

Plasma Adiponectin Does Not Correlate With Insulin Resistance and Cardiometabolic Variables in Nondiabetic Asian Indian Teenagers

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OBJECTIVE — The objectives of this study were to determine age- and sex-specific concentrations of adiponectin in Asian Indian teenagers and adults and to assess whether its blood levels correlated with insulin resistance and other cardiometabolic parameters.

RESEARCH DESIGN AND METHODS — We studied 196 teenagers (94 boys, 102 girls) 12–18 years of age, selected from a cohort of 2,640 individuals from a cross-sectional school-based survey in Chennai, India. For comparison, adiponectin and plasma insulin were measured in 84 healthy adults. Correlation of adiponectin with plasma levels of insulin, proinsulin, insulin resistance, anthropometry, and family history of diabetes were studied.

RESULTS — Adiponectin showed a sex dimorphism, with girls having higher values (in $\mu\text{g/ml}$) (10.3 ± 5.0) than boys (8.4 ± 3.5) ($P < 0.0001$), and it showed a positive correlation with HDL cholesterol in boys only and not with other lipid parameters, insulin resistance, proinsulin, anthropometry, and family history of diabetes. In the adults, adiponectin correlated with fasting glucose and inversely with triglycerides.

CONCLUSIONS — In Asian Indian adults and teenagers, adiponectin did not correlate directly with measures of insulin sensitivity, overweight, and other cardiometabolic variables. This was at variance with several reports in other populations showing an inverse association of adiponectin with insulin resistance, proinsulin, and BMI, suggesting ethnic differences in the relationship of adiponectin with insulin sensitivity. The role of adiponectin in relation to action of insulin needs more detailed studies in Asian Indians.

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A variety of adipokines have been implicated in causation of insulin resistance, systemic inflammation, and atherosclerotic processes (1–5). Among these, Adiponectin is the most abundant and is shown to have insulin-sensitizing, antiatherogenic, and anti-inflammatory properties (3–5). Sex dimorphism is generally observed, with females having higher concentrations (5–7). Hypoadiponectinemia is common in obese adults (4), obese children and adolescents (5,6,8–10), and subjects having

insulin resistance at all ages (3,9,10). Low adiponectin is shown to be predictive of future diabetes, in many populations, including the Asian Indians (7,11). Adiponectin is inversely related to proinsulin (9). Higher concentrations of proinsulin are associated with cardiovascular risk in adults (12,13) and also in adolescents (14). A raised proinsulin-to-insulin ratio, often found in diabetes, is considered an index of β -cell dysfunction.

Our recent study in adolescents showed a high prevalence of insulin resis-

tance and cardiovascular risk factors; 65% of normal weight and 85% of overweight children and adolescents showed presence of at least one cardiovascular risk factor (15). Whereas many studies in white teenagers had demonstrated such abnormalities in obese subjects (10), we observed these abnormalities even in nonobese subjects. In light of evidence showing an important role for adiponectin in regulation of insulin action and having antiatherogenic properties, we studied its association with cardiometabolic variables including insulin resistance and proinsulin in Asian Indian teenagers. A subsample from the cohort of our previous study (15) was used for this analysis.

The objectives of the study were 1) to determine age- and sex-specific values of adiponectin and proinsulin in Asian Indian teenagers, 2) to assess the association of adiponectin with cardiometabolic risk variables, 3) to see if abnormal proinsulin-to-insulin ratio suggestive of early β -cell dysfunction was present in association with other abnormalities, and 4) to see if positive family history of diabetes influenced the levels of adiponectin, insulin, proinsulin, and proinsulin/insulin.

RESEARCH DESIGN AND METHODS

A school-based cross-sectional survey of 2,640 teenagers (1,323 boys and 1,317 girls) aged 12–19 years from 16 schools in Chennai, India, was done (15). Approximately 200 subjects of the cohort were selected for this analysis, which had an equal number of boys and girls of normal weight and overweight, with a fair representation of age-groups. Samples from 94 boys and 102 girls were used for the analysis. The study was approved by the institutional ethics committee, and informed consent was obtained from the parents.

Details of demography, medical history, parental history of diabetes, height (nearest cm), weight (nearest 0.1 kg) and waist circumference (smallest girth between the costal margin and iliac crest, in centimeters), average of two readings of

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blood pressure, and body fat percentage measured using the Tanita body composition analyzer (Model TBF-300; Tanita, Tokyo, Japan; calibrated to suit Indian population) were recorded.

