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Insulin Sensitivity, Lipids, and Body Composition in Childhood: Is "Syndrome X" Present?*

SILVA ARSLANIAN AND CHITTIWAT SUPRASONGSIN

Division of Pediatric Endocrinology, Metabolism, and Diabetes Mellitus, Children's Hospital, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

ABSTRACT

Syndrome X, or the syndrome of insulin resistance, is a cluster of related metabolic abnormalities of hyperinsulinemia, glucose intolerance, increased very low density lipoprotein (VLDL), decreased high density lipoprotein (HDL), and hypertension in nonobese adults and plays an important role in the genesis of cardiovascular disease. The aim of the present study was to examine the relationships among insulin sensitivity, plasma lipid levels, and body composition in the pediatric age group to determine whether these associations are present in childhood.

Twenty healthy Caucasian Tanner stage I (TI) children (age, 10.7 ± 0.3 yr; body mass index, 18.9 ± 0.8 kg/m^2) and 22 pubertal Tanner stage II–IV (TII–IV) adolescents (age, 14.0 ± 0.3 yr; body mass index, 20.0 ± 0.4 kg/m^2) were studied. *In vivo* insulin-mediated glucose disposal (Rd) was evaluated during a 40 mu/m^2·min hyperinsulinemic-euglycemic clamp. Body composition was assessed isotopically by the $H_2{}^{18}O$ dilution principle. Fasting blood was obtained for cholesterol, triglyceride (TG), VLDL, low density lipoprotein (LDL), and HDL determinations.

In both groups, the strongest correlation of Rd was with percent body fat (%BF) (TI: r = −0.82; $P < 0.001$; TII–IV: r = −0.73; $P < 0.001$). In addition, in TI, Rd was correlated with TG (r = 0.64; $P = 0.001$), VLDL (r = 0.64; $P = 0.001$), and diastolic blood pressure (r = −0.50; $P = 0.01$). There were no such correlations in TII–IV. In TI, %BF correlated positively with LDL and negatively with TG and VLDL. In TII–IV, %BF correlated positively with cholesterol and LDL. After correcting for %BF, partial correlation analysis revealed no relationship between Rd and lipid levels in either group. This suggests that the relationship of insulin sensitivity to lipid levels was secondary to the effect of body composition on lipid levels. However, regardless of body composition, the basal insulin level was correlated with TG (r = 0.38; $P = 0.04$) and VLDL (r = 0.40; $P = 0.04$) in TII–IV subjects.

We conclude that 1) the primary correlate of insulin sensitivity is %BF in both prepubertal and pubertal subjects, with no relationship to plasma lipids; 2) in prepubertal children, diastolic blood pressure is negatively correlated with insulin sensitivity and positively with insulin levels, independent of adiposity; and 3) after the onset of puberty, basal insulin levels are positively correlated with VLDL and TG regardless of the degree of adiposity. This observation could be a very early manifestation of the genesis of syndrome X in childhood. (*J Clin Endocrinol Metab* **81:** 1058–1062, 1996)

SYNDROME X, or the syndrome of insulin resistance, is a cluster of related metabolic abnormalities of hyperinsulinemia, glucose intolerance, increased very low density lipoproteins (VLDL) and triglycerides (TG), decreased high density lipoprotein (HDL), and hypertension in nonobese individuals and plays an important role in the genesis of cardiovascular disease (CVD) (1–9). Several epidemiological and clinical studies in adults have provided evidence in favor of this syndrome, in which insulin resistance is proposed to be the primary abnormality and the other alterations secondary to it (1, 9). The ongoing debate, however, is whether syndrome X is the result of differences in body composition and body fat (BF) topography or is independent of obesity.

In the pediatric age group, studies are scarce regarding the relationship of insulin sensitivity to body composition and serum lipoprotein levels. A study in Finnish children has shown that high TG and low levels of HDL cholesterol cluster among subjects within the highest insulin quartile (10). Furthermore, it was recently demonstrated that in obese adolescents, insulin resistance explains some of the variance in TG, low density lipoprotein (LDL), and HDL levels (11). Therefore, we hypothesized that the parameters associated with syndrome X in adults could be detected early in childhood, but with a variable expression of the cluster of metabolic alterations. Thus, the aim of the present study was to examine the relationships between insulin sensitivity (measured by hyperinsulinemic-euglycemic clamp), plasma lipid levels, and isotopically determined body composition in normal prepubertal children and pubertal adolescents.

