# Serum Adiponectin Is Associated With High-Density Lipoprotein Cholesterol, Triglycerides, and Low-Density Lipoprotein Particle Size in Young Healthy Men

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**The chromosomal localization of adiponectin has been found to be mapped to human chromosome 1q21.4-1q23, a region that was identified as a susceptibility locus for familial combined hyperlipidemia and polygenic type 2 diabetes. As these 2 disorders are associated with low high-density lipoprotein (HDL)-cholesterol, high triglycerides, and insulin resistance (IR), we examined the relation of serum adiponectin concentrations to serum lipid and lipoprotein profiles as well as IR in young healthy men. Serum adiponectin levels were positively associated with HDL-cholesterol, apolipoprotein (apo) A1, and low-density lipoprotein (LDL) particle size, and negatively associated with triglycerides and apo B. Negative associations were also found between adiponectin and body mass index (BMI), percent body fat, and IR,as determined by homeostasis model assessment (HOMA). However, after adjustment for BMI, no significant associations were found between adiponectin and LDL particle size and apo B. In a multiple regression analysis including all variables that showed significant univariate associations with adiponectin, associations of adiponectin with HDL-cholesterol ($\beta = 0.079$, $P = .0009$), percent body fat ($\beta = -0.165$, $P = .002$), and serum leptin ($\beta = -0.291$, $P = .01$) were statistically significant. HDL-cholesterol ($\beta = 0.077$, $P = .001$), percent body fat ($\beta = -0.078$, $P = .03$), and LDL size ($\beta = 0.092$, $P = .03$) emerged as significant and independent determinants of adiponectin after HOMA IR, fasting glucose, triglycerides, and systolic blood pressure (BP) were taken into account. Together, these variables explained 19% of adiponectin variability in the 2 models. HOMA IR did not emerge as a determinant of adiponectin in both models. These findings suggest that in young healthy men hypoadiponectinemia is more closely related to adiposity and dyslipidemia than IR.**

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INSULIN RESISTANCE (IR) is one of the important risk factors associated with atherosclerosis and diabetes. Recent studies have provided evidence that adipose tissue may play a crucial role in the development of IR, type 2 diabetes, and their complications through the secretion of a variety of biologically active molecules.[1] Leptin is an adipose-specific hormone contributing to the regulation of energy expenditure and food intake.[2] Leptin also affects insulin sensitivity and may participate in the development of hypertension.[3-7] Tumor necrosis factor-$\alpha$ (TNF$\alpha$) overproduced in adipose tissue in obesity has been reported to contribute to the development of insulin resistance.[8] Plasminogen activator inhibitor-1, which is increased in obesity and diabetes, may also contribute to thrombosis and the development of vascular disease.[9,10]

More recently, a novel adipose-specific protein, adiponectin, has been discovered.[11-14] Adiponectin, the gene product of the adipose most abundant gene transcript-1 (*apM1*) gene, which is exclusively and abundantly expressed in white adipose tissue, is a 244–amino acid protein with high structural homology to collagens VIII and X, and to complement C1q 11-14 as well as TNF$\alpha$.[15] Although the physiological role of adiponectin is yet to be fully determined, the chromosomal localization of adiponectin has been found to be mapped to human chromosome 1q21.4-1q23, a region that was identified as a susceptibility locus for familial combined hyperlipidemia and polygenic type2 diabetes.[16,17] As these 2 disorders are associated with low high-density lipoprotein (HDL)-cholesterol, high triglycerides, and IR, we examined the relation of serum adiponectin concentrations to serum lipid and lipoprotein profiles as well as IR in young healthy men.

## MATERIALS AND METHODS

One hundred ninety-eight men entered Kobe University of Mercantile Marine, Kobe, Japan, in 1997.[18,19] They all were Japanese and were aged 18 to 22 years. Serum samples from 179 men were available for adiponectin measurements and there were no significant differences between the 179 men and the remaining 11 men whose sera were not available for adiponectin determinations in physical and biochemical variables described in Table 1 (data not shown). Students were asked to fast overnight and to refrain smoking and alcohol overnight before attending the Center. Body weights and percent body fat were measured after they voided. This was done using an impedance fat meter (TBF-202, Tanita Corp, Tokyo, Japan), which employs 2-foot pad electrodes with a corresponding digital scale, as previously reported.[20]

Blood pressure (BP) was measured with a standard mercury sphygmomanometer after the students had rested at least 10 minutes. Systolic BP was recorded at the appearance of sounds and diastolic BP was recorded at the disappearance of sounds (V-phase Korotkov). The measurements were repeated after 2 to 3 minutes and the average of the measurements was used in analysis.

