Adiponectin in Childhood and Adolescent Obesity and Its Association with Inflammatory Markers and Components of the Metabolic Syndrome

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Recent work from our group in obese youth with the metabolic syndrome and impaired glucose tolerance (IGT) revealed a phenotype characterized by altered partitioning of abdominal and muscle lipid, profound insulin resistance, and impaired β-cell function. In addition, these children have a dysfunctional adipose tissue microenvironment that overproduces IL-6 and, perhaps more importantly, underproduces adiponectin—a cytokine that is secreted exclusively by adipocytes (1, 2). In adults, dysregulation of the expression and secretion of adiponectin may play a role in the pathogenesis of type 2 diabetes (3–6). In fact, studies in adults have shown that hypoadiponectinemia is an independent risk factor for the progression of type 2 diabetes (7–9). The predictable value of adiponectin may be due to its close link with insulin resistance (5). Indeed, adiponectin levels are more strongly related to insulin sensitivity than to adiposity (5). However, the effects of adiponectin are truly pleiotropic, encompassing glucose and lipid metabolism (10, 11).

Adiponectin is also emerging as an important mediator of risk for cardiovascular disease (12, 13). Adiponectin levels have been found in a number of studies to be inversely associated with markers of endothelial dysfunction and systemic inflammation, such as TNF-α and C-reactive protein (CRP) (14). Recently, however, a reciprocal association between CRP and adiponectin mRNA levels was reported in human adipose tissue (15). This finding was further assessed in adiponectin knockout mice, where the CRP mRNA levels in the adipose tissue of the knockout mice were shown to be higher than those in the wild-type mice (15). Therefore, hypoadiponectinemia per se appears to contribute to a low-grade systemic chronic inflammatory state, which is closely related to increased CRP levels.

It is not known whether the low-grade inflammatory state that is associated with childhood obesity, as evidenced by the biomarker CRP, is related to adiponectin independently of insulin resistance and adiposity. In a multiethnic cohort of obese children and adolescents studied cross-sectionally, we tested the following hypotheses: 1) low adiponectin levels are associated with higher CRP levels, and this inverse relationship persists after controlling for adiposity and insulin resistance; 2) components of the metabolic syndrome, such as low high-density lipoprotein (HDL), high triglyceride levels, and IGT, are associated with low adiponectin levels, irrespective of obesity and insulin resistance.

Subjects and Methods

The cohort

As part of a longitudinal study aimed at defining the prevalence and metabolic phenotype of prediabetes and the metabolic syndrome in...
obese youth, we formed a multiethnic cohort of 589 obese children and adolescents. The subjects were recruited from our Pediatric Obesity Clinic and were eligible if they were healthy, between the ages of 5 and 19, and had a body mass index (BMI) greater than the 95th percentile for their age and gender. The physical examination allowed determination of the pubertal status; the majority of the subjects (85%) were in puberty, as indicated in Table 1 (16). Exclusion criteria included the known presence of diabetes and chronic use of medication that affects glucose, blood pressure, or lipid metabolism. Some of these subjects have been previously reported in other publications (2, 17–20). More specifically, data on plasma adiponectin levels were previously reported on 398 subjects, and CRP levels were reported on 293 subjects (2). The current study provides substantial new data about the relationship between the pro and antiinflammatory markers in an expanded multiethnic cohort of obese children and adolescents. As described in Table 1, there were a total of 354 (60%) girls and 235 (40%) boys. There were 238 (40%) white, 179 (30%) black, and 172 (30%) Hispanic children and adolescents. The Yale University School of Medicine Human Investigation Committee approved the study. Written informed consent was obtained from parents, and written assent was obtained from children and adolescents after the nature of the procedures was explained.

