

Adiponectin Independently Predicts Metabolic Syndrome in Overweight Latino Youth

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Context: Adiponectin may be important in the pathogenesis of insulin resistance and the metabolic syndrome in youth.

Objective: The objective of the study was to determine the unique effect of adiponectin on the metabolic syndrome in overweight Latino youth.

Participants: Participants included 175 overweight children (aged 11.1 ± 1.7 yr, body mass index percentile 97.3 ± 2.9) with a family history of type 2 diabetes.

Methods: Metabolic syndrome was defined according to a pediatric adaptation of the Adult Treatment Panel III report and included dyslipidemia, abdominal obesity, elevated blood pressure, and prediabetes (impaired fasting glucose or impaired glucose tolerance from a 2-h oral glucose tolerance test). Body composition was estimated via dual-energy x-ray absorptiometry, insulin sensitivity was quantified by the frequently sampled iv glucose tolerance test, visceral fat was measured using magnetic resonance imaging, and adiponectin was determined in fasting serum.

Results: In simple linear regression, adiponectin was significantly and inversely related to systolic blood pressure ($P < 0.05$), waist circumference ($P < 0.001$), triglycerides ($P < 0.001$), and 2-h glucose levels ($P < 0.05$) and positively related to high-density lipoprotein-cholesterol ($P < 0.001$). In multiple linear regression, adiponectin was significantly related to triglycerides ($P < 0.01$) and high-density lipoprotein-cholesterol ($P < 0.01$) independent of age, gender, Tanner stage, body composition, and insulin sensitivity. Analyses of covariance established that adiponectin levels were approximately 25% higher in healthy overweight youth, compared with those with the metabolic syndrome (12.5 ± 3.5 vs. 9.4 ± 2.8 $\mu\text{g/ml}$; $P < 0.05$). In multiple logistic regression, adiponectin was a significant independent predictor of the metabolic syndrome, even after adjustment for confounders including insulin sensitivity and visceral fat.

Conclusions: Hypoadiponectinemia is an independent biomarker of the metabolic syndrome, and thus, adiponectin may play a role in the pathophysiology of the disorder in overweight youth. (*J Clin Endocrinol Metab* 92: 1809–1813, 2007)

THE METABOLIC SYNDROME is a constellation of risk factors predictive of future cardiovascular disease and type 2 diabetes in adults (1, 2). Recently several studies (3–5) found that the metabolic syndrome is present in pediatric populations, suggesting that the origins of chronic metabolic diseases manifest relatively early in life. Although the underlying pathophysiology of the metabolic syndrome is unclear, insulin resistance is thought to be a central abnormality in the pathogenesis of the disorder (6).

We recently observed that overweight Latino youth with the metabolic syndrome are significantly more insulin resistant, compared with those without the metabolic syndrome (3). Furthermore, these findings were independent of total body composition. Given that total fat mass was not independently associated with the metabolic syndrome phenotype and that visceral fat is independently related to insulin resistance in youth, the effect of adiposity on the metabolic syndrome may be mediated through insulin resistance.

In addition to insulin resistance, recent studies suggested that the adipocyte-derived hormone adiponectin may be an important predictive marker for the metabolic syndrome (7, 8). Low plasma adiponectin levels are predictive of insulin resistance and type 2 diabetes in adults (9). Moreover, Latino children with type 2 diabetes have significantly lower adiponectin levels, compared with their normoglycemic counterparts (10). Thus, it is thought that low levels of circulating adiponectin may be an early marker of metabolic disease risk in children. To date, limited investigations have examined the associations between adiponectin and the metabolic syndrome in children, and none have done so while controlling simultaneously for directly measured insulin sensitivity.

Because adiponectin is related to, and may be contributory to, the development of insulin resistance and the metabolic syndrome, investigations examining the independent associations may offer further insight into the pathways mediating obesity and chronic disease in children. Thus, the primary aim of the study was to examine the relationship between adiponectin and the metabolic syndrome phenotype in overweight Latino youth with a family history of type 2 diabetes. We hypothesized that: 1) serum adiponectin would be significantly and independently related to the individual components of the metabolic syndrome, 2) youth

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Abbreviation: HDL, High-density lipoprotein.

