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Adiponectin and Insulin Resistance in Childhood Obesity

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ABSTRACT

Objectives: To measure adiponectin serum levels in Greek children and adolescents and correlate them with body fat and insulin resistance.

Patients and Methods: Forty-six obese prepubertal children (19 M, 27 F) and 34 obese adolescents (17 M, 17 F) ages 9.33 ± 1.57 and 13.6 ± 1.42 years, respectively, and 43 matched control individuals were studied. Body mass index standard deviation score and percent body fat were measured by bioelectric impedance analysis. Fasting indices of insulin resistance (HOMA-IR and fasting glucose-to-insulin ratio) were calculated for all participants. Indices of insulin resistance derived from oral glucose tolerance tests were estimated in obese participants. Adiponectin was measured by enzyme-linked immunosorbent assay.

Results: (Mean ± SD): Adiponectin serum levels were significantly lower in obese participants than in nonobese participants (8.11 ± 3.80 vs 11.81 ± 4.98 μg/mL, $P < 0.001$), in obese children than in nonobese children (8.86 ± 3.86 vs 13.08 ± 5.48 μg/mL, $P < 0.001$), in obese adolescents than in nonobese adolescents (7.04 ± 3.43 vs 10.47 ± 4.10 μg/mL, $P = 0.002$), and in obese adolescent boys than in obese adolescent girls (5.87 ± 3.52 vs 8.31 ± 3.16 μg/mL, $P = 0.042$). There were significant correlations between adiponectin and age, body mass index, body mass index standard deviation score, homeostasis model assessment for insulin resistance, and fasting glucose-to-insulin ratio. Adiponectin correlated with percent body fat after adjustment for sex. Adiponectin correlated significantly with several indices of insulin resistance, such as the areas under the curves for glucose and insulin, whole-body insulin sensitivity index, $glucose_{120'}$, and $insulin_{30'}$, in obese participants.

Conclusions: Adiponectin was significantly lower in obese participants than in nonobese participants in general, and it correlated significantly with fasting indices of insulin resistance and with indices derived from oral glucose tolerance tests. It is worthwhile to further investigate the option of applying a simple measurement of serum adiponectin as a screening tool before applying more time-consuming techniques in young obese individuals. ***JPGN 47:356–362, 2008.*** **Key Words:** Adiponectin—Childhood obesity—Insulin resistance—Greece—Oral glucose tolerance test. © 2008 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

The discovery of adipokines altered the idea that adipose tissue is solely an energy storage depot. Adipokines, such as leptin, resistin, tumor necrosis factor-α, interleukin-6, adipsin, visfatin, and adiponectin, are biologically active molecules produced by adipose tissue. They play an important role in energy homeostasis and in glucose and lipid metabolism (1). Adiponectin is an adipokine secreted exclusively by adipocytes (2). It circulates abundantly in the blood in the form of multimers (3). It exhibits structural homology to collagen and tumor necrosis factor-α, and it has 2 receptors (AdipoR1 and AdipoR2) that are mainly expressed in the muscles and liver, respectively (3). Unlike other adipokines, its concentration in the blood is inversely related to the degree of obesity (3). It is, therefore, reduced in obese individuals, and it increases after weight loss (4). It has been associated with both central obesity and the amount of visceral adipose tissue (3). Adiponectin also has anti-inflammatory, antiatherogenic, and potent insulin-sensitizing (antidiabetic) effects (3,5,6). It has been proposed as a marker of coronary heart disease (7), insulin resistance, and the development of type 2 diabetes mellitus in adults (3,8). Adiponectin and its relation to insulin resistance have been studied in healthy adults and adolescents of various ethnic backgrounds, pregnant women, obese individuals, and patients with coronary heart disease, type 2 diabetes mellitus, polycystic ovary syndrome, chronic renal failure, and cancer (3,5,9–12). It has been reported that low adiponectin levels can predict

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type 2 diabetes mellitus in Mexican children (13). Adiponectin levels differ between various ethnic groups. This may be the effect of genetic factors such as adiponectin gene polymorphisms or environmental factors such as diet. Close adherence to a Mediterranean-type diet (enriched in alcohol, nuts, and whole grains) is associated with higher adiponectin concentration (14). Greek children usually consume a traditional Mediterranean diet.

The aims of the present study were to evaluate the levels of adiponectin in a population of nonobese and obese children and adolescents of Greek ethnic background, to investigate the association of adiponectin with body composition, and to examine the association of adiponectin with insulin resistance in these patients.