Metabolic phenotyping of the cohort

All subjects were invited to come to the Yale General Clinical Research Center at 0800 h after an overnight fast, as previously reported (2). Their weight and height were measured, and their BMI was calculated. Blood pressure was measured three times while the subjects were seated, and the two last measurements were averaged for analysis. Thereafter, an indwelling venous line was inserted after the use of local anesthetic (0.1 cc buffered lidocaine) and maintained patent by a normal saline drip. Baseline samples were drawn at 0 h and 30 min for measurements of plasma glucose, insulin, c-peptide, adiponectin, CRP, IL-6, and a fasting lipid profile. Subsequently, a flavored glucose (Orangedex, Custom Laboratories, Baltimore, MD) was given orally (1.75 g of glucose/kg body weight) over 30 min, and blood samples were obtained every 30 min for 180 min for the measurements of plasma glucose, insulin, and c-peptide.

Definition of the metabolic syndrome

Currently, a standardized definition of the metabolic syndrome exists for adults, but not for children and adolescents. As previously reported, we modified the criteria from the National Cholesterol Education Adult Treatment Program and the World Health Organization to apply to making the diagnosis of the metabolic syndrome in children (2). As in adults, children are classified as having the metabolic syndrome if they meet three or more of the following criteria for age, gender, and ethnicity: BMI above the 97th percentile (BMI z-score > 2) (21), triglyceride level above the 95th percentile, HDL cholesterol below the 5th percentile (22), systolic or diastolic blood pressure above the 95th percentile (23), and IGT as defined by the American Diabetes Association (24).

Indices of insulin sensitivity

Two indices of insulin sensitivity were used: the homeostasis model assessment of insulin resistance (HOMA), calculated as the product of the fasting plasma insulin level in microunits and the fasting plasma glucose level in millimoles per liter, divided by 22.5 (25); and the whole body insulin sensitivity index (WBISI), calculated using the Matsuda Index (26). These two indices have been validated in our group by comparing them to the measure of insulin sensitivity obtained during the euglycemic-hyperinsulinemic clamp in obese children and adolescents (18). Both the HOMA and the WBISI correlated strongly with the M value, or insulin-stimulated glucose metabolism (r = −0.57 for HOMA, r = 0.78 for WBISI; P < 0.005) (18).

Biochemical analysis

Plasma adiponectin levels were measured by a double antibody-antibody RIA assay from Linco Research, Inc. (St. Charles, MO). The intra- and interassay coefficients of variation are 7.1% and 9.5%, respectively. Plasma glucose levels were measured using the YSI 2700 STAT STATISTICIAN SOFTWARE SYSTEM, Yellow Springs, OH.

TABLE 1. Baseline anthropometric characteristics of the study cohort across adiponectin quartiles

| Characteristic          | Quartile 1 6.8–7.4 µg/ml (n = 149) | Quartile 2 7.5–8.1 µg/ml (n = 149) | Quartile 3 8.8–9.5 µg/ml (n = 151) | Quartile 4 9.9–10.2 µg/ml (n = 149) | P value* Unadjusted |
|------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|---------------------|
| Gender (no., %)         | 76 (53) 88 (61) 92 (61) 98 (66)     | 69 (47) 56 (39) 59 (39) 51 (34)     | 48 (33) 55 (38) 61 (40) 74 (50)     | 45 (31) 48 (33) 53 (35) 33 (22)     | <0.001              |
| Ethnicity (no., %)      | 48 (33) 55 (38) 61 (40) 74 (50)     | 45 (31) 48 (33) 53 (35) 33 (22)     | 37 (25) 41 (29) 37 (25) 42 (28)     | 36 (24) 36 (24) 37 (25) 42 (28)     | 0.006               |
| Pubertal status (no., %)| 17 (11) 17 (11) 23 (15) 29 (19)     | 12 (8) 12 (8) 12 (8) 12 (8)         | 128 (88) 128 (88) 128 (85) 120 (81) | 0.01                               |
| Age (yr)                | 13.6 13.3 12.9 12.5                 | 13.2–14.1 12.8–13.7 12.5–13.4 12.0–12.9 | 161.4 160.8 157.3 154.7             | 159.3–163.5 158.9–162.7 155.4–159.3 152.6–156.8 | <0.001              |
| Height (cm)             | 95% CI 12.5–13.4 12.0–12.9           | 95% CI 161.4 160.8 157.3 154.7       | 159.3–163.5 158.9–162.7 155.4–159.3 152.6–156.8 | 161.4 160.8 157.3 154.7               | <0.001              |
| Weight (kg)             | 99.2 97.8 89.7 82.1                 | 95% CI 94.7–103.8 93.5–102.1 85.2–94.2 77.8–86.5 | 94.7–103.8 93.5–102.1 85.2–94.2 77.8–86.5 | 94.7–103.8 93.5–102.1 85.2–94.2 77.8–86.5 | <0.001              |
| BMI (kg/m²)             | 37.5 37.3 35.5 33.5                 | 95% CI 36.3–38.7 36.1–38.6 34.3–36.7 32.9–34.7 | 36.3–38.7 36.1–38.6 34.3–36.7 32.9–34.7 | 36.3–38.7 36.1–38.6 34.3–36.7 32.9–34.7 | <0.001              |
| BMI z-score             | 2.48 2.48 2.39 2.32                 | 95% CI 2.42–2.54 2.42–2.53 2.34–2.45 2.26–2.38 | 2.42–2.54 2.42–2.53 2.34–2.45 2.26–2.38 | 2.42–2.54 2.42–2.53 2.34–2.45 2.26–2.38 | <0.001              |
| BMI percentiles         | 98.1 98.6 98.5 96.4                 | 95% CI 97.1–99.2 97.9–99.4 98.0–99.0 94.5–98.2 | 97.1–99.2 97.9–99.4 98.0–99.0 94.5–98.2 | 97.1–99.2 97.9–99.4 98.0–99.0 94.5–98.2 | <0.001              |