Alcohol consumption and smoking habits were determined by an interview at the time of each participant's physical examination. Data with respect to diet and exercise were not available. No subjects received any medications.

Twelve-lead electrocardiograms were recorded at a 25 mm/s paper speed and at 10 mm/mV gain by means of an automated electrocardiogram (FCP-4266, Fukuda Denshi, Tokyo, Japan). Sinus rhythm was

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**Table 1. Descriptive Data of 179 Young Healthy Men, and Simple and Partial Spearman's Correlation Coefficients Between Adiponectin and Other Variables Measured**

| | Mean | SD | Median | Simple *r* | Partial *r* |
|---|---|---|---|---|---|
| BMI (kg/m$^2$) | 21.8 | 3.7 | 21.1 | −0.26‡ | Adjusted |
| Percent body fat (%) | 18.6 | 6 | 17.4 | −0.32‡ | 0.20* |
| Serum leptin (ng/mL) | 2.3 | 2.9 | 1.4 | −0.17* | NS |
| Systolic BP (mm Hg) | 121 | 13 | 122 | −0.19* | NS |
| Diastolic BP (mm Hg) | 72 | 8 | 71 | −0.11 | NS |
| Total cholesterol (mg/dL) | 177 | 29 | 170 | −0.06 | NS |
| LDL cholesterol (mg/dL) | 107 | 27 | 102 | −0.13 | NS |
| HDL cholesterol (mg/dL) | 57 | 10 | 56 | 0.34‡ | 0.31‡ |
| Triglyceride (mg/dL) | 63 | 33 | 57 | −0.26‡ | −0.19* |
| apo A1 (mg/dL) | 132 | 18 | 131 | 0.23† | 0.24† |
| apo B (mg/dL) | 73 | 20 | 69 | −0.23† | NS |
| LDL diameter (Å) | 270 | 5 | 269 | 0.16* | NS |
| Fasting glucose (mg/dL) | 89 | 7 | 89 | −0.14* | NS |
| Fasting insulin ($\mu$U/mL) | 8.4 | 3.6 | 8 | −0.30‡ | −0.25† |
| HOMA IR | 1.87 | 0.84 | 1.75 | −0.30‡ | −0.25† |
| HOMA $\beta$ cell | 6.66 | 3.09 | 6.08 | −0.13 | NS |
| CRP ($\mu$g/mL) | 0.51 | 1.45 | 0.16 | −0.07 | NS |
| Adiponectin ($\mu$g/mL) | 6.9 | 2.8 | 6.4 | | |

*$P < .05$; †$P < .01$, ‡$P < .001$ or less.

Abbreviation: NS, not significant.

present in all participants and repolarization disturbances were not detectable in any of the electrocardiograms.

Venous blood was sampled after an overnight fast and centrifuged at 3,000 rpm for 30 minutes at 4°C. Plasma glucose was measured by the glucose oxidase method. Insulin and leptin were assayed using commercially available kits (Pharmacia, Tokyo, Japan and Linco Research, St Charles, MO, respectively). Cholesterol, triglyceride, HDL-cholesterol, and apolipoproteins were measured as previously reported.[20] Low-density lipoprotein (LDL)-cholesterol was calculated using the formula of Friedwald et al.[21] The diameter of the major LDL fraction was determined by gradient gel electrophoresis on 2% to 16% polyacrylamide gels (Biocraft, Tokyo, Japan) according to the method of Nicols et al.[22]

IR and secretion ($\beta$ cell) determined by homeostasis model assessment (HOMA)[23] were calculated using fasting plasma glucose and insulin levels in each participant. HOMA IR has been validated by comparison with results of glucose clamp studies,[23,24] intravenous glucose tolerance tests,[23,25] and continuous infusion of glucose with minimal model assessment.[25] The HOMA $\beta$-cell method has been validated by comparison with the intravenous glucose model assessment.[26] Application of HOMA has also been used in epidemiological studies.[23,27,28]

Serum levels of adiponectin and C-reactive protein (CRP) were measured in sera stored at −70°C. Adiponectin was assayed by a sandwich enzyme-linked immunosorbent assay employing an adiponectin-specific antibody,[29] with a range of 1.0 to 20.0 $\mu$g/mL. Intra-assay and interassay coefficients of variation were 3.3% and 7.5%, respectively. CRP was measured using a highly sensitive immunonephelometric assay,[30] with a range of 0.02 to 10 $\mu$g/mL. Coefficients of variation for repeated measurements of CRP were less than 5% over all ranges.