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with the metabolic syndrome would have lower adiponectin levels than those without the metabolic syndrome, and 3) serum adiponectin would be predictive of the metabolic syndrome phenotype in this population and that this effect would be independent of general and visceral adiposity and insulin sensitivity.

Subjects and Methods

Subjects

The 175 children who participated are part of the University of Southern California Study of Latino Adolescents at Risk Diabetes Project. The study is an ongoing longitudinal investigation to explore risk factors for the development of type 2 diabetes in at-risk youth. Participants were recruited from the greater Los Angeles County and were required to meet the following inclusion criteria at baseline: 1) Latino ethnicity, 2) age 8–13 yr, 3) a family history of type 2 diabetes, and 4) age and gender body mass index at the 85th percentile or greater. Children were excluded if they had a prior major illness, took medications, or had a condition known to influence insulin sensitivity or body composition. This study was approved by the University of Southern California Institutional Review Board. Written informed consent and assent were obtained from all parents and children before any testing procedures. Data from this cohort have been reported previously (3, 11).

Protocol

The methodologies used in the present investigation have been previously reported (3), and the reader is referred to this publication for specifics. Briefly, physical maturation was assessed by a pediatrician according to the criteria of Tanner (12), hyperglycemia was established via fasting and 2-h glucose levels during a standardized oral glucose tolerance test, insulin sensitivity was determined by the frequently sampled iv glucose tolerance test, dyslipidemia was determined from fasting triglycerides and high-density lipoprotein (HDL)-cholesterol, abdominal adiposity was quantified by waist circumference measured at the umbilicus, blood pressure was measured in the seated position on two separate occasions, and body composition was determined by dual-energy x-ray absorptiometry.

In addition to these previously reported measures, visceral fat distribution was measured directly by magnetic resonance imaging (1.5 Signa LX-Echospeed device with a 1.5-Tesla magnet; General Electric, Waukesha, WI) using a single-slice axial TR 400/16 view of the abdomen at the level of the umbilicus and total plasma adiponectin levels were measured using RIA kits obtained from Linco Research (St. Charles, MO).

Definition of the metabolic syndrome

Previously we used a pediatric adaptation of the Adult Treatment Panel III definition of the metabolic syndrome. Although there remains

no accepted definition of the metabolic syndrome in children, revisions to the original Adult Treatment Panel III definition have been implemented. As such, we incorporated these revisions and used the best available published evidence to define the metabolic syndrome in this pediatric cohort as having at least three of the following features: abdominal obesity (waist circumference \geq 90th percentile for age, gender, and Latino ethnicity) (13), hypertriglyceridemia (triglycerides \geq 90th percentile for age and gender) (14), low HDL cholesterol (\leq 10th percentile for age and gender) (14), elevated blood pressure [systolic or diastolic blood pressure $>$ 90th percentile adjusted for height, age, and gender (15)], and hyperglycemia (fasting glucose \geq 100 mg/dl or 2-h postchallenge glucose \geq 140 mg/dl) (16). Notable updates include a revised threshold for impaired fasting glucose (lowered from 110 to 100 mg/dl), use of published waist circumference percentiles from a nationally representative sample of youth, and the incorporation of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Children void of any risk factors will be referred to as healthy youth.