The day before blood collection, children were instructed by the teachers to come in the fasting state for blood tests. Blood samples were collected between 7:00 and 8:00 A.M., from children of one class per day, numbering 40–50, after ensuring that they were fasting. Samples were brought in ice to the laboratory.

Fasting plasma glucose (glucose-oxidase peroxidase method) and lipid profile (standard enzymatic procedures using Roche Diagnostic reagents, Mannheim, Germany) were estimated using the Hitachi 912 autoanalyzer. Plasma insulin was measured using a radioimmunoassay kit (Diasorin, Saluggia, Italy), which had a sensitivity of 4 $\mu\text{U/ml}$ (24 pmol/l), and intra- and interassay coefficients of variations were <10%. Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR). Plasma proinsulin and adiponectin were measured using radioimmunoassay kits provided by Linco Diagnostics (St. Louis, MO). Sensitivity of the kit for proinsulin was 2.0 pmol/l and intra- and interassay variations were <7–11%. Plasma samples of adiponectin were diluted 1:200, yielding an effective range of 0.2–40 $\mu\text{g/ml}$, with the intra- and interassay variations of <7 and 10%, respectively.

Molar ratio of proinsulin to insulin was calculated. HOMA-IR was considered as the index of insulin sensitivity. Cutoff values were derived for BMI (≥ 85 th percentile), waist circumference (> 75 th percentile adjusted for age and sex), and blood pressure (> 90 th percentile adjusted for age and sex). The cutoff values for triglycerides (TG) (≥ 1.1 mmol/l) and HDL cholesterol (< 1.3 mmol/l) for girls of all ages and boys aged <15 years; <1.17 mmol/l for boys aged 15–19 years) were used, as suggested by De Ferranti et al. (16). Normal fasting glucose was taken as < 5.6 mmol/l. The 75th percentile of HOMA-IR in normal-weight teenagers without any risk factors was considered the cutoff for normal. The value was > 3.62 (15). Cardiometabolic variables studied were blood pressure, plasma cholesterol, TG, HDL cholesterol, fasting plasma glucose, and insulin resistance (HOMA-IR) in subjects dichotomized as overweight and normal, based

on the BMI. Waist circumference was also included as a risk variable.

Occupation of parents, possession of automobiles, and location and type of residence gave a reliable index of the socioeconomic status. Physical activity score was calculated based on sports activities, kilometers walked per day, and mode of transport to school. Activity score ranged from 0 to 7: 0, least physical activity at work and during leisure time; 7, maximum walking/cycling to school and sports activities. Diet score was calculated by adding the frequency per week of intermediate food items such as ice cream, sweets, soft drinks, chocolate, fried foods, and eating out, and daily consumption of calories was calculated by using a 24-h diet recall method. The total score was divided into tertiles.

Adiponectin, proinsulin, insulin, and HOMA-IR were studied in relation to sex, BMI, and family history of diabetes. The parameters were also analyzed in relation to the cardiovascular risk variables.

For comparative purposes, adiponectin and fasting plasma insulin levels in 84 normoglycemic healthy adults (male:female 44:40) with a mean age of 45.6 ± 5.2 years and BMI of 26.5 ± 3.0 kg/m^2 were also analyzed. These samples were available from a community survey in the city.

Statistical analysis

Pearson's correlations between the variables were assessed. HOMA-IR values were log-transformed before statistical analysis. Mean and SD or median values are reported. Unpaired *t* test or median test was used for group comparisons. Comparison of levels of adiponectin, proinsulin, proinsulin-to-insulin ratio, and HOMA-IR in the presence of single or multiple cardiovascular abnormalities was done. *P* values ≤ 0.05 were considered statistically significant.

RESULTS — The study group of 196 individuals (94 boys and 102 girls) had a mean \pm SD age of 15.5 ± 1.3 years, BMI of 23.4 ± 5.5 kg/m^2 , and waist circumference of 72.3 ± 13.7 cm.

Table 1 shows the values of adiponectin, insulin, and proinsulin in the teenagers and adiponectin and insulin values in the adults (proinsulin was estimated in 160 teenagers). Girls had higher values of adiponectin and HOMA-IR. Plasma insulin, HOMA-IR, and proinsulin were higher in overweight teenagers of both sexes, but adiponectin was not influenced

by body weight. The findings in adults related to adiponectin and insulin were similar. Parental history of diabetes did not influence the hormonal levels or insulin resistance in teenagers, but in adults, insulin concentrations were higher with positive family history. Socioeconomic differences showed no influence on the hormonal levels.