Statistical analysis was performed with the SAS statistical software system (SAS Institute, Cary, NC). Significance of in mean values was assessed by 2-away analysis of variance (ANOVA) and then analysis of covariance (ANCOVA). Spearman's correlation coefficients were calculated to determine the relationship between serum adiponectin concentrations and BP, and anthropometric and metabolic variables. Partial Spearman's correlation coefficients adjusting for body mass index (BMI) were used to ascertain the direct relationship between serum adiponectin and other variables. Finally, multiple regression analysis with backward elimination procedure was carried out to discriminate variables affecting adiponectin. Because the distribution became normally distributed after log transformation, logarithmically transformed values of CRP (log CRP) were used. *P* values less than .05 were considered significant.

## RESULTS

Characteristics of the young men are shown in Table 1. No individual had abnormalities in electrocardiograms or fasting glucose ≥7.0 mmol/L, and none received any medical treatment. Only one student had hypertriglyceridemia (fasting triglyceridemia ≥200 mg/dL) or low HDL-cholesterol (<35 mg/dL). In addition, they had a low prevalence of obesity (5%), hypertension (5%), and high LDL-cholesterol (6%), as previously reported.[7,20] Finally, the proportion of current smokers was low (5%). As a consequence, the subjects had low circulating CRP concentrations with a median value of 0.16 $\mu$g/mL, which is close to the median of 0.15 $\mu$g/mL in children aged 10 to 11 years.[31] Adiponectin averaged 6.9 ± 2.8 $\mu$g/mL with a median of 6.4 $\mu$g/mL.

Compared with young men in a high adiponectin tertile, young men in the low adiponectin tertile were characterized by higher BMI, percentage body fat, and serum leptin, although there was no difference in systolic and diastolic BP between the 2 groups (data not shown). In addition, young men in the low adiponectin tertile had higher triglycerides and apolipoprotein (apo) B concentrations, and reduced levels of HDL-cholesterol and apo A1, whereas there was no difference in total and LDL-cholesterol, or LDL size. Higher fasting insulin, comparable fasting glucose, and therefore, higher HOMA IR further distinguished men in the low from the high adiponectin tertile. Results from men in the median adiponectin tertile were intermediate between the 2 groups. After adjustment for BMI using ANCOVA, the difference was still significant in HDL-choles-

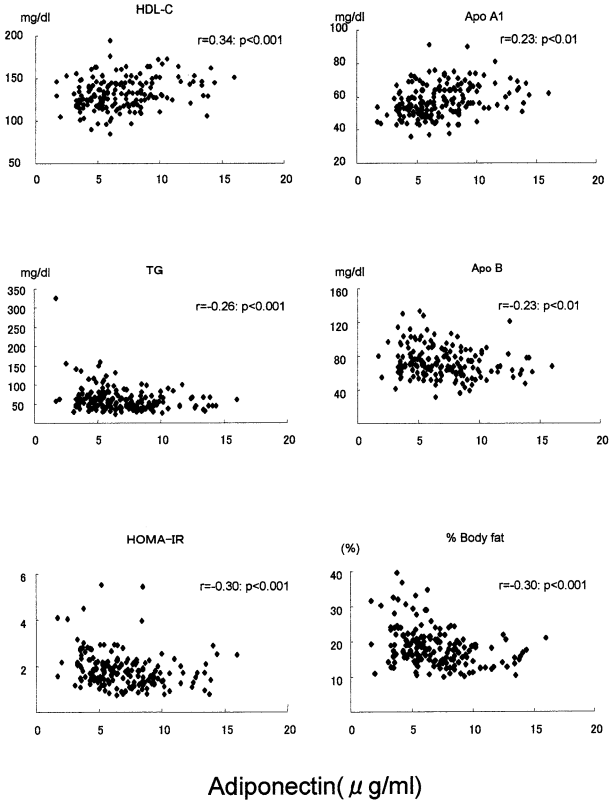


**Fig 1. Relationship between serum lipoproteins and adiponectin concentrations in 179 young healthy male college students aged 18 to 20. Adiponectin is positively correlated with HDL-cholesterol and apo A1, and negatively correlated with triglyceride, apoB, HOMA IR, and percent body fat. After adjustment for BMI, no significant association exists between adiponectin and LDL particle size and apo B.**

terol ($P = .01$). Least square means (±SE) of HDL-cholesterol were 55.3 ± 1.7, 56.7 ± 1.2, and 60.2 ± 1.2 mg/dL in the low, median, and high adiponectin tertiles, respectively. Changes in serum triglycerides and apo A1 did not reach statistical significance ($P = .06$ and $P = .07$, respectively).

