were unchanged during puberty. As expected, puberty was associated with an increase in IGF-I and leptin levels. Puberty was also associated with a decrease (~50%) in adiponectin levels and a decrease in total and high-density lipoprotein cholesterol, without significant changes in the remaining components of the lipid profile.

Fat metabolism. Total body lipolysis (glycerol R_a) was higher (175 ± 13 *versus* 233 ± 21 $\mu mol/m^2/min$, $p = 0.028$) during puberty (Fig. 1*A*). When corrected for fat mass, rates of lipolysis were not significantly higher during puberty (36.7 ± 4.8 *versus* 42.6 ± 8.8 μmol/kg fat mass/min, $p = 0.47$). The ratio of fat to glucose oxidation (FOX/GOX) increased by

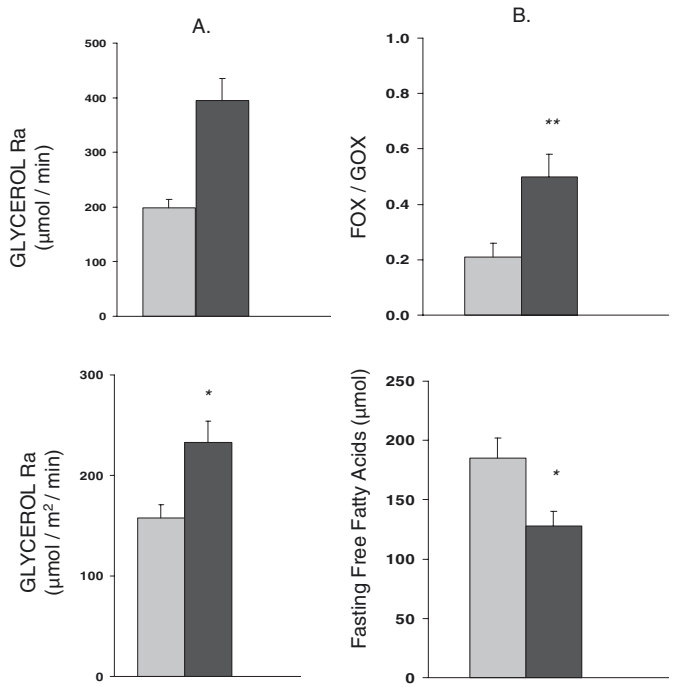

Figure 1. Rates of total body lipolysis (glycerol R_a) (*A*) and substrate oxidation (FOX/GOX ratio) and FFA levels (*B*) at the prepubertal (*shaded columns*) *vs* pubertal (*filled columns*) time points ($n = 9$). *$p < 0.05$; **$p < 0.01$.

~125% during puberty (0.22 ± 0.05 *versus* 0.50 ± 0.08, $p = 0.005$), with significantly lower plasma FFA levels (~31%) at the pubertal time point (Fig. 1*B*).

Glucose metabolism. Longitudinal changes in insulin-mediated glucose metabolism among participants are summarized in Figs. 2 and 3. Insulin-stimulated total, oxidative, and nonoxidative glucose disposal decreased significantly during puberty (Fig. 2). During the hyperinsulinemic-euglycemic clamp, there were no significant differences between prepubertal and pubertal studies in steady-state clamp glucose (101 ± 0.8 *versus* 101 ± 0.4 mg/dL, $p = 0.989$) or insulin (102 ± 5 *versus* 148 ± 20 μU/mL, $p = 0.059$) concentrations. There was ~50% decrease in insulin sensitivity at the pubertal time point, which was accompanied by a near doubling of first-phase insulin secretion, allowing for maintenance of the glucose disposition index (Fig. 3).

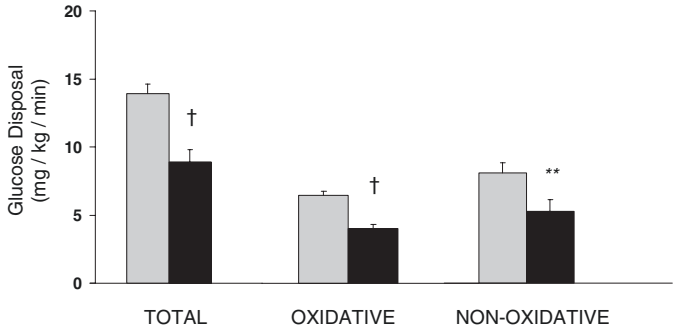

Figure 2. Insulin-stimulated glucose metabolism during the hyperinsulinemic-euglycemic clamp at the prepubertal (*shaded columns*) *vs* pubertal (*filled columns*) time points ($n = 9$). Total glucose disposal = 13.9 ± 0.7 *vs* 8.9 ± 0.9 mg/kg/min. Nonoxidative glucose disposal = 7.7 ± 0.7 *vs* 5.0 ± 0.8 mg/kg/min. Oxidative glucose disposal = 6.3 ± 0.3 *vs* 3.9 ± 0.3 mg/kg/min. **$p < 0.01$; †$p < 0.001$.