Sex dimorphism was seen in adiponectin in the adults also. The value was 13.4 ± 7.0 $\mu\text{g/ml}$ in men and 16.5 ± 6.3 $\mu\text{g/ml}$ in women (*P* = 0.037).

Table 2 shows correlations of the hormones with cardiometabolic variables. Sex differences were seen in the correlations with some variables. In both sexes, insulin and HOMA-IR significantly correlated with BMI, waist circumference, body fat percentage, blood pressure, TG, and proinsulin. Insulin and adiponectin were not correlated and HOMA-IR showed significant correlation with fasting glucose in both sexes. Inverse correlations with HDL cholesterol were present in girls only. In boys, proinsulin correlated with age, TG, insulin, and HOMA-IR and, in girls, with BMI, waist circumference, blood pressure, TG, HDL cholesterol, insulin, and HOMA-IR. Adiponectin showed a correlation with HDL cholesterol and insulin in boys only.

In adults, adiponectin showed a positive correlation with fasting glucose (*r* = 0.237, *P* = 0.012), inverse correlation with TG (*r* = -0.02 , *P* = 0.032), and no significant correlation with fasting insulin or HOMA-IR.

As shown in Table 3, adiponectin was not affected by the presence of cardiometabolic abnormalities, while elevated anthropometry, blood pressure, plasma glucose, TG, and lower HDL cholesterol showed an associated increase in insulin and insulin resistance. As the changes were similar in boys and girls, data for the total group are shown. Proinsulin was higher in the presence of overweight or increased waist circumference and with increased plasma glucose. The proinsulin-to-insulin ratio was normal in the presence of abnormalities, except with elevated fasting glucose.

Presence of abnormalities was significantly associated with higher plasma insulin levels and insulin resistance (Table 3). Adiponectin showed no difference with levels of physical activity (low 9.2 ± 4.3 $\mu\text{g/ml}$ and high 10.0 ± 5.0 $\mu\text{g/ml}$; *P* = 0.29) or with differences in diet habits.

Table 1—Hormonal profile in teenagers, in relation to sex, obesity, and parental history in teenagers and adults

| | Teenagers | | | | | Adults | | | | |
|------------------------------|-----------|---------------------|------------------|------------|-------------------------------|---------------------------------|----|---------------------|------------------|------------|
| | n | Adiponectin (µg/ml) | Insulin (pmol/l) | HOMA-IR | Proinsulin (pmol/l) (n = 160) | Proinsulin-to-insulin (n = 160) | n | Adiponectin (µg/ml) | Insulin (pmol/l) | HOMA-IR |
| Total | 196 | 9.4 ± 4.5 | 134 ± 80 | 4.0 ± 2.0 | 7.1 | 0.049 | 84 | 15.4 ± 7.9 | 96.6 ± 63.6 | 4.0 ± 2.6 |
| Male | 94 | 8.4 ± 3.5 | 123 ± 73 | 3.5 ± 2.2 | 7.9 | 0.069 | 44 | 13.4 ± 7.0 | 99.6 ± 72.0 | 4.1 ± 2.8 |
| Female | 102 | 10.3 ± 5.0† | 144 ± 85 | 4.5 ± 1.8† | 6.5 | 0.041 | 40 | 16.5 ± 6.3* | 93.6 ± 53.4 | 3.9 ± 2.5 |
| Normal weight | 87 | 9.0 ± 4.5 | 87.7 ± 57.8 | 3.1 ± 2.0 | 4.6 | 0.042 | 58 | 14.8 ± 6.1 | 87.0 ± 54.0 | 3.7 ± 2.5 |
| Overweight | 109 | 9.7 ± 4.4 | 171.3 ± 75.3§ | 6.3 ± 2.9§ | 8.3§ | 0.05 | 26 | 16.0 ± 9.8 | 124.6 ± 66.8† | 5.0 ± 2.9* |
| Male | | | | | | | | | | |
| Normal weight | 44 | 8.0 ± 3.4 | 78.0 ± 52.0 | 2.1 ± 2.1 | 5.1 | 0.07 | 33 | 15.0 ± 7.4 | 79.8 ± 43.8 | 3.4 ± 2.0 |
| Overweight | 50 | 8.8 ± 3.6 | 163 ± 65† | 5.5 ± 1.6† | 9.1† | 0.06 | 11 | 14.2 ± 7.3 | 141.6 ± 99.0† | 5.7 ± 3.6† |
| Female | | | | | | | | | | |
| Normal weight | 43 | 10.0 ± 5.3 | 97.0 ± 62.0 | 3.0 ± 1.7 | 3.2 | 0.025 | 25 | 16.6 ± 5.9 | 96.0 ± 64.2 | 4.0 ± 3.0 |
| Overweight | 59 | 10.5 ± 4.9 | 179.0 ± 83.0† | 5.9 ± 1.5† | 7.4† | 0.047 | 15 | 15.5 ± 8.1 | 147.4 ± 68.6† | 5.0 ± 2.4 |
| Parental history of diabetes | | | | | | | | | | |
| Negative | 106 | 9.6 ± 4.7 | 134.0 ± 83.0 | 3.9 ± 1.9 | 6.4 | 0.043 | 67 | 14.3 ± 6.5 | 80.2 ± 41.6 | 3.9 ± 2.8 |
| Positive | 90 | 9.2 ± 4.2 | 134.0 ± 76.0 | 4.1 ± 2.0 | 7.5 | 0.051 | 17 | 16.2 ± 8.9 | 135.6 ± 60.8‡ | 5.2 ± 3.7 |