PATIENTS AND METHODS

This prospective observational study was conducted in the pediatric department of a university hospital between January 2005 and December 2005. All of the participants were white and of Greek origin, and they were recruited from patients who had been referred for evaluation of obesity. Inclusion criteria were obesity as defined by a body mass index (BMI) above the 95th percentile for age and sex according to both the National Growth Charts (15) and the International Obesity Task Force criteria (16), and age between 5 and 17 years. Exclusion criteria were endocrine diseases (eg, hypothyroidism and premature puberty), infections, chronic illnesses, and use of prescription medication.

Methods

Eighty obese children and adolescents were included in the study and were compared with 43 nonobese children and adolescents matched for age and sex. The study participants were admitted in the morning after an overnight fast. A SECA weighing scale and stadiometer (SECA 711 and SECA 220) were used to measure patient weight to the nearest 0.1 kg and height to the nearest centimeter. Each participant's BMI was calculated (BMI: weight in kilograms divided by the square of height in meters). Additionally, the BMI *z* score (BMI-Standard Deviation Score) was calculated for all of the participants by use of the online software provided by the Baylor College of Medicine (17). Waist circumference was measured at the level of the umbilicus with a tape measure to the nearest 0.1 cm (18).

Detailed medical and family history was obtained. All of the subjects underwent a complete physical examination. Blood pressure was measured twice with a sphygmomanometer, and values were averaged. The presence of acanthosis nigricans was noted. The stage of puberty was determined according to the Tanner criteria (19). Individuals in Tanner Stage I were considered prepubertal (children), and those in stages II through V were considered pubertal (adolescents).

Body Composition Analysis

The body composition of the participants was determined by bioelectric impedance analysis. The device used was a single-frequency (50 kHz) hand-foot MALTRON BF-906 body composition analyzer. The percent of body fat (%BF) was calculated from the impedance values, height, weight, and sex for all of the individuals according to the equations of Segal et al (20). Measurements were conducted according to the instructions of the manufacturer and the National Institutes of Health (21).

Biochemistry

Levels of serum glucose, insulin, and lipid—total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglycerides—were determined on fasting blood samples.

Insulin Sensitivity

A standard 75-g oral glucose tolerance test (OGTT) was performed; 1.75 g D-glucose per kilogram of body weight (maximum 75 g) diluted in 200 mL of water was ingested in 5 minutes. Blood samples for glucose and insulin were obtained 30, 60, 90, and 120 minutes after the glucose load. Serum glucose concentrations were measured with the glucose hexokinase enzymatic method (Architect c8000, Abbott Laboratories, Abbott Park, IL). Serum insulin levels were measured by the application of a solid-phase, 2-site chemiluminescent immunometric assay (DPC Immulite 2000, Diamond Diagnostics, Holliston, MA) with 2 μIU/mL sensitivity. For the estimation of insulin resistance, indices derived from the fasting glucose and fasting insulin values were used: the homeostasis model assessment for insulin resistance (HOMA-IR) = [(fasting glucose [mmol/L]) × (fasting insulin [μU/mL])]/22.5 (22) and the fasting glucose-to-insulin ratio (FGIR). For obese individuals who underwent OGTT, the whole-body insulin sensitivity index (WBISI) was calculated: ISI-composite index (WBISI): $10\,000/\sqrt{}$[fasting glucose (mg/dL) × fasting insulin (μU/mL) × (mean OGTT glucose × mean OGTT insulin)] (22). Additionally, the areas under the curves were calculated for glucose and insulin according to the model of Tai (23): 1/2 × 30 × (y0 min + 2y30 min + 2y60 min + 2y90 min + y120 - y120 min), where y represents insulin or glucose values at the different time points.

Adiponectin Measurement

Fasting whole blood samples were centrifuged immediately after collection, and serum samples were stored at −24°C for the measurement of adiponectin. For this purpose, a commercial quantitative sandwich enzyme immunoassay technique was used according to the manufacturer's guidelines (Quantikine Human Adiponectin, R & D Systems, Minneapolis, MN). The minimum detectable level of the assay was 0.25 ng/mL.

Statistical Analysis

This was a prospective observational study. Adiponectin levels were measured in a group of obese children and adolescents and compared (via a Student *t* test for independent samples) to the levels of nonobese age-matched and sex-matched control individuals. Our null hypothesis was that adiponectin levels would be lower among obese individuals.