* P values are for trend across all adiponectin quartiles.
Analyzer (Yellow Springs Instruments, Inc., Yellow Springs, OH), and lipid levels were measured using an Autoanalyzer (model 747–200; Roche-Hitachi, Basel, Switzerland). Plasma insulin and leptin levels were measured using an RIA assay from Linco (insulin intra- and interassay coefficients of variation: 6.8 and 11.6%, respectively; leptin intra- and interassay coefficients of variation: 6.5 and 8.0%, respectively). CRP levels were measured using the ultrasensitive assay (Kamiya Bio-medical, Seattle, WA). (For CRP, the intraassay coefficient of variation is no greater than 3.0%, and the interassay coefficient of variation is no greater than 11.6%). IL-6 levels were measured using a highly sensitive solid phase enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) (lower limit of detection: 0.16 pg/ml, intra- and interassay coefficients of variation: 7.4 and 7.8%, respectively).

Statistical analysis

Positively skewed variables were log-transformed for analysis. Frequencies and means or least squares means with 95% confidence intervals (CIs) for demographic, anthropometric, metabolic, and inflammatory variables are presented by quartiles of adiponectin. Associations between these variables and adiponectin quartiles were evaluated using linear and logistic regression for continuous and binomial outcomes, respectively. Monotonic relations were examined using tests for linear trend with and without adjustment for age, gender, ethnicity, BMI z-score, and WBISI, as specified. To further examine the independent association between CRP and adiponectin, we used a stepwise forward multiple regression analysis. To do this, we used six steps in the total cohort and then stratified by race. In step 1, we entered age, sex, and race; in step 2, pubertal status was added; in step 3, BMI z-score was added; in step 4, leptin was added; in step 5, insulin sensitivity was added (WBISI); and finally in step 6, adiponectin was added to the model. Analyses were performed using R (version 2.1.1, R Project, Vienna, Austria) and SPSS (version 12, SPSS, Chicago, IL).

Results

Anthropometric characteristics of the cohort according to quartiles of adiponectin

The subjects from the cohort were divided into quartiles of adiponectin levels to examine the association between varying levels in adiponectin and multiple risk factors associated with the metabolic syndrome. As shown in Table 1, the gender composition varied significantly from quartile 1 to 4. Specifically, the percentage of male subjects was highest in quartile 1 and lowest in quartile 4, indicating that males had a lower mean adiponectin level than females (geometric mean, 6.1 vs. 7.0, respectively; P < 0.001). The ethnic composition was also significantly different among quartiles of adiponectin. The increasing percentage of obese whites from quartile 1 to 4 illustrates the higher adiponectin levels in whites in the study compared with the other ethnicities (geometric mean, 7.2 in whites vs. 6.2 in blacks and 6.3 in Hispanics; P = 0.006). Unsurprisingly, the mean age was lower with higher adiponectin values, and, of note, there were more prepubertal subjects in quartile 4. This difference can be accounted for by the fact that adiponectin levels tend to decrease throughout puberty, which parallels the development of insulin resistance (27). In agreement with other reports, our study confirms that gender and puberty have effects on adiponectin (28, 29). Thus, older children tend to have lower adiponectin levels.