Data are means ± SD or median unless otherwise indicated. Test of significance: * P > 0.05; † P < 0.02; ‡ P < 0.0001; § P < 0.0002.

CONCLUSIONS — In Asian Indian adolescents, association of adiponectin with insulin sensitivity and cardiometabolic variables varied from reports in other populations. This study had been one among the few reports on the relationship of adiponectin with markers of insulin sensitivity, β-cell function, and cardiovascular risk in native Asian Indian children of peripubertal age. Our previous prospective study in adults showed a predictive role for hypoadiponectinemia for future diabetes (7). This study did not support the hypothesis that adiponectin could possibly be the link for pathological components such as insulin resistance. Insulin resistance and adiponectin were not directly associated either in the youth or in healthy adults. Similarly, a direct link was not seen between adiponectin and cardiometabolic abnormalities present in the teenagers.

Racial differences in adiponectin concentrations had been observed in adults (17) and in adolescents (5,10). Asian Indians were shown to have lower values than their coinhabitants of other races (17,18). We found that Asian Indian teenagers had lower BMI but had lower adiponectin values than their white peers, and the values were similar to African Americans (9). Teenagers had lower values than the adults (7). Sex dimorphism with higher values in females was seen, in agreement with other studies in children and adolescents (5,6). Age-related reduction in adiponectin attributed to hormonal changes and increasing fat mass, occurring in pubertal stage, had been reported (5,8,9). Adiponectin concentrations in Asian Indian teenagers were not age-related, as was reported in a French study (19).

Adiponectin did not correlate with measures of adiposity either in the Indian teenagers or adults, in contrast with many other studies in children (6,8,9) and in adults (4,11,17), which showed an inverse association between these variables. Kettaneh et al. (19) noted that adiponectin correlated with waist circumference and BMI in boys but not in girls. With the degree of obesity being generally low in the teenagers, the influence of true obesity could not be studied.

Indians have a higher body fat percentage for a given BMI than the white populations. In a study of Asian Indian males of 14–18 years, from northern India, inverse correlation of adiponectin with fasting insulin and HOMA-IR was observed, which became insignificant af-

Table 2—Correlation of adiponectin, insulin, and proinsulin with anthropometry, blood pressure, glucose, and lipids in the teenagers