Subjects and Methods

Subjects

Twenty healthy Caucasian prepubertal children (age, 10.7 ± 0.3 yr) and 22 pubertal adolescents (age, 14.0 ± 0.3 yr; Table 1) were studied at the General Clinical Research Center (GCRC) at Children's Hospital of Pittsburgh. All studies were approved by the human rights committee of Children's Hospital of Pittsburgh.

All subjects and parents gave written informed consent after full explanation of the proposed studies. All subjects were in good health, as assessed by medical history, physical examination, and routine hematological and biochemical tests. Pubertal development was assessed by physical examination according to the criteria of Tanner (12) and confirmed by measurements of plasma testosterone in males and estradiol in females. All subjects had normal glycosylated hemoglobin values. None was receiving any medications. Some of these subjects have been reported previously (13).

Experiments were performed in the postabsorptive state after a 12-h

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Address all correspondence and requests for reprints to: Silva Arslanian, M.D., Division of Endocrinology, Children's Hospital of Pittsburgh, 3705 Fifth Avenue at DeSoto Street, Pittsburgh, Pennsylvania 15213.

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TABLE 1. Clinical and biochemical characteristics of study subjects

	Tanner I (n = 11♂ + 9♀)	Tanner II–IV (n = 13♂ + 9♀)
Age (yr)	10.7 ± 0.3	14.0 ± 0.3
BMI (kg/m^2)	18.9 ± 0.8	20.0 ± 0.4
%BF	12.9 ± 2.1	12.5 ± 1.8
FFM (kg)	33.6 ± 1.7	47.9 ± 2.0[a]
Insulin (pmol/L)	86 ± 10 (14.4 ± 1.6)	97 ± 7 (16.1 ± 1.1)
Cholesterol (mmol/L)	4.0 ± 0.1 (155 ± 4)	3.9 ± 0.1 (150 ± 5)
Triglyceride (mmol/L)	1.0 ± 0.1 (86 ± 7)	0.9 ± 0.1 (81 ± 7)
LDL (mmol/L)	2.4 ± 0.1 (93 ± 5)	2.5 ± 0.1 (96 ± 5)
VLDL (mmol/L)	0.4 ± 0.03 (14 ± 1)	0.3 ± 0.02 (12 ± 1)
HDL (mmol/L)	1.2 ± 0.1 (48 ± 2)	1.1 ± 0.1 (43 ± 2)
Systolic BP (mm Hg)	104 ± 2	108 ± 1
Diastolic BP (mm Hg)	66 ± 2	69 ± 1
Rd (μmol/kg · min)	66.1 ± 5.0 (11.9 ± 0.9)	55.5 ± 2.8 (10.0 ± 0.5)[b]

Metric units are added in *parentheses:* for lipids, mg/dL; for insulin, μU/mL; and for Rd, mg/kg · min.
[a] $P < 0.05$.
[b] $P < 0.001$.

overnight fast. For each study, two iv catheters were inserted. One was placed in an antecubital vein for the infusion of insulin and exogenous glucose, and the second was placed in a vein on the dorsum of the contralateral heated hand for sampling of arterialized venous blood (13).

Insulin-stimulated glucose disposal

In vivo insulin sensitivity was evaluated by the hyperinsulinemic-euglycemic clamp (14). Intravenous crystalline insulin (Humulin, Eli Lilly Co., Indianapolis, IN) was infused at a constant rate of 40 mU/m^2·min to elevate the plasma insulin concentration to a steady state level (~100 μU/mL). Plasma glucose was clamped at 100 mg/dL with a variable rate infusion of 20% dextrose. The rate of glucose infusion was adjusted based on arterialized plasma glucose measurements every 5 min. Insulin stimulated glucose disposal (Rd) was calculated during the last 30 min of the clamp to be equal to the rate of the exogenous glucose infusion, as insulin at this dose level inhibits hepatic glucose production (15). Before the start of the clamp, a fasting blood sample was obtained for determination of cholesterol, HDL, LDL, TG, and VLDL.