Sample size estimation was completed by use of software available on line (24). The power and level of significance were set at 80% and 5%, respectively. A minimum of at least 25 individuals had to be included in each group (obese and nonobese). Descriptive statistics were computed for all variables of interest. The Kolmogorov-Smirnov test was used to test the normality of distribution. For variables that were normally distributed (demographic, anthropometric, and metabolic), differences between subgroups were calculated by use of a Student *t* test for independent samples. For parameters that were not normally distributed, the Mann-Whitney *U* test was used. A Pearson or Spearman correlation analysis was used to analyze bivariate relations and to test for associations between adiponectin concentration and obesity measures (BMI, BMI-SDS, and %BF), metabolic parameters (fasting insulin, glucose, and serum lipid levels), and insulin resistance indices. Where necessary, partial correlation and stepwise multiple linear regression were applied to examine what parameters affected adiponectin levels and HOMA-IR. A χ^2 test was used for categorical variables. Statistical analysis was performed with SPSS version 12.0 software (SPSS Inc, Chicago, IL). Statistical significance was set at the $P < 0.05$ level.

Ethical Considerations

The study was approved by the Aristotle University of Thessaloniki Medical School Ethics Committee and fulfilled the criteria of the Helsinki Declaration. Informed consent was obtained from the parents of all of the children and adolescents who agreed to participate.

RESULTS

Forty-six obese children (19 M, 27 F; mean age ± SD 8.83 ± 1.98 years, range 5.33–12 years) and 34 obese adolescents (17 M, 17 F; mean age ± SD: 13.40 ± 1.60 years, range 11.58–17 years) were compared with 43 nonobese children and adolescents matched for age and sex.

Demographic and anthropometric characteristics are shown in Table 1. The weight, height, BMI, waist circumference, and systolic blood pressure of obese male children were significantly higher than those of obese female children. Acanthosis nigricans was present in about one third of the obese children and adolescents. The results of the biochemical investigations are shown in Table 2. HDL cholesterol was significantly reduced in obese individuals ($P < 0.05$). Levels of other lipids and fasting glucose were comparable between obese and nonobese subgroups. Fasting insulin levels were significantly higher in obese children and adolescents than in nonobese children and adolescents ($P < 0.05$). The FGIR was significantly lower and HOMA-IR was significantly higher in obese children and adolescents than in nonobese children and adolescents. Obese male children had significantly higher HOMA-IR and lower WBISI than did obese female children. As shown in Table 3, adiponectin levels differed significantly between obese and nonobese children and adolescents. Furthermore, there was a significant difference between obese male and female adolescents (5.87 ± 3.52 vs 8.31 ± 3.16 μg/mL, $P = 0.03$).

When adiponectin levels were correlated with anthropometric and biochemical indices in all 123 participants (regardless of obesity, sex, or pubertal status), significant correlations were demonstrated with age, BMI, BMI-SDS, fasting insulin, FGIR, HOMA-IR, and HDL cholesterol (Table 4, Fig. 1). Controlling for sex revealed that adiponectin levels were also correlated with %BF ($r = -0.200$, $P < 0.5$). In a stepwise multiple regression analysis with adiponectin as a dependent variable and age, sex, %BF, and HOMA-IR as independent variables, we observed that only sex and %BF were important determinants of adiponectin levels (Table 5). Similarly, in a stepwise multiple regression analysis with HOMA-IR as a dependent variable and age, sex, %BF, and adiponectin as independent variables, we demonstrated