| | Age | | BMI | Waist circumference | Body fat % | Systolic blood pressure | Diastolic blood pressure | Fasting plasma glucose | Cholesterol | Triglycerides | HDL cholesterol | Insulin resistance | Proinsulin | Adiponectin |
|--------------|-----|-------|--------|---------------------|------------|-------------------------|--------------------------|------------------------|-------------|---------------|-----------------|--------------------|------------|-------------|
| | r | P | | | | | | | | | | | | |
| Total | | | | | | | | | | | | | | |
| Insulin* | r | -0.02 | 0.58 | 0.44 | 0.51 | 0.40 | 0.32 | 0.19 | 0.06 | 0.21 | -0.15 | — | 0.44 | 0.07 |
| | P | 0.82 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.01 | 0.38 | 0.003 | 0.03 | — | 0.33 |
| HOMA-IR* | r | -0.03 | 0.60 | 0.46 | 0.52 | 0.42 | 0.31 | 0.35 | 0.06 | 0.19 | -0.16 | — | 0.43 | 0.06 |
| | P | 0.68 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.43 | 0.01 | 0.03 | — | 0.0001 | 0.38 |
| Proinsulin† | r | -0.16 | 0.19 | 0.23 | 0.04 | 0.20 | 0.16 | 0.09 | 0.05 | 0.25 | -0.13 | 0.44 | — | -0.03 |
| | P | 0.05 | 0.02 | 0.004 | 0.63 | 0.01 | 0.05 | 0.25 | 0.51 | 0.002 | 0.12 | 0.0001 | 0.0001 | 0.76 |
| Adiponectin* | r | 0.09 | 0.02 | -0.04 | 0.11 | 0.02 | 0.05 | 0.02 | 0.01 | -0.11 | 0.14 | 0.07 | 0.06 | — |
| | P | 0.19 | 0.78 | 0.55 | 0.13 | 0.77 | 0.45 | 0.83 | 0.85 | 0.11 | 0.05 | 0.33 | 0.38 | 0.76 |
| Boys | | | | | | | | | | | | | | |
| Insulin* | r | -0.12 | 0.34 | 0.30 | 0.39 | 0.27 | 0.20 | 0.15 | 0.07 | 0.20 | 0.05 | — | 0.32 | 0.16 |
| | P | 0.12 | 0.0001 | 0.002 | 0.0001 | 0.004 | 0.03 | 0.07 | 0.25 | 0.03 | 0.33 | — | 0.003 | 0.07 |
| HOMA-IR* | r | -0.14 | 0.39 | 0.34 | 0.44 | 0.30 | 0.19 | 0.33 | 0.07 | 0.17 | 0.03 | — | 0.33 | 0.16 |
| | P | 0.09 | 0.0001 | 0.0001 | 0.0001 | 0.002 | 0.031 | 0.001 | 0.24 | 0.05 | 0.39 | — | 0.002 | 0.07 |
| Proinsulin† | r | -0.28 | 0.10 | 0.09 | 0.10 | 0.04 | 0.11 | 0.14 | 0.12 | 0.24 | -0.03 | 0.32 | — | 0.01 |
| | P | 0.01 | 0.19 | 0.201 | 0.19 | 0.35 | 0.18 | 0.12 | 0.16 | 0.02 | 0.39 | 0.003 | 0.002 | 0.46 |
| Adiponectin* | r | -0.04 | -0.01 | -0.03 | 0.04 | 0.04 | 0.09 | -0.03 | -0.06 | -0.16 | 0.18 | 0.17 | 0.16 | — |
| | P | 0.34 | 0.48 | 0.41 | 0.36 | 0.36 | 0.19 | 0.38 | 0.28 | 0.06 | 0.04 | 0.05 | 0.07 | 0.46 |
| Girls | | | | | | | | | | | | | | |
| Insulin* | r | -0.01 | 0.32 | 0.26 | 0.23 | 0.34 | 0.19 | 0.12 | 0.03 | 0.22 | -0.19 | — | 0.58 | -0.01 |
| | P | 0.44 | 0.0001 | 0.005 | 0.01 | 0.0001 | 0.03 | 0.11 | 0.37 | 0.01 | 0.02 | — | 0.0001 | 0.46 |
| HOMA-IR* | r | -0.02 | 0.36 | 0.29 | 0.25 | 0.37 | 0.2 | 0.29 | 0.03 | 0.21 | -0.21 | — | 0.57 | -0.01 |
| | P | 0.41 | 0.0001 | 0.002 | 0.006 | 0.0001 | 0.014 | 0.001 | 0.39 | 0.01 | 0.01 | — | 0.0001 | 0.47 |
| Proinsulin† | r | 0.098 | 0.34 | 0.33 | 0.15 | 0.32 | 0.25 | 0.04 | 0.01 | 0.24 | -0.18 | 0.58 | — | -0.01 |
| | P | 0.21 | 0.001 | 0.001 | 0.09 | 0.001 | 0.011 | 0.37 | 0.45 | 0.01 | 0.05 | 0.0001 | 0.0001 | 0.47 |
| Adiponectin* | r | 0.07 | 0.005 | 0.02 | 0.02 | 0.08 | 0.03 | 0.05 | 0.03 | -0.05 | 0.06 | -0.01 | -0.01 | — |
| | P | 0.25 | 0.48 | 0.43 | 0.42 | 0.20 | 0.38 | 0.29 | 0.39 | 0.29 | 0.25 | 0.45 | 0.47 | — |

*Adiponectin (n = 196); Boys:girls = 94:102. †Proinsulin (n = 160); Boys:girls = 76:84.