Mean height was lower with higher adiponectin values. This trend was still significant (P = 0.01) after adjusting for age, gender, and ethnicity. Mean weight (P < 0.001), BMI (P < 0.001), and BMI z-score (P < 0.001) were also lower with higher adiponectin levels. These associations retained significance after adjusting for age, gender, and ethnicity (P < 0.001, 0.007, and 0.001).

Metabolic characteristics of the cohort according to quartiles of adiponectin

The relationship between adiponectin levels and glucose and lipid variables was analyzed with and without adjusting for age, gender, ethnicity, BMI z-score, and WBISI. Fasting blood glucose was not significantly associated with adiponectin before or after adjustment (P = 0.24 unadjusted, P = 0.26 adjusted). Two-hour postchallenge blood glucose and average blood glucose were negatively associated with adiponectin before adjustment (P = 0.01 and 0.012, respectively), but most of the difference was due to differences in insulin sensitivity; when adjusted for age, gender, ethnicity, BMI z-score, and WBISI, the associations lost their significance (P = 0.71 and 0.59, respectively) (data not shown).

Fasting insulin, 2-h post-glucose-challenge insulin, and average insulin levels were highly negatively associated with adiponectin before adjustment (P < 0.001). When adjusted, the associations lost significance (P = 0.24, 0.72, and 0.40, respectively). HOMA was negatively associated with adiponectin before adjustment (P < 0.001), but this association disappeared after adjustment (P = 0.48) (data not shown).

Total cholesterol and low-density lipoprotein cholesterol were not significantly associated with adiponectin levels, unadjusted (P = 0.233 and 0.574, respectively) or adjusted (P = 0.47 and 0.75, respectively).

Proinflammatory markers according to level of adiponectin (Fig. 1)

There were significant inverse relationships between CRP levels and adiponectin levels, as illustrated in Fig. 1; higher adiponectin levels were significantly associated with lower CRP levels, even after adjustment for the potential confounding variables of age, ethnicity, gender, BMI z-score, and WBISI (unadjusted P < 0.001, adjusted P = 0.003). In contrast, circulating levels of IL-6 showed no significant relationship with adiponectin, either unadjusted or adjusted (P = 0.813, P = 0.65).

In the unadjusted analysis, leptin showed no significant association with adiponectin levels (P = 0.102). However, after adjusting for age, gender, ethnicity, BMI z-score, and WBISI, a significantly positive relationship emerged (adjusted P < 0.001). There were also significant differences between quartile 1 and the remaining quartiles (P < 0.05, P < 0.01, and P < 0.001).

Components of the metabolic syndrome according to level of adiponectin (Fig. 2)

WBISI was positively associated with adiponectin levels, both unadjusted (P < 0.001) and after adjusting for age, gender, ethnicity, and BMI z-score (P = 0.04). Quartiles 1 and 2 were significantly different from the highest adiponectin quartile (P < 0.01 and P < 0.001, respectively). The prevalence of IGT did not change significantly by quartiles of adiponectin (P = 0.54), whereas high HDL-cholesterol levels were significantly associated with higher levels of adiponec-
tin (unadjusted \( P < 0.001 \)). The strong linear relationship between adiponectin and HDL persisted after adjusting for potential confounders, such as age, gender, ethnicity, BMI z-score, and WBISI (unadjusted \( P = 0.003 \) for the association of CRP with adiponectin levels. There were no significant differences among quartiles. B, IL-6 levels (geometric mean and 95% CI). \( P = 0.65 \) for the association of IL-6 with adiponectin levels. There were no significant differences among quartiles. C, Leptin levels (geometric mean and 95% CI). \( P < 0.001 \) for the association of leptin with adiponectin levels. There were significant differences between quartile 1 and the remaining quartiles (\( P < 0.05, P < 0.01, P < 0.001 \), respectively).