Statistics

Gender differences in physical and metabolic characteristics were examined using independent sample *t* tests and χ^2 analysis. Variables that were not normally distributed were log transformed for analysis but are presented as untransformed data for ease of interpretation. Associations between adiponectin and the individual features of the metabolic syndrome were examined using univariate linear regression analysis. These associations were further examined by multiple linear regression for each metabolic syndrome risk factor; along with adiponectin, the following variables were also included in each model: gender, age, Tanner stage, total fat mass, fat-free mass, and insulin sensitivity. To establish group differences in adiponectin in children with and without the metabolic syndrome, analysis of covariance was used adjusting for gender, age, Tanner stage, total fat mass, fat-free mass, and insulin sensitivity. Finally, multiple logistic regression analysis was used to determine the relative contribution of adiponectin (independent continuous variables) to the metabolic syndrome (dichotomous dependent variable), while considering the confounding effects of gender, age, Tanner stage, total fat mass, fat-free mass, insulin sensitivity, and visceral fat. All analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL) with a type I error set at 0.05.

Results

Descriptive characteristics

Physical and metabolic profiles of the children are presented in Table 1. Girls were significantly more advanced in maturation than boys (Tanner = 2.8 ± 1.4 vs. 2.7 ± 1.0 , $P < 0.05$) and had significantly lower fasting glucose levels (89.5 ± 6.8 vs. 92.7 ± 6.1 mg/dl, $P < 0.05$). The lower fasting

TABLE 1. Descriptive and metabolic characteristics

Characteristic	Boys	Girls	Total
n	101	74	175
Age (yr)	11.2 \pm 1.6	11.1 \pm 1.8	11.1 \pm 1.7
Height (cm)	149.8 \pm 10.7	148.7 \pm 11.7	149.3 \pm 11.2
Weight (kg)	64.0 \pm 18.9	64.8 \pm 19.5	64.4 \pm 19.1
Body mass index percentile	97.1 \pm 3.1	97.5 \pm 2.6	97.3 \pm 2.9
Insulin sensitivity ($\times 10^{-4}$ min ⁻¹ /μU·ml)	2.2 \pm 1.4	1.9 \pm 1.3	2.0 \pm 1.4
Adiponectin (μg/ml)	10.2 \pm 3.4	10.0 \pm 3.1	10.1 \pm 3.2
Visceral fat (cm ²)	47.3 \pm 21.6	49.6 \pm 19.3	48.3 \pm 20.6
Elevated triglycerides [n (%)]	35 (33.7)	6 (7.7) ^a	41 (23.4)
Elevated HDL-cholesterol [n (%)]	65 (62.3)	43 (57.1)	108 (61.7)
Elevated blood pressure [n (%)]	15 (14.4)	19 (24.4)	34 (19.4)
Elevated waist circumference [n (%)]	71 (68.3)	61 (78.2)	132 (75.4)
Hyperglycemia [n (%)]	33 (31.7)	24 (30.8)	57 (32.6)
Metabolic syndrome [n (%)]	42 (41.6)	23 (31.1)	65 (37.8)

Data are means \pm SD or observed incidence (percentage of study population).

^a $P < 0.05$.

glucose level observed in girls corresponded to a significantly lower proportion of girls with impaired fasting glucose (four vs. 15, $P < 0.05$). A trend was noted for a higher proportion of boys exhibiting the metabolic syndrome phenotype, compared with girls, but this did not reach the level of significance ($P = 0.1$). Data from both genders were combined for further analyses.

Adiponectin and the individual metabolic syndrome risk factors

Univariate associations between adiponectin and the individual components of the metabolic syndrome revealed that adiponectin was significantly and negatively correlated with systolic blood pressure ($P \leq 0.05$) (but not diastolic), waist circumference ($P \leq 0.001$), triglycerides ($P \leq 0.001$), and 2-h plasma glucose ($P \leq 0.05$) and was positively correlated with HDL-cholesterol ($P \leq 0.05$). In multiple linear regression analyses, adiponectin remained independently and positively associated with HDL-cholesterol ($P \leq 0.01$) and negatively associated with triglycerides ($P \leq 0.01$). No other feature was significantly associated with adiponectin.