TABLE 1. *Anthropometric and demographic data from the study participants*

	Obese children		Obese adolescents		Nonobese children		Nonobese adolescents	
	Female	Male	Female	Male	Female	Male	Female	Male
No.	27	19	17	17	13	9	11	10
Age, y	8.99 ± 1.26	9.81 ± 1.86	13.21 ± 1.53	13.71 ± 1.55	8.39 ± 2.40	8.73 ± 1.93	12.81 ± 1.01	13.12 ± 1.27
Weight, kg	54.41 ± 8.74*	65.44 ± 18.59*	80.49 ± 16.01	81.10 ± 20.7	29.09 ± 6.9	35.95 ± 12.47	52.04 ± 6.92	51.05 ± 12.87
Height, cm	139 ± 8*	145 ± 11*	158 ± 8	159 ± 11	134 ± 10	135 ± 13	161 ± 5	162 ± 12
WC, cm	84 ± 7.2*	94 ± 9*	98 ± 14	101 ± 10	52 ± 7	55 ± 6	60 ± 7	62 ± 9
BMI, kg/m^2	27.94 ± 2.88*	30.57 ± 4.01*	31.80 ± 5.24	31.7 ± 5.48	15.99 ± 1.88	18.98 ± 3.2	20.04 ± 2.19	18.6 ± 2.75
BMI-SDS	2.36 ± 0.29	2.53 ± 0.40	2.11 ± 0.30	2.14 ± 0.37	−0.28 ± 1.03	0.91 ± 0.98	0.40 ± 0.64	−0.12 ± 1.03
%BF	34.6 ± 4.58	35.7 ± 4.86	37.62 ± 4.95	33.8 ± 6.8	20.4 ± 4.05	23.95 ± 8.37	25.71 ± 6.23	15.46 ± 5.80
AN, %	33.3%*	29%*	57%*	44%	0	0	0	0
SBP, mmHg	109 ± 11*	120 ± 11*	113 ± 15†	126 ± 12†	–	–	–	–
DBP, mmHg	68 ± 8	68 ± 11	66 ± 9	64 ± 10	–	–	–	–

Results are expressed as mean ± standard deviation. AN = acanthosis nigricans; DBP = diastolic blood pressure; SBP = systolic blood pressure; WC = waist circumference.

*†Statistically significant differences between male and female obese individuals.

TABLE 2. *Biochemical and metabolic profile of the study participants*

	Obese children		Obese adolescents		Nonobese children		Nonobese adolescents	
	Female	Male	Female	Male	Female	Male	Female	Male
Cholesterol, mg/dL	157 ± 40	162 ± 34	168 ± 42	160 ± 27	166 ± 27	155 ± 22	154 ± 16	158 ± 23
Triglycerides, mg/dL	97 ± 62	82 ± 44	80 ± 36	91 ± 55	83 ± 47	92 ± 25	57 ± 18	70 ± 28
HDL cholesterol	36 ± 6*	43 ± 10*	42 ± 5	38 ± 8	62 ± 10	44 ± 6	48 ± 6	50 ± 13
LDL cholesterol	101 ± 37	98 ± 14	108 ± 38	103 ± 21	91 ± 22	100 ± 15	106 ± 36	91 ± 21
Glucose 0 min	86 ± 8*	93 ± 11*	86 ± 5†	94 ± 13†	86 ± 11	87 ± 6	85 ± 8	89 ± 8
Glucose 120 min	114 ± 19	120 ± 17	115 ± 17	113 ± 26	–	–	–	–
Mean glucose	122 ± 15	126 ± 19	119 ± 10	126 ± 22	–	–	–	–
$AUC_{Glucose}$	15,418 ± 2092	15,748 ± 2414	14,962 ± 1412	15,838 ± 2935	–	–	–	–
Insulin 0 min	13.8 ± 8.5	20.9 ± 17	17.2 ± 7.2	17 ± 8	8.1 ± 4.4	8.3 ± 3.5	10.5 ± 2.9	7.1 ± 1.5
Insulin 30 min	128 ± 63	158.7 ± 88	109 ± 53	143 ± 77	–	–	–	–
Insulin 120 min	121 ± 84	122 ± 88	95 ± 40	108 ± 70	–	–	–	–
Mean insulin	107 ± 58	111.3 ± 58	85 ± 25	102 ± 52	–	–	–	–
$AUC_{Insulin}$	13,171 ± 7097	15026 ± 7880	11,151 ± 3276	13926 ± 7439	–	–	–	–
FGIR	8.61 ± 5.22	6.29 ± 3.23	5.85 ± 2.42	6.47 ± 2.5	13.8 ± 7.5	14.36 ± 10.94	8.54 ± 2.05	12.84 ± 2.46
HOMA-IR	2.93 ± 1.67*	4.23 ± 2.21*	3.69 ± 1.64	4.1 ± 2.3	1.81 ± 1.29	1.8 ± 0.75	2.23 ± 0.79	1.56 ± 0.36
WBISI	3.62 ± 2.29*	2.35 ± 1.15*	2.81 ± 0.91	2.58 ± 1.42	–	–	–	–

Data are expressed as mean ± standard deviation. $AUC_{Glucose}$ = area under the curve for glucose; $AUC_{Insulin}$ = area under the curve for insulin during OGTT.
*†Statistically significant differences between male and female obese individuals.

that only age and %BF were important determinants (Table 5).