Body composition analysis

Assessment of total body water was made with the use of $H_2{}^{18}O$, with measurement of the stable isotope ^{18}O in the expired CO_2 (16, 17). After a baseline breath sample was obtained, a weighed amount of $H_2{}^{18}O$ (0.03 g/kg), 95–98 atom% excess ^{18}O (Isotec, Miamisburg, OH), was given 3 h before the clamp study. Breath samples were collected while the subjects breathed normally through a mouthpiece and one-way valve connected to a 5-L anesthesia bag. An aliquot of this sample was placed into a glass vacuum tube. Separation of CO_2 was performed by cryogenic distillation in a vacuum, as described previously (13, 17). Three breath samples were obtained at the end of the 3-h equilibration before the start of the insulin clamp. Blood pressure was measured in the supine position with a mercury sphygmomanometer. The mean of two readings, one on admission to the GCRC and one at 0000 h while the patient was asleep, was used in statistical analyses.

Biochemical measurements

Plasma glucose was measured by the glucose oxidase method with the use of a Yellow Springs Instrument Co. glucose analyzer (Yellow Springs Instrument Co., Yellow Springs, OH). Plasma insulin was analyzed by RIA (18). Plasma lipid levels were measured using Center for Disease Control protocols. Cholesterol determinations were performed using the Cholesterol High Performance-K enzymatic kit method (Boehringer Mannheim, Indianapolis, IN). For HDL measurements, serum was precipitated by dextran sulfate using HDL cholesterol determination (Seradyn, Indianapolis, IN). The supernatant then was measured for its cholesterol content. TG levels were measured using TG-glycerol blank reagents (Boehringer Mannheim). This method gives true TG measurements. LDL cholesterol was computed using cholesterol, HDL cholesterol, and TG levels.

The O^{18} enrichment of expired CO_2 distilled from breath was measured with the use of an isotope ratio mass spectrometer. Total body water was calculated from ^{18}O enrichment of expired CO_2. Fat-free mass (FFM) and fat mass were calculated from total body water measurements on the basis of the concept that water occupies 73.2% of the FFM (13, 16, 17).

Statistical analysis

Statistical analyses were performed using Student's t test. Pearson correlation coefficients were computed to assess bivariate relationships. Partial correlation coefficients were used to control for the effect of different interrelated variables on the dependent variable. Data are presented as the mean ± SE. $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the clinical and biochemical characteristics of the study subjects. As expected, FFM was higher in pubertal than prepubertal children. There were no significant differences in percent adiposity and plasma lipid levels between the two groups. Insulin-stimulated glucose disposal was significantly lower in pubertal than in prepubertal subjects.

Table 2 shows the correlations among insulin-stimulated glucose disposal, plasma lipid levels, and percent BF (%BF) in prepubertal and pubertal subjects. In both groups, the strongest correlation of glucose disposal was with %BF (Fig.

TABLE 2. Relationship of insulin-stimulated glucose disposal to lipid levels and adiposity

Correlations: Rd *vs.*	Tanner I [r (*P* value)]	Tanner II–IV [r (*P* value)]
Cholesterol	−0.15	−0.30
TG	0.64 (.001)	−0.11
LDL	−0.32	−0.20
HDL	0.14	−0.18
VLDL	0.64 (0.001)	−0.05
% Body fat	−0.82 (<0.001)	−0.74 (<0.001)
Basal insulin	−0.80 (<0.001)	−0.46 (0.02)
Diastolic BP	−0.51 (0.012)	0.12
Systolic BP	−0.17	0.20

P values are indicated in *parentheses* when significant.

1). In prepubertal children, glucose disposal was correlated positively with TG and VLDL and negatively with diastolic blood pressure. There were no such correlations in pubertal adolescents.

Table 3 depicts the correlations between %BF and plasma lipid levels. In prepubertal children, %BF showed a positive correlation with LDL and negative correlations with TG and VLDL. In pubertal adolescents, the correlations of %BF were limited to total and LDL cholesterol. Blood pressure did not correlate with %BF in either group. Because of these strong associations between %BF and lipid levels, the correlations between insulin-stimulated glucose disposal and plasma lipid levels were analyzed using partial correlation coefficients after adjusting for differences in %BF (Table 4). As indicated in Table 4, all associations between Rd and lipid levels disappeared, suggesting that the above-described relationships of insulin sensitivity to lipid levels were not primary associations, but, rather, secondary to the relationship of body composition to lipids. However, the correlations between Rd and fasting insulin levels and diastolic blood pressure persisted in prepubertal children (Table 4). Furthermore, in pubertal adolescents, despite correction for differences in %BF, fasting insulin levels showed significant positive correlations with TG ($r = 0.38$; $P = 0.04$) and VLDL ($r = 0.40$; $P = 0.04$).