In simple correlation analysis (Table 1), adiponectin was positively associated with HDL-cholesterol, apo A1, and LDL particle size (Fig 1). In contrast, adiponectin showed negative associations with triglycerides and apo B, although there was no association with total and LDL-cholesterol. Significant and negative associations were found between adiponectin and BMI, percent body fat, fasting insulin, and HOMA IR (Fig 1). There were also weak but significant associations with serum leptin, systolic BP, and fasting plasma glucose, whereas no relation was observed with HOMA $\beta$ cell and CRP. After adjustment for BMI (Table 1), associations remained significant between adiponectin and percent body fat, triglycerides, HDL-cholesterol, apo A1, fasting insulin, and HOMA IR. However, LDL particle size and apo B were not associated with adiponectin.

The association of adiponectin with HDL-cholesterol, percent body fat, and serum leptin was statistically significant in a multiple regression analysis (Table 2, model A) that included all variables that showed significant univariate associations with adiponectin in Table 1. HDL-cholesterol, percent body fat, and LDL size emerged as significant and independent determinants of adiponectin after HOMA IR, fasting glucose, triglycerides, and systolic BP were taken into account in a stepwise multiple regression analysis (model B). Altogether these variables explained 19% of the adiponectin variability in the 2 models. HOMA IR did not emerge as a determinant of adiponectin in either model.

## DISCUSSION

The present study demonstrates that in healthy young men, lower serum adiponectin concentrations are related to lower HDL-cholesterol, smaller LDL particle size, higher triglycerides, and higher serum leptin concentrations independently of BMI or percent body fat. HOMA IR, however, did not emerge as a significant predictor of adiponectin in both models of multiple regression analysis. It is worthy noting that in the present study these observations were found in a homogeneous sample of male college students: most of them were non-obese, normolipidemic, nondiabetic, and normotensive. In addition, no subject had any abnormalities in electrocardiograms and none was receiving any medications.

The adipocyte-specific adiponectin gene could be mapped to human chromosome 1q21.3-q23, a region to which familial combined hyperlipidemia (FCH) has been mapped.[16,17] Individuals with FCH showed elevated serum concentrations of very-low-density lipoprotein and/or LDL. Common features of FCH also are reduced HDL concentrations, elevated apo B levels, and an increase in small dense LDL particles. These lipoprotein abnormalities may be compatible with the present finding that lower adiponectin serum levels are independently associated with higher triglycerides, lower HDL-cholesterol, and smaller LDL particle size in young healthy men. In this context, the present findings may support the hypothesis that FCH is a genetic disorder of adipose tissue.[32] Serum adiponectin concentrations have been reported to be associated positively with HDL-cholesterol and negatively with serum triglycerides in type 2 diabetic patients[23] and in women with dyslipidemia.[33]

Adiponectin concentrations have been shown to be related to intra-abdominal fat, sex, and age in middle-aged, apparently healthy men.[34] In addition, insulin sensitivity was related to

**Table 2. Stepwise Multiple Regression Analysis for Adiponectin as the Dependent Variable**

| Independent Variable | $\beta$ | SE ($\beta$) | *P* Value | *r* |
|---|---|---|---|---|
| Model A ($r^2 = 0.195$) | | | | |
| HDL-cholesterol | 0.079 | 0.023 | .0009 | 0.350 |
| Percent body fat | −0.165 | 0.055 | .0029 | 0.221 |
| Serum leptin | −0.291 | 0.122 | .0183 | 0.153 |
| Model B ($r^2 = 0.193$) | | | | |
| HDL-cholesterol | 0.077 | 0.023 | .0011 | 0.350 |
| Percent body fat | −0.078 | 0.036 | .0318 | 0.221 |
| LDL size | 0.092 | 0.043 | .0328 | 0.143 |

NOTE. Model A includes all variables that showed a significant, simple association with adiponectin in Table 1. Model B includes percent body fat, HOMA IR, fasting glucose, HDL-cholesterol, triglyceride, LDL size, and systolic BP as independent variables.