In obese individuals, significant correlations were found between adiponectin and various OGTT-derived insulin resistance indices. These indices included insulin at 30 minutes, mean insulin, and the area under the curve for insulin in all subgroups except obese female adolescents; HOMA-IR in obese female adolescents; FGIR in obese female children; and WBISI in obese female children and obese male adolescents (Table 6, Fig. 2).

DISCUSSION

The first aim of this study was to define the levels of adiponectin in nonobese and obese children and adolescents of Greek ethnic background. To our knowledge, this is the first report on adiponectin levels in Greek children and adolescents, and it shows that they are significantly lower in obese individuals than in nonobese individuals.

TABLE 3. *Adiponectin levels (μg/mL)*

	Children		
	Obese	Nonobese	*P*
All	8.86 ± 3.86	13.08 ± 5.48	<0.001
Male	7.96 ± 4.35	11.74 ± 3.55	0.032
Female	9.49 ± 3.42	14.01 ± 6.48	0.032
		Adolescents	
All	7.04 ± 3.43	10.47 ± 4.10	0.002
Male	5.87 ± 3.52*	9.76 ± 3.76	0.017
Female	8.31 ± 3.16*	11.39 ± 4.07	0.033

Data are expressed as mean ± standard deviation.
* $P = 0.03$.

These data are comparable to those described for people of other ethnic groups, such as African Americans (11,25), Mexicans (13), Pima Indians (3), Japanese (26), and Taiwanese (27). Negative correlations between adiponectin and age, BMI, and BMI-SDS were also demonstrated in this study. Similar findings have been reported in the literature (8,28). Adiponectin was found to decline throughout puberty. Obese male adolescents had the lowest levels. These data are in agreement with other reports in the literature. Tsou et al (27) demonstrated a transient drop in the level of adiponectin during puberty that correlated with increased testosterone in boys (10–12 years). The same study showed an inverse correlation of adiponectin with obesity and insulin resistance in both sexes during puberty. Woo et al (29) reported sex differences of adiponectin in adolescents and these differences were dependent on both pubertal stage and adiposity.

The second aim of this study was to investigate the association of adiponectin and body composition. According to our data, adiponectin was negatively

TABLE 4. *Correlation of adiponectin with anthropometric and biochemical indices in all individuals (N = 123)*

Index	*r*	*P*
Age	−0.227	0.009
BMI	−0.359	0.000
BMI-SDS	−0.211	0.023
Fasting insulin	−0.282	0.002
FGIR	0.292	0.001
HOMA-IR	−0.291	0.015
HDL cholesterol	0.237	0.016