Discussion

In his 1988 Banting lecture, Reaven put forward the argument that variations in insulin-stimulated glucose uptake determine to an enormous degree the likelihood that an individual will develop premature atherosclerotic vascular disease (1). This argument was based on the proposal that the cluster of highly atherogenic metabolic abnormalities of syndrome X (hyperinsulinemia, glucose intolerance, increased VLDL and TG, decreased HDL, and hypertension) are likely to be secondary to the basic abnormality of insulin resistance (1). Several epidemiological and clinical studies in adults have provided evidence in favor of this syndrome (1–9, 19–23). The aim of the present study was to investigate whether the metabolic characteristics of syndrome X had their onset in childhood. Our results demonstrate that 1) the primary correlate of insulin-stimulated glucose disposal in a normal pediatric population is %BF in both prepubertal and pubertal children, with no relationship to plasma lipid levels; 2) in prepubertal children, diastolic blood pressure is negatively correlated with insulin sensitivity and positively with insulin levels, independent of adiposity; and 3) during puberty, basal insulin levels are positively correlated with VLDL and triglycerides regardless of the degree of adiposity. Whether the two latter observations represent a partial expression of the metabolic cluster of syndrome X remains to be determined.

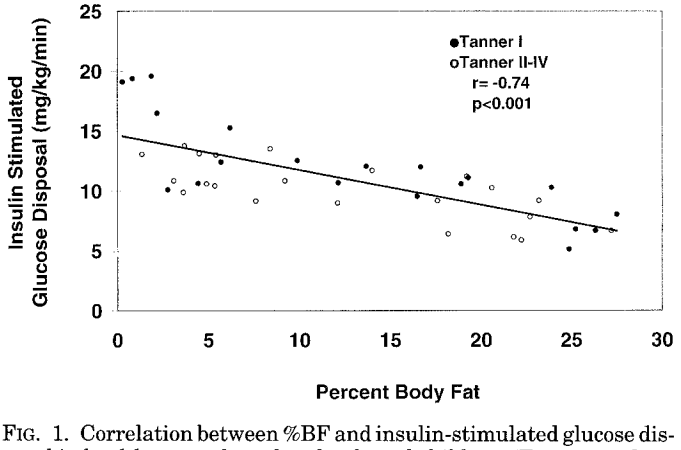

FIG. 1. Correlation between %BF and insulin-stimulated glucose disposal in healthy prepubertal and pubertal children. (To convert from milligrams per kg/min to micromoles per kg/min, multiply by 5.551.)

TABLE 3. Correlations between percent body fat (%BF) and plasma lipid levels

Correlations: %BF *vs.*	Tanner I [r (*P* value)]	Tanner II–IV [r (*P* value)]
Cholesterol	0.24	0.52 (0.007)
TG	−0.62 (0.002)	0.30
LDL	0.45 (0.02)	0.49 (0.01)
HDL	−0.33	−0.003
VLDL	−0.61 (0.002)	0.18
Basal insulin	0.67 (0.001)	0.42 (0.03)

P values are indicated in *parentheses* when significant.

TABLE 4. Correlations between insulin-stimulated glucose disposal and serum lipid levels after correcting for percent body fat

Correlations: Rd *vs.*	Tanner I [r (*P* value)]	Tanner II–IV [r (*P* value)]
Cholesterol	−0.08	0.14
Triglyceride	0.30	0.17
LDL	−0.10	0.26
HDL	−0.23	−0.26
VLDL	0.30	0.13
Basal insulin	−0.60 (0.004)	−0.25
Diastolic BP	−0.48 (0.02)	0.01
Systolic BP	−0.07	0.15

P values are indicated in *parentheses* when significant.