Correlations. IGF-I levels were negatively correlated with glucose oxidation ($r = -0.48$, $p = 0.05$), and positively correlated with total body lipolysis ($r = 0.69$, $p = 0.003$) and fat oxidation ($r = 0.47$, $p = 0.05$). There was no significant relationship between levels of sex steroids and measures of carbohydrate metabolism during puberty. In a multiple linear regression analysis with insulin sensitivity as the dependent variable and IGF-I, BMI percentile, and visceral adipose tissue as the independent variables ($R^2 = 0.44$, $p = 0.05$), the only significant contributor to the model was IGF-I, explaining 34% of the variance in insulin sensitivity (partial correlation of IGF-I = −0.58, $p = 0.01$).

DISCUSSION

This is the first report of a longitudinal study of insulin sensitivity and insulin secretion that includes information on substrate utilization among children during the prepubertal and pubertal periods. Our results confirm and extend previous published longitudinal and cross-sectional studies examining developmental changes in insulin sensitivity. Consistent with cross-sectional observations, the present longitudinal study demonstrates that in otherwise healthy adolescents: 1) insulin sensitivity decreases by ~50% during puberty; 2) the decrease in insulin sensitivity is compensated by a doubling of insulin secretion, maintaining the glucose disposition index and glucose homeostasis; and 3) the decrease in insulin sensitivity is not dependent on changes in the percentage of body fat. Moreover, and for the first time, the data show that during puberty basal rates of total body lipolysis increase significantly, with ~125% increase in the ratio of fat to glucose oxidation.

In a previous longitudinal study of pubertal insulin resistance, Hoffman *et al.* (16) did not find a significant relationship between Tanner stage and insulin sensitivity, but did demonstrate significant relationships between insulin sensitivity and BMI and insulin sensitivity and peripheral GH action (IGF-I levels). In the Hoffman *et al.* study, participants ($n = 24$) were separated into individual Tanner stage groups, which is ideal, but may have limited the ability to detect significant associations between pubertal development and insulin resistance. Previous cross-sectional studies have shown that pubertal insulin resistance is present during all stages of puberty and returns to near prepubertal levels at Tanner stage V (2,25). Our results demonstrate significant changes in insulin action and substrate utilization, despite grouping the subjects into only two groups (prepubertal and pubertal).

Our results indicating that puberty is associated with decreased insulin sensitivity and increased insulin secretion are consistent with results of previous longitudinal studies by Goran and Gower (15) and Ball *et al.* (14), both of which used the frequently sampled i.v. glucose tolerance test. These previous studies included larger numbers of participants ($n = 60$ for the Goran and Gower study; $n = 92$ for the Ball *et al.* study), consisting of a mixed population of white and black

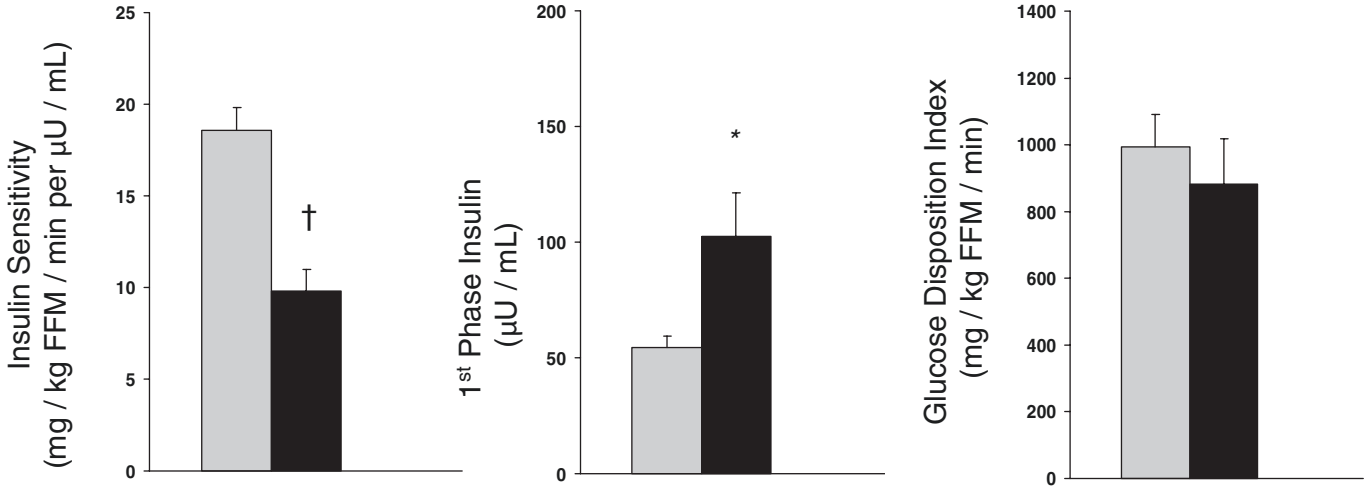

Figure 3. Insulin sensitivity calculated from the hyperinsulinemic-euglycemic clamp, first-phase insulin secretion during the hyperglycemic clamp, and glucose disposition index (insulin sensitivity × first-phase insulin) at the prepubertal (*shaded columns*) *vs* pubertal (*filled columns*) time points ($n = 9$). Insulin sensitivity = 18.6 ± 1.2 *vs* 10.0 ± 1.2 mg/kg FFM/min per μU/mL. First-phase insulin secretion = 54 ± 5 *vs* 102 ± 19 μU/mL. *$p < 0.05$; †$p < 0.001$.