Table 3—Hormonal profile in relation to abnormalities in cardiometabolic variables

| | Mean values (n = 196) | | | | Median values (n = 160) | | |
|---------------------------------|-----------------------|---------------------|------------------|--------------|-------------------------|---------------------|-----------------------|
| | n (%) | Adiponectin (µg/ml) | Insulin (pmol/l) | HOMA-IR | n (%) | Proinsulin (pmol/l) | Proinsulin-to-insulin |
| BMI (kg/m ²) | | | | | | | |
| Normal | 87 (44.3) | 9.0 ± 4.5 | 87.7 ± 57.8 | 3.1 ± 2.0 | 62 (38.8) | 4.6 | 0.042 |
| Abnormal | 109 (55.7) | 9.7 ± 4.4 | 171.3 ± 75.3† | 6.3 ± 2.9† | 98 (61.2) | 8.3† | 0.05 |
| Waist circumference (cm) | | | | | | | |
| Normal | 89 (45.4) | 9.4 ± 4.7 | 98.5 ± 66.2 | 2.9 ± 2.0 | 65 (40.1) | 5.2 | 0.042 |
| Abnormal | 107 (54.6) | 9.4 ± 4.3 | 163.8 ± 77.9* | 5.3 ± 1.8* | 95 (59.9) | 7.9‡ | 0.05 |
| Body fat (%) | | | | | | | |
| Normal | 102 (52.0) | 9.3 ± 4.6 | 102.8 ± 72.6 | 2.9 ± 2.0 | 76 (47.5) | 5.7 | 0.053 |
| Abnormal | 94 (48.0) | 9.4 ± 4.3 | 168.2 ± 73.0* | 5.7 ± 1.6† | 84 (52.5) | 7.5 | 0.047 |
| Blood pressure (mmHg) | | | | | | | |
| Normal | 161 (82.1) | 9.3 ± 4.2 | 120.8 ± 69.5 | 3.6 ± 1.9 | 133 (83.1) | 6.9 | 0.051 |
| Abnormal | 35 (17.9) | 9.8 ± 5.5 | 195.4 ± 94.7† | 6.4 ± 1.9† | 27 (16.9) | 9.1 | 0.042 |
| Triglycerides (mmol/l) | | | | | | | |
| Normal | 143 (72.0) | 9.6 ± 4.7 | 124.5 ± 75.1 | 3.7 ± 2.0 | 115 (71.9) | 6.9 | 0.05 |
| Abnormal | 53 (27.0) | 8.7 ± 3.8 | 160.2 ± 86.3‡ | 4.9 ± 1.8‡ | 45 (28.1) | 8.9 | 0.05 |
| Cholesterol (mmol/l) | | | | | | | |
| Normal | 163 (83.2) | 9.5 ± 4.5 | 132.4 ± 79.1 | 3.9 ± 2.0 | 130 (81.3) | 6.6 | 0.046 |
| Abnormal | 33 (16.8) | 9.0 ± 4.6 | 143.0 ± 63.1 | 4.4 ± 2.0 | 30 (18.7) | 9.3 | 0.064 |
| Fasting plasma glucose (mmol/l) | | | | | | | |
| Normal | 183 (93.4) | 9.4 ± 4.5 | 131.0 ± 77.5 | 3.9 ± 1.9 | 150 (93.8) | 7.0 | 0.048 |
| Abnormal | 13 (6.6) | 8.5 ± 3.9 | 178.4 ± 98.1‡ | 5.4 ± 3.5‡ | 10 (6.2) | 12.3* | 0.092* |
| HDL cholesterol (mmol/l) | | | | | | | |
| Normal | 64 (32.7) | 9.5 ± 4.5 | 120.0 ± 79.6 | 3.5 ± 1.9 | 102 (63.8) | 7.2 | 0.05 |
| Abnormal | 132 (67.3) | 9.5 ± 4.4 | 141.0 ± 79.0‡ | 4.3 ± 2.0‡ | 58 (39.2) | 7.0 | 0.043 |
| Abnormalities | | | | | | | |
| None | 88 (44.9) | 9.3 ± 4.5 | 112.0 ± 66.3 | 4.0 ± 2.5 | 70 (43.8) | 7.1 | 0.054 |
| 1 | 80 (40.1) | 9.4 ± 4.5 | 134.2 ± 79.6§ | 4.9 ± 3.0§ | 66 (41.3) | 6.4 | 0.042 |
| ≥2 | 28 (14.3) | 9.0 ± 3.8 | 176.6 ± 91.9 ¶ | 6.6 ± 3.5 ¶ | 24 (15.0) | 9.0 | 0.051 |

Data are means ± SD or median unless otherwise indicated. *P < 0.0001; †P < 0.001; ‡P < 0.05; §P < 0.05 vs. none; ||P < 0.0001 vs. none; ¶P < 0.02 vs. 1.

ter correcting for BMI and body fat percentage (20).