intra-abdominal fat and adiponectin. Further, both intra-abdominal fat and adiponectin contributed independently to triglyceride, HDL-cholesterol, and LDL particle size. The authors hypothesized that adiponectin could link intra-abdominal fat with IR and an atherogenic lipoprotein profile.[34] In contrast to middle-aged, healthy men, IR was not associated independently with adiponectin in young healthy men in the present study, although Spearman's association between the two was significant after adjustment for BMI. The most striking difference between the 2 studies is in BMI in addition to their age. BMI averaged 27.0 and 21.8 kg/m$^2$ in middle-aged and young healthy men, respectively. Circulating adiponectin concentrations did not change following exercise training that did not alter body mass,[35] whereas weight loss increased adiponectin levels,[35,36] although both exercise training and weight loss improved insulin resistance. In addition, serum adiponectin levels have been shown to decrease in parallel to weight gain, as well as the progression of IR in rhesus monkeys.[37] Further, peroxisome proliferator-activated gamma agonists increased circulating adiponectin levels in humans and rodents[38] and stimulated adiponectin gene expression in adipose tissue in rodents while they suppressed gene expression of TNF-$\alpha$,[38] which is released from adipocytes and is one of the candidate molecules responsible for causing IR in obesity. These findings suggest that adiponectin may contribute primarily to changes in insulin action associated with adiposity change. Therefore, we believe that the failure to demonstrate the independent relationship between adiponectin and IR assessed by HOMA-IR in young healthy men suggests that adiponectin may be associated primarily with adiposity and atherogenic lipoprotein profile, and then modified by abdominal fat and IR, although the fact that the young healthy men had a narrow range of HOMA-IR might make it impossible to associate adiponectin with HOMA-IR in the present study. The lack of association between adiponectin and insulinemia has been reported in Pima Indian children.[39]

The finding of an inverse relationship between percent body fat and adiponectin levels is in keeping with previous reports of an inverse association between BMI and adiponectin concentrations in Japanese subjects,[29] Pima Indians, and Caucasians.[40]

Adiponectin concentrations in young healthy men in the present study averaged 6.9 $\pm$ 2.8 $\mu$g/mL, which is at the lower end of the normal range in the literature. This may be due in part to a positive association between adiponectin and age[34] or it may reflect different assays used for determining adiponectin concentrations.

We found an inverse association between adiponectin and leptin serum concentrations independent of BMI or percent fat mass. Part of explanations for this observation may relate to the association of leptin with IR. Several investigators have reported correlations between plasma leptin and fasting insulin independent of BMI,[41,42] whereas others have shown that hyperleptinemia correlates with IR independent of changes in body weight.[43] In line with these observations, leptin seems to predict subsequent development of type 2 diabetes[44] and cardiovascular disease.[45] Of course, associations between IR, type 2 diabetes, and cardiovascular disease are well established.

We have previously shown in young healthy men that serum HDL-cholesterol concentrations[20] and LDL particle diameter[46] are both negatively associated with body fat independent of fasting serum triglycerides concentrations. These observations are compatible with the present findings that serum HDL-cholesterol concentrations and LDL particle diameter were associated with serum levels of adiponectin, an adipocyte-derived protein, independent of serum triglycerides concentrations, respectively.

We have also recently reported that young healthy men with high-normal BP have lower adiponectin, smaller LDL size, and faster resting heart rate than those with optimal BP.[18] In the present study, however, adiponectin was not related to BP after adjustment for BMI. This is presumably because of the fact that adiponectin did not show a stepwise decrease; rather adiponectin was lower to the same extent in young men with normal and high-normal BP than those with optimal BP.

The cross-sectional design of the present study complicates the drawing of causal inferences, and a single measurement of biochemical variables may be susceptible to short-term variation, which would bias the results toward the null. It has been shown that adiponectin levels normally undergo a diurnal variation in humans, corresponding to about 40% of variations from its 24-hour mean value.[47] Therefore, the associations between plasma variables and adiponectin should be interpreted with caution.

In conclusion, hypoadiponectinemia was associated more closely with atherogenic lipid phenotype including hypertriglyceridemia, low HDL-cholesterol, and small LDL particle size, and with hyperleptinemia than IR in young healthy men. If this relationship is confirmed, its underlying mechanism will become one of the important questions in dyslipidemia which may lead to new therapeutic avenues in the lipid management of the metabolic syndrome.

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