subjects with variable percentages of body fat, including overweight prepubertal subjects. The Goran and Gower study showed that after controlling for measures of adiposity, children transitioning to puberty had decreased insulin sensitivity (−32%), increased insulin secretion (+30%), and a decreased glucose disposition index, suggesting pancreatic β-cell decompensation. The study by Ball *et al.* (14) confirmed the earlier findings and reported differences in the glucose disposition index among white and black children as they transitioned to puberty. Results of this study indicate that black children, but not white children, have a decreased glucose disposition indicative of declining pancreatic β-cell function during puberty. We have also previously shown that in high-risk children with a family history of type 2 diabetes mellitus, there is an impaired relationship between insulin action and pancreatic β-cell compensation even among those with normal glucose tolerance (26). In the present study, we found that despite a 50% decrease in insulin sensitivity during puberty, the glucose disposition index was maintained *via* a compensatory increase in insulin secretion.

Consistent with previous cross-sectional studies, our data indicate that puberty-induced changes in insulin-stimulated fuel metabolism include reduced peripheral glucose uptake, reduced oxidative and nonoxidative glucose metabolism, and preservation of hepatic insulin sensitivity (decreased fasting hepatic glucose production) during puberty (2,5,25). Previous studies have also shown that the ability of insulin to suppress hepatic glucose production is preserved during normal puberty (25). Increased total body lipolysis and decreased FFA levels during puberty were associated with decreased glucose oxidation. Previous cross-sectional studies have shown that total body lipolysis is higher in pubertal subjects than in prepubertal or adult subjects and those rates of lipolysis correlate positively with IGF-I levels (3). When lipolysis is expressed per unit of body weight or body fat, rates have been shown to be comparable between prepubertal and pubertal subjects (3,27). Our data are in agreement with this and support the concept that physiologic pubertal insulin resistance affects glucose oxidation to a greater extent than fat oxidation, increasing the ratio of fat to glucose oxidation during puberty. This is consistent with our previous proposal that decreased glucose oxidation may be secondary to the Randle cycle of competition between fat and glucose oxidation (3,10).

GH is known to increase total body lipolysis and fat oxidation (28,29). Moreover, data from previous studies support the concept that the GH/IGF-I axis is an important contributor to pubertal insulin resistance (8,9,30,31). It has been shown that children on exogenous GH therapy exhibit GH-induced changes in insulin-mediated glucose metabolism similar to those observed among pubertal children (30,32). Our data support the concept that changes in the GH/IGF-I axis are associated with changes in insulin-sensitive fuel metabolism and contribute to pubertal insulin resistance; however, a causal relationship cannot be implied.

A novel observation from our data is the significant (~50%) decrease in adiponectin levels as children transitioned to puberty. We show here for the first time that adiponectin levels decrease in proportion to the decrease in insulin sensitivity during puberty. The decrease in adiponectin was not significantly correlated with change in the percentage of body fat ($r = 0.65$, $p = 0.16$), nor was it correlated with change in visceral fat ($r = -0.313$, $p = 0.55$). However, failure to detect a significant correlation here may be due to error because of the small number of participants in the study. Previous cross-sectional studies have shown that obese adolescents have ~50% lower adiponectin than normal-weight peers, with adiponectin levels being inversely correlated with visceral adipose tissue (21) and positively correlated with insulin sensitivity and secretion (33,34). Our data suggest that puberty alone may contribute to decreasing adiponectin levels; however, further study with larger numbers of participants is needed to verify this.

Our study is limited by a small subject population that included both males and females. Although the subject number was small, the prospective study design allowed for identical studies to be performed twice in the same subjects.

Metabolic differences between the prepubertal period and the postpubertal period were highly significant, and results from this study contribute further to the knowledge base in the field of pediatric insulin resistance. In a complex longitudinal study of this nature, there is a risk that the study population would become more heterogeneous during the transition to puberty. In the current study, only one subject became overweight during the transition to puberty. Although pubertal insulin resistance is a normal physiologic process, it may contribute to a pathologic process in the presence of obesity and/or pancreatic β-cell dysfunction; thus, the risk of developing impaired glucose tolerance or type 2 diabetes mellitus is increased during adolescence (14,33,35). This highlights the need for prevention/intervention of obesity during this most pivotal period of growth and development.

In conclusion, puberty was associated with a significant reduction in insulin sensitivity that was not explained by increased adiposity, with sufficient pancreatic β-cell compensation to maintain glucose homeostasis in this longitudinal study of healthy participants. Adiponectin levels were reduced in proportion to the reduction in insulin sensitivity. Puberty was also associated with increased total body lipolysis, decreased glucose oxidation, and increased ratio of fat to glucose oxidation. These changes are proposed to be partially mediated by GH/IGF-I and are consistent with the Randle cycle of competition between glucose and fat oxidation.

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