Among other cardiometabolic variables, adiponectin correlated positively with HDL cholesterol only in boys, an association that had been reported in different populations (5,9,10,18,19). Low adiponectin values in South Asians are considered to be consistent with the low HDL cholesterol levels in the population (17).

Whereas a number of studies in children showed negative association of insulin resistance and adiponectin independent of adiposity (9,10), some others failed to do so (6,19). The former studies had a large proportion of obese subjects. Punthakee et al. (6) found a strong interaction between BMI z score and adiponectin on insulin concentration. Plasma adiponectin did not show an association with insulin and insulin resistance in the teenagers or adults, in contrast to the observations in other populations (4). Recently, a comparative

analysis of South Asian and Caucasian women in the U.S. showed findings similar to ours indicating ethnic differences in the relationship of adiponectin and insulin sensitivity (21). South Asian women had lower adiponectin than the Caucasian counterparts. However, insulin-resistant status was not associated with lower adiponectin in South Asians, in contrast to the Caucasian women. Both the total and high molecular form of adiponectin were low in South Asian women irrespective of the degree of insulin sensitivity (21).

Insulin resistance increased with increasing number of cardiometabolic abnormalities, with no corresponding change in adiponectin, proving insulin resistance and adiponectin were not correlated. Studies in white children and adolescents (9) found adiponectin to be the possible key molecule linked to components of the metabolic syndrome. These studies were also done in obese subjects. Kantartzis et al. (22) noted that

adiponectin correlated significantly with insulin sensitivity in glucose-tolerant obese subjects. Such a mechanism may be operative in Asian Indians.

The concentration of proinsulin in the teenagers (median 7.1 pmol/l) was similar to the mean value reported by us in normoglycemic adults in another study (7.0 ± 0.52 pmol/l) (23). In the teenagers and in the adults, proinsulin concentrations increased with overweight and elevated fasting glucose. In the teenagers, parallel elevations in proinsulin and insulin, with a normal proinsulin-to-insulin ratio, indicated that there was no defect in processing of the proinsulin molecule.

Lack of correlation of adiponectin with proinsulin and proinsulin-to-insulin ratio in our study was in contrast to a report in white adolescents showing a suppressive effect of adiponectin on proinsulin (9).

Presence of family history of diabetes did not alter adiponectin secretion in Asian Indians. This was also shown by

Punthakee et al. (6) in Canadians, in contrast to other observations in Swedish populations (3). Level of physical activity also had no correlation with plasma adiponectin.

The cross-sectional nature of the study has been the major limitation. The lack of an association between adiponectin and many of the cardiometabolic variables can only be suggestive, but does not prove, that adiponectin has no important role in causation of these disorders. The results may be influenced by the low levels of adiponectin present in the population. Prospective studies are needed to answer these questions. We had also used proxy measurements for insulin resistance and β -cell function. Hitherto, a majority of population studies had used such a methodology, since direct measurements of these functions are not feasible on a large scale.

We had not assessed the stages of puberty in our study subjects. Insulin and adiponectin concentrations did not show variations with age, and hence the results might not have been influenced by the stages of puberty. However, considering a strong inhibitory effect of testosterone on total adiponectin, and its sex-specific influence on adiponectin during puberty (24), studies addressing these aspects are warranted in Asian Indians.

Asian Indians have a strong racial predisposition for insulin resistance with a peculiar phenotype characterized by lean BMI and higher upper-body adiposity and high body fat percentage. They also show distinct features associated with insulin resistance, such as a lack of association of intramuscular triglycerides with insulin resistance and lack of deranged mitochondrial ATP production, in contrast to the white population (25). High concentration of adiponectin was found to be protective against diabetes (7). It was intriguing to note that adiponectin did not show correlations with insulin, insulin resistance, and proinsulin in teenagers and adults in this population. More detailed prospective studies on the complex nature of relations between adiponectin and insulin sensitivity are required to answer these questions.