Adiponectin and the metabolic syndrome

Figure 1 displays the means for adiponectin in healthy youth and those with the metabolic syndrome. After controlling for covariates, adiponectin levels were approximately 25% higher in healthy overweight children, compared to their counterparts with the metabolic syndrome ($P < 0.05$). This difference remained significant, even after including visceral adiposity in the model (12.5 ± 3.6 vs. 9.4 ± 3.1 ; $P < 0.05$).

To determine whether visceral fat mediates the relationship between adiponectin and the metabolic syndrome, two

multiple logistic regression models were created. In the first model, adiponectin, gender, age, Tanner stage, body composition, and insulin sensitivity were entered as covariates (Table 2). A second model was created that included the variables from the first model along with visceral fat. Confirming our previous report, insulin sensitivity was a significant independent predictor of the metabolic syndrome phenotype as was age. In addition, adiponectin remained a significant independent predictor of the metabolic syndrome in both of these models, whereas visceral fat was not a significant determinant of the phenotype (Table 2).

Discussion

In this cross-sectional analysis of overweight Latino youth at risk for diabetes, we found that serum adiponectin levels were significantly and independently associated with several components of the metabolic syndrome. Furthermore, adiponectin was approximately 25% lower in youth with the metabolic syndrome, compared with healthy overweight counterparts. Lastly, we found that in addition to age and insulin sensitivity, adiponectin was a significant predictor of the metabolic syndrome; however, visceral fat was not.

Despite recent controversy regarding its utility (17, 18), the metabolic syndrome has been shown to predict cardiovascular disease, type 2 diabetes, and all-cause mortality in adults (19). A substantial amount of literature supports both obesity and insulin resistance as early defects in the pathophysiology of metabolic syndrome (20). A growing body of evidence now indicates that hypo adiponectinemia may be contributing to the abnormalities of the metabolic syndrome (21). However, the majority of work examining the etiology of the metabolic syndrome has been performed in adult populations with relatively few investigations in pediatric populations.

We previously reported that insulin sensitivity is a significant independent correlate of the metabolic syndrome in overweight Latino youth (3). Others have demonstrated that serum adiponectin is significantly lower in obese children with the metabolic syndrome (5, 7). To date, the current investigation is the first to examine the contributions of adiponectin to the metabolic syndrome and simultaneously controlling for insulin sensitivity, body composition, and visceral fat in overweight youth. Although cross-sectional in nature, the current results in combination with our previous findings suggest that adiponectin and insulin sensitivity may play important independent roles in the pathogenesis of the metabolic syndrome. Therefore, it is plausible that interventions targeting improvements in these parameters may lead to reductions in overall chronic diseases such as diabetes and cardiovascular disease.

In both children and adults, studies have demonstrated that like insulin sensitivity, adiponectin is significantly and inversely associated with adiposity (22, 23). Furthermore, both insulin sensitivity and serum adiponectin levels predict future risk of type 2 diabetes (24). It is presently unclear whether low levels of adiponectin and low insulin sensitivity act independently or in concert to confer increased diabetes risk. Given that the metabolic syndrome is a significant clinical predictor of type 2 diabetes in adults and that adiponec-

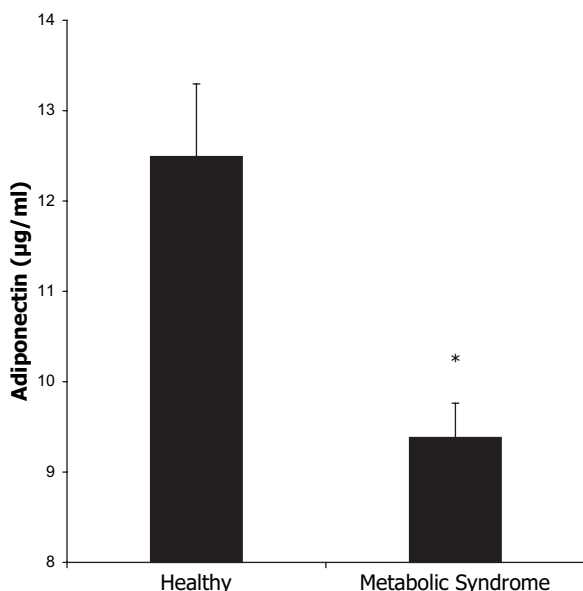


FIG. 1. Adiponectin and the metabolic syndrome. Estimated marginal means (\pm SE) of serum adiponectin in healthy overweight youth and those with the metabolic syndrome. Data are adjusted for gender, age, Tanner stage, total fat mass, total lean tissue mass, and insulin sensitivity. *, $P < 0.05$.