Prevalence of the metabolic syndrome according to adiponectin levels (Fig. 3)

The prevalence of the metabolic syndrome was significantly lower with higher levels of adiponectin (unadjusted \( P = 0.002 \)) (Fig. 3). However, the significance disappeared after adjusting for age, gender, ethnicity, and WBISI (\( P = 0.15 \)).

The odds ratio for meeting the criteria for the metabolic syndrome, shown in Fig. 3, decreased linearly with higher levels of adiponectin, but the significance was lost after controlling for potential confounders.

Regression analysis (Table 2)

To identify independent associations between adiponectin and CRP, we performed stepwise forward multiple regression analysis in the total cohort and separately in each ethnic group.

As shown in Table 2, CRP was the dependent variable. In steps 1 and 2, where age, gender, race (step 1), and pubertal status (step 2) were entered, no significant relationships were found. In contrast, when BMI z-score was entered in the model (step 3), the total \( r^2 \) increased significantly, explaining 26% of the variance in CRP. This relationship appears to be
FIG. 2. WBISI and components of the metabolic syndrome according to level of adiponectin. For all panels, unadjusted and adjusted values are represented. An adjusted trend across all adiponectin quartiles (adjusted for age, gender, ethnicity, BMI z-score, and WBISI) is indicated. Likewise, significant differences among quartiles are noted. A, WBISI levels (arithmetic mean and 95% CI). $P = 0.04$ for the association of WBISI with adiponectin level. Quartiles 1 and 2 were significantly different from the highest adiponectin quartile ($P = 0.01$, $P = 0.001$, respectively). B, Prevalence of IGT. $P = 0.54$ for the association of IGT with adiponectin level. C, HDL cholesterol levels (geometric mean and 95% CI). $P < 0.001$ for the association of HDL with adiponectin levels. There are significantly higher HDL concentrations in the highest adiponectin quartile compared with the lowest adiponectin quartile ($P < 0.05$). D, Total triglyceride levels (geometric mean and 95% CI). $P = 0.51$ for the association of triglycerides with adiponectin levels. No significant differences existed among quartiles. E, Systolic blood pressure (arithmetic mean and 95% CI). $P = 0.14$ for the association of systolic blood pressure with adiponectin levels. No significant differences among quartiles. F, Diastolic blood pressure (arithmetic mean and 95% CI). $P = 0.18$ for the association of diastolic blood pressure with adiponectin levels. No significant differences among quartiles.
stronger in Hispanic children and adolescents ($r^2 = 0.315$, $P < 0.001$). The addition of leptin to the model (step 4) and insulin sensitivity (WBISI) (step 5) further increased the $r^2$ to 0.316 ($P < 0.001$). Finally, adding adiponectin to the entire model (step 6) resulted in a significant increase in the total $r^2$ (0.348, $P < 0.001$). Thus, adiponectin explained 4% of the variance in CRP levels. Stratifying the analysis by race indicated that in Hispanic children and adolescents, adiponectin explained 13% of the variance in CRP levels.

Discussion

The coexistence of obesity and a low-grade inflammatory state has been found to be present during the earliest stage of obesity and is strongly dependent on the degree of obesity (2, 30). In an attempt to understand the relationship between obesity and inflammation, we elected to analyze the relationship between adiponectin, a key molecule uniquely secreted by the adipocyte, and CRP, the prototype of inflammation, in a large multiethnic cohort of obese children and adolescents. Stratifying the cohort into quartiles of adiponectin levels and adjusting for potential confounding variables, including age, gender, pubertal stage, ethnicity, BMI z-score, and WBISI, the present study revealed the following:

1. Low levels of adiponectin are associated with higher CRP levels.

2. HDL cholesterol was the only component to show association with adiponectin. Hence, the relationships between adiponectin levels and both CRP and HDL cholesterol appear to be independent of obesity and insulin resistance in childhood obesity and are not influenced by ethnicity ($P$ value adjusted for ethnicity $< 0.003$). The prevalence of the metabolic syndrome did not change with quartiles of adiponectin after adjusting for insulin resistance.