Several studies in adults have shown an inverse relationship between %BF and insulin-stimulated glucose disposal ranging in correlation coefficients from −0.35 to −0.7 (24, 25). To our knowledge, the present study is the first to investigate this relationship in pediatrics. In agreement with the literature for adults, our findings demonstrate that %BF is a strong negative correlate of insulin-stimulated glucose disposal ($r = -0.74$) in prepubertal and pubertal healthy children. Based on these results it could be concluded that adiposity accounts for 55% of the variability in insulin sensitivity in normal children. Previous studies in pediatrics have used body mass index (BMI) as a measure of adiposity and have shown correlations of −0.49 to −0.58 between insulin sensitivity and BMI (26, 27). However, BMI is not a sensitive indicator of body composition, especially during puberty. In our study the correlation between BMI and %BF is only 0.44 in pubertal children and 0.81 in prepubertal children. On the other hand, studies that have used more sensitive techniques to assess body composition, *e.g.* dual energy x-ray absorptiometry, have only looked at the relationship to fasting insulin rather than at insulin sensitivity (28). In the latter, the relationship between %BF and fasting insulin levels appeared to be much steeper above a fatness level of 35% than below that level in 7- to 11-yr-old children. All of our subjects had less than 30% body fat.

The association of obesity with dyslipidemia in adults and children is well recognized. Several pediatric publications

using BMI or skinfold thickness measurements have shown that higher levels of body fatness are associated with higher cholesterol and LDL levels and lower HDL levels (11, 29–32). In agreement with these reports, our study demonstrates that higher levels of %BF, even in normal weight children, are associated with an atherogenic lipid profile, as reflected in higher levels of LDL in prepuberty and higher levels of total cholesterol and LDL in puberty. On the other hand, the present finding of a negative correlation between %BF and plasma TG in prepubertal children is in contrast to previous reports showing higher TG levels with higher fatness levels (28, 29, 31, 33). Our study, however, targets a narrow age range of prepubertal nonobese children between 8–11 yr of age, a period characterized by significant fat deposition (34). Thus, the observed differences could be due to differences in study subject selection, the wide range of age and developmental stages studied previously, the degree of overweight, or the methodology of assessing fatness. The present observation, however, could potentially be explained on the basis of developmental differences in the regulation of fat deposition and differential regulation of tissue lipoprotein lipase activity in prepuberty *vs.* puberty. Prepuberty has been shown to be an insulin-sensitive state compared with puberty (13, 15, 26). It is possible that lipoprotein lipase is more sensitive to insulin during prepuberty, leading to increased TG clearance from the circulation and increased TG storage in adipose tissue (35). Studies are needed to pursue this hypothesis. On the other hand, even though pubertal subjects are insulin resistant compared with prepubertal children, there are no discernible differences in lipid profile or blood pressure levels between the two groups. This could be due to the temporary nature of pubertal insulin resistance, which appears to be mediated through pubertal elevations in GH levels (13, 26), a situation quite different from syndrome X. If the insulin resistance of puberty were to be sustained, the cluster of syndrome X abnormalities may have become more evident with time, as indicated by the finding that basal insulin levels were positively correlated with VLDL and TG regardless of the degree of adiposity.

Last, but not least, is the observation that despite accounting for differences in adiposity, insulin sensitivity correlated negatively with diastolic blood pressure in prepubertal children, whereas insulin correlated positively with TG and VLDL in pubertal adolescents. These are some of the components of syndrome X described in lean adults that are important risk factors for CVD. Could this be a very early, but partial, expression of syndrome X in a nonobese pediatric population? In a recent study of obese adolescents, insulin sensitivity was negatively correlated with serum TG levels (11). This is contrary to our findings, but an important difference is that our study was performed in nonobese adolescents. Obesity and its resultant insulin resistance and dyslipidemia could cloud the physiological interrelationships between these variables. As all previous studies of syndrome X have been conducted in adult subjects with a very wide age range of 21–69 yr, longitudinal studies in specific age groups are needed to better describe the natural history and progression of syndrome X.

In summary, we have demonstrated that in nonobese normal children, percent adiposity is an important correlate of *in vivo* insulin sensitivity. Moreover, increases in %BF are associated with an atherogenic lipid profile of increased LDL and total cholesterol starting as early as 8 yr of age. However, independent of degree of adiposity, there remains significant relationships between diastolic blood pressure and insulin sensitivity as well as insulin levels in prepuberty, and insulin levels and VLDL in pubertal subjects, possibly signaling the initiation of syndrome X in childhood. Therefore, it is our proposal that the genesis of an atherogenic pattern of risk factors starts in childhood and may be present for many years before more than one derangement clusters in the same individual, thus contributing to the risk of CVD later in adulthood.

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