TABLE 2. Multivariate logistic regression with the presence of the metabolic syndrome as the dependent variable

Variable	Beta	SE	OR	95% CI	P
Model 1					
Gender	−0.92	0.51	0.40	0.15–1.07	0.07
Age	−0.44	0.17	0.64	0.46–0.90	0.01
Tanner	0.13	0.26	1.14	0.68–1.89	0.62
Fat mass	0.000	0.000	1.0	1.00–1.00	0.72
Lean tissue mass	0.000	0.000	1.0	1.00–1.00	0.96
Insulin sensitivity	−0.70	0.22	0.49	0.32–0.76	0.001
Adiponectin	−0.14	0.06	0.87	0.77–0.98	0.03
Model 2					
Gender	−0.96	0.51	0.38	0.14–1.05	0.06
Age	−0.44	0.17	0.65	0.46–0.91	0.01
Tanner	0.16	0.26	1.18	0.70–1.97	0.53
Fat mass	0.000	0.000	1.0	1.00–1.00	0.86
Lean tissue mass	0.000	0.000	1.0	1.00–1.00	0.95
Insulin sensitivity	−0.68	0.22	0.51	0.33–0.78	0.002
Adiponectin	−0.14	0.07	0.87	0.77–0.99	0.04
Visceral fat	0.01	0.01	1.0	0.99–1.03	0.21

OR, Odds ratio; CI, confidence interval.

tin levels are reduced in overweight Hispanic youth with type 2 diabetes (10), our combined results suggest that both adiponectin and insulin sensitivity impart unique contributions to long-term disease risk in children.

Because visceral adiposity is intimately linked with insulin resistance and the regulation adiponectin secretion (25), we controlled for this fat depot in our analyses and found the relationship between adiponectin and the metabolic syndrome remained significant. This provides further support for the importance of adiponectin as a key metabolic regulator of chronic disease risk. In adults, visceral fat has been shown to be a major determinant of the metabolic syndrome (26). Although the analyses were adjusted for obesity and insulin resistance, adiponectin data were not available. Salmenniemi *et al.* (27) used factor analysis to examine the concurrent associations among adiponectin, insulin sensitivity, visceral fat, and the metabolic syndrome. The authors found that adults with the metabolic syndrome had significantly lower insulin sensitivity and circulating adiponectin levels, even after adjustment for visceral adiposity. Although the authors concluded that the metabolic syndrome is characterized by a myriad of coexisting metabolic abnormalities, they were unable to determine whether a primary abnormality links the putative components of the disorder.

Although it is difficult to extrapolate findings in adults to younger populations, we did note that age remained a significant predictor of the metabolic syndrome in our models. Whereas the metabolic syndrome may exist in children, cardiovascular disease and type 2 diabetes remain primarily adult outcomes. It is interesting to note, however, that adiponectin levels have been shown to decrease with age in both normoweight (28) and overweight youth (29), and thus, aging and maturation may be important regulators of adiponectin metabolism and disease risk in youth.

In summary, our results indicate that adiponectin is significantly and independently associated with several components of the metabolic syndrome. Furthermore, after controlling for insulin sensitivity, total body composition, and visceral adiposity, adiponectin remained an independent predictor of the metabolic syndrome phenotype in over-

weight Latino youth. These data extend previous findings related to the pathophysiology of metabolic syndrome in children and contribute to the growing body of evidence linking obesity with chronic disease in youth.

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