Over the past few years, accumulating evidence has indicated that obesity is associated with a subclinical chronic inflammation (31–33). One revolutionary concept is that the adipose tissue is not merely a simple reservoir of energy stored as triglycerides but also serves as an active secretory organ, releasing many peptides, complement factors, and cytokines into the circulation (31). In the presence of obesity, the balance between these numerous molecules is altered such that enlarged adipocytes and macrophages embedded within them produce more proinflammatory cytokines, such as TNF-α and IL-6, and fewer antiinflammatory peptides, such as adiponectin (33). The dysregulated production of
adipocytokines has been found to participate in the development of metabolic and vascular diseases related to obesity (34). Our present study suggests that adiponectin could play a role in modulating CRP levels and thus be a potential molecular link between adiposity and inflammation. However, this link may not be entirely due to its well-known explanation of how obesity might be related to markers of inflammation. However, mechanistic studies are needed to understand whether the link is indeed real and, more importantly, how these various factors interact with one another during the development of the metabolic syndrome and cardiovascular disease.

High adiponectin levels were found in association with high levels of HDL cholesterol and a low triglyceride-to-HDL ratio, after controlling for age, gender, ethnicity, BMI z-score, and WBISI. The mechanism by which adiponectin influences lipid metabolism remains unclear. It has been suggested that the positive effects of adiponectin on HDL and triglyceride levels might result from the significant positive relationship with lipoprotein lipase activity (39). The prevalence of the metabolic syndrome did not vary significantly with increasing levels of quartiles of adiponectin after controlling for insulin resistance (Fig. 3B).

In a recent study conducted in a cohort of Japanese men, adiponectin was shown to have a consistent relationship with each component of the metabolic syndrome and a stronger association with the metabolic syndrome than TNF-α, IL-6, and CRP. This finding suggests that adiponectin may be considered a substantial key molecule in the development of the metabolic syndrome and a comprehensive marker of the condition (40).

Few studies have examined the relationship between adiponectin levels and the metabolic syndrome in children. A recent study conducted in a cohort of obese children found that hypoadiponectinemia was an independent risk factor for the metabolic syndrome (41). Furthermore, adiponectin was the only factor that, in addition to correlating with all components of the metabolic syndrome, significantly correlated with most inflammatory markers (41). Ethnic differences in adiponectin levels have been reported by others (42).
Recently Bush et al. (42) showed that adiponectin levels were lower among African-American children and were positively related to insulin sensitivity. Our study is consistent with these findings and further suggests that this ethnic difference is also seen in the presence of obesity. To our knowledge, this is the first study that shows that adiponectin levels are also lower in Hispanic obese children after controlling for differences in degree of obesity. It is unclear at the present time why adiponectin levels are lower among obese African-American and Hispanic youth. Nevertheless, the low adiponectin levels may contribute to the greater risk of type 2 diabetes among African-American and Hispanic individuals. Analyzing the relationship between adiponectin and CRP within each ethnic group, our data may suggest an ethnic difference. The magnitude of the relationship between adiponectin and CRP appeared to differ by race and was stronger in Hispanics than both whites and African Americans.

Another interesting finding of our study is that, among children and adolescents, adiponectin levels were lower with older children. This is consistent with a study by Butte et al. (27), which found that adiponectin levels decline with age in association with changes in sex hormones and growth factors. Thus, reduced adiponectin levels may contribute to the insulin-resistant state associated with puberty (42).

Limitations of our study are mostly due to its cross-sectional nature and to the fact that we have measured total adiponectin levels rather than the low and high molecular forms. It is likely that the high molecular form is more strongly related to insulin sensitivity than is total adiponectin (34). However, it is not known whether the antiinflammatory effects of adiponectin are also more closely related to its high molecular form.

In conclusion, our study demonstrates that the association between adiponectin levels and a strong marker of inflammation, CRP, is independent of insulin resistance and adiposity in a multiculutural cohort of obese children and adolescents. Thus, adiponectin may be one of the molecular signals linking inflammation to obesity and the metabolic syndrome in childhood obesity.

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