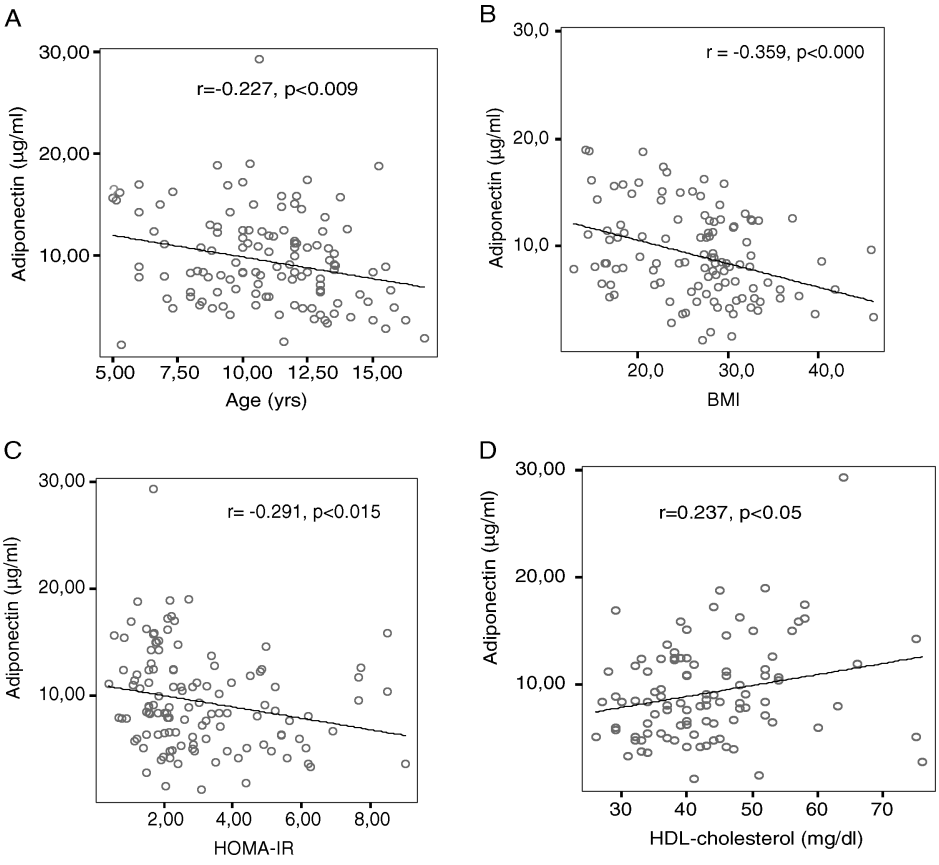

FIG. 1. Association between adiponectin levels and age (A), BMI (B), HOMA-IR (C), and HDL cholesterol (D).

correlated with the percent of total body fat as measured by a bioelectric impedance analysis. However, this difference did not reach statistical significance except after adjustment for sex. It is possible that the relationship may have been different if we had used other methods to assess body composition. A relation between adiponectin and %BF was demonstrated by the application of dual x-ray absorptiometry DEXA (30). The decreased adiponectin has been attributed to the accumulation of visceral fat (28). However, Lee et al (31) reported an association of adiponectin with insulin sensitivity independent of

TABLE 5. *Stepwise multiple linear regression analysis in all individuals for serum adiponectin (A) and HOMA-IR (B)*

	B	*P*
(A)		
Constant	14.594	0.000
Sex	−0.255	0.007
%BF	−0.196	0.037
(B)		
Constant	−0.621	0.000
Age	0.221	0.016
%BF	0.272	0.003

TABLE 6. *Correlations of adiponectin and insulin resistance indices in obese individuals (*r)

	Obese children		Obese adolescents		
	Female	Male	Female	Male	All obese
Fasting glucose	0.153	0.114	0.493*	−0.194	−0.028
Total glucose	−0.528†	−0.165	−0.083	−0.355	−0.333†
AUC $_{Glucose}$	−0.506*	−0.166	−0.123	−0.322	−0.321†
Fasting insulin	−0.404*	0.163	0.554*	−0.184	−0.105
Insulin 30 min	−0.438*	−0.609*	0.515*	−0.634*	−0.366†
Insulin 120 min	−0.365	−0.402	0.421	−0.493*	−0.259*
Mean insulin	−0.523†	−0.568*	0.461	−0.579*	−0.383‡
AUC $_{Insulin}$	−0.456*	−0.552*	−0.370	−0.643*	−0.413‡
HOMA-IR	−0.277	0.257	0.490*	−0.167	−0.039
FGIR	0.435*	−0.168	−0.480	0.252	0.092
WBISI	0.663‡	0.338	−0.455	0.675†	0.470‡
Cholesterol	−0.263	−0.042	−0.006	−0.102	−0.122
Triglycerides	−0.291	−0.310	−0.054	−0.484	−0.282*
HDL cholesterol	0.302	0.083	−0.226	0.200	0.056
LDL cholesterol	−0.276	0.204	0.045	0.044	−0.067

$AUC_{Glucose}$ = area under the curve for glucose; $AUC_{Insulin}$ = area under the curve for insulin during OGTT.

* $P < 0.05$.

† $P < 0.01$.

‡ $P < 0.001$.