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References

- Murdolo G, Smith U: The dysregulated adipose tissue: a connecting link between insulin resistance, type 2 diabetes mellitus and atherosclerosis. *Nutr Metab Cardiovasc Dis* 16:S35–S38, 2006
- Balagopal P, George D, Yarnandi H, et al: Reversal of obesity-related hypoadiponectinemia by lifestyle intervention: a controlled, randomized study in obese adolescents. *J Clin Endocrinol Metab* 90:6192–6197, 2005
- Tschritter O, Fritsche A, Thamer C, et al: Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. *Diabetes* 52:239–243, 2003
- Weyer C, Funahashi T, Tanaka S, et al: Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinaemia. *J Clin Endocrinol Metab* 86:1930–1935, 2001
- Winer JC, Zern TL, Taksali SE, et al: Adiponectin in childhood and adolescent obesity and its association with inflammatory markers and components of the metabolic syndrome. *J Clin Endocrinol Metab* 91:4415–4423, 2006
- Punthakee Z, Delvin EE, O'Loughlin J, et al: Adiponectin, adiposity, and insulin resistance in children and adolescents. *J Clin Endocrinol Metab* 91:2119–2125, 2007
- Snehalatha C, Ramachandran A, Mukesh B, et al: Plasma adiponectin is an independent predictor of type 2 diabetes in Asian Indians. *Diabetes Care* 26:3226–3229, 2003
- Stefan N, Bunt JC, Salbe AD, et al: Plasma adiponectin concentrations in children: relationships with obesity and insulinemia. *J Clin Endocrinol Metab* 87:4652–4656, 2002
- Bacha F, Saad R, Gungor N, Arslanian SA: Adiponectin in youth: relationship to visceral adiposity, insulin sensitivity, and β -cell function. *Diabetes Care* 27:547–552, 2004
- Weiss R, Dziura J, Burgert TS, et al: Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 350:2362–2374, 2004
- Lindsay RS, Funahashi T, Hanson RL, et al: Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 360:57–58, 2002
- Yudkin JS, Denver AE, Mohamed-Ali V, et al: The relationship of concentrations of insulin and proinsulin-like molecules with coronary heart disease prevalence and incidence. *Diabetes Care* 20:1093–1100, 1997
- Snehalatha C, Ramachandran A, Sathyamurthy I, et al: Association of proinsulin and insulin resistance with coronary artery disease in non-diabetic south Indian men. *Diabet Med* 18:706–708, 2001
- Tsou PI, Jiang YD, Chang CC: Sex-related differences between adiponectin and insulin resistance in school children. *Diabetes Care* 27:308–313, 2004
- Ramachandran A, Snehalatha C, Yamuna A, et al: Insulin resistance and clustering of cardiometabolic risk factors in urban teenagers in southern India. *Diabetes Care* 30:1–6, 2007
- De Ferranti SD, Gauvreau K, Ludwig DS, et al: Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. *Circulation* 110:2494–2497, 2004
- Retnakaran R, Hanley AJG, Zinman B: Does hypoadiponectinemia explain the increased risk of diabetes and cardiovascular disease in South Asians? *Diabetes Care* 29:1950–1954, 2006
- Valsamakis G, Chetty R, McTernan PG, et al: Fasting serum adiponectin concentration is reduced in Indo-Asian subjects and is related to HDL cholesterol. *Diabetes Obes Metab* 5:131–135, 2003
- Kettaneh A, Heude B, Oppert JM, et al: Serum adiponectin is related to plasma high-density lipoprotein cholesterol but not to plasma insulin-concentration in healthy children: the FLVS II study. *Metabolism* 55:1171–1176, 2006
- Vikram NK, Misra A, Pandey RM, et al: Adiponectin, insulin resistance and C-reactive protein in postpubertal Asian Indian adolescents. *Metabolism* 53:1336–1341, 2004
- Martin M, Palaniappan LP, Kwan AC, Reaven GM: Ethnic differences in the relationship between adiponectin and insulin sensitivity in South Asian and Caucasian women. *Diabetes Care* 31:798–801, 2008
- Kantartzis K, Fritsche A, Tschritter O, et al: The association between plasma adiponectin and insulin sensitivity in human depends on obesity. *Obes Res* 13:1683–1691, 2005
- Snehalatha C, Ramachandran A, Satyavani K, et al: Specific insulin and proinsulin concentrations in nondiabetic south Indians. *Metabolism* 47:230–233, 1998
- Böttner A, Kratzsch J, Müller G, et al: Gender difference of adiponectin levels develop during the progression of puberty and are related to serum androgen levels. *J Clin Endocrinol Metab* 89:4053–4061, 2004
- Nair KS, Maureen LB, Asmann YW, et al: Asian Indians have enhanced skeletal muscle mitochondrial capacity to produce ATP in association with severe insulin resistance. *Diabetes* 57:1166–1175, 2008