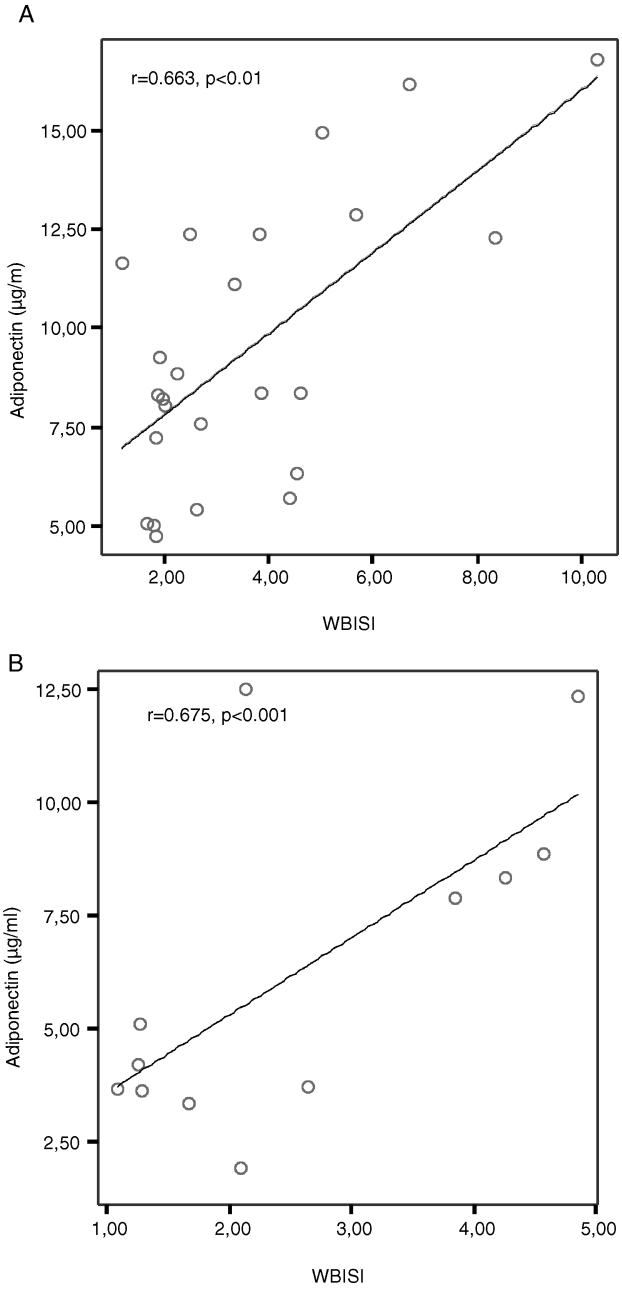

FIG. 2. Correlation between adiponectin levels and OGTT-derived indices of insulin resistance. A, Adiponectin—WBISI in obese prepubertal girls. B, Adiponectin—WBISI in obese pubertal boys.

visceral adipose tissue in both African American and white youths. In this study, we measured total body fat using bioelectric impedance analysis, a method that provides no information on regional fat distribution or the amount of visceral fat. Furthermore, no correlation was found between adiponectin and waist circumference. This measure may be used as an indicator of visceral adiposity in adults, but its value in children has not been validated, and we are unaware of any reference values related to puberty and growth (32).

Our third aim was to investigate the association of adiponectin with insulin sensitivity. In this study, significant correlations were demonstrated with fasting insulin resistance indices when nonobese and obese individuals were examined as a whole. In the obese subgroups, adiponectin also correlated significantly with indices such as insulin at 30 minutes, mean insulin, the area under the curve for insulin, and the WBISI derived from the OGTT. A negative correlation between adiponectin and insulin resistance has been reported by several authors. Huang et al (33) demonstrated a negative correlation with various metabolic factors in healthy nondiabetic adolescents. Cruz et al (13) described a strong association with HOMA-IR in Mexican children and concluded that low adiponectin may predict type 2 diabetes mellitus in that ethnic group. Weiss et al (34) reported decreasing adiponectin concentrations with increasing adiposity. Low adiponectin was associated with high insulin resistance. Winer et al (35) reported that adiponectin may function as a biomarker of the metabolic syndrome in childhood obesity because of its strong correlation with several indices of insulin resistance. Lee et al (31) suggested that low adiponectin in African American youths may be a biological marker of predisposition to insulin resistance. Similarly, Gilardini et al (36) reported that hypoadiponectinemia may be associated with a high risk for the metabolic syndrome. A dissociation between adiponectin and insulin resistance has also been reported by some authors. Punthakee et al (37) did not find any correlation between adiponectin and markers of insulin resistance. Ong et al (38) reported that the secretion of adiponectin may be influenced by other factors. Butte et al (39) suggested that genetic and environmental factors may influence fasting adiponectin in Hispanic children.

In summary, adiponectin was significantly lower in obese than in nonobese children and adolescents of Greek origin. Adiponectin correlated significantly with %BF in all individuals as well as with OGTT-derived indices of insulin resistance in obese individuals.

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