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Adiponectin Relationship with Lipid Metabolism Is Independent of Body Fat Mass: Evidence from Both Cross-Sectional and Intervention Studies

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Adiponectin influences insulin sensitivity and lipid metabolism, but it is not clear whether these effects are correlated with fat mass or distribution. We studied the relationship between plasma adiponectin and leptin levels, insulin sensitivity, and serum lipids by a cross-sectional study (n = 242 subjects) and by an intervention study (95 of 242) to evaluate the effect of weight loss (WL).

Considering all subjects both together and subdivided into nonobese (n = 107) and obese (n = 135) groups, plasma adiponectin, but not plasma leptin, was significantly ($P < 0.01$) correlated with insulin sensitivity [homeostasis model assessment of insulin-resistance index ($HOMA_{IR}$), insulin sensitivity index (ISI) at oral glucose tolerance test, and clamp in 115 of 242 individuals], high-density lipoprotein cholesterol, and triglycerides. These relationships were still significant ($P < 0.01$) after adjusting for age, gender, body mass index (BMI), and ISI. After WL (−16.8 ± 0.8%), plasma adiponectin increased, and plasma leptin decreased ($P < 0.0001$ for both). Their changes (Δ) were significantly correlated with Δ-BMI ($P < 0.05$ for both). Δ-Adiponectin, but not Δ-leptin, significantly ($P < 0.001$) correlated with Δ-high-density lipoprotein cholesterol and Δ-triglycerides; these correlations were independent of age, gender, Δ-BMI, and Δ-ISI ($P < 0.005$). In conclusion, both cross-sectional and intervention studies indicate that plasma adiponectin level correlates with serum lipids independently of fat mass. The intervention study also suggests that adiponectin increase after WL is correlated with serum lipid improvement independently of insulin sensitivity changes. (*J Clin Endocrinol Metab* 89: 2665–2671, 2004)

THE INSULIN RESISTANCE syndrome (*i.e.* the variable association between insulin resistance, hyperinsulinemia, obesity, dyslipidemia, and high blood pressure) plays an important role in the pathogenesis of type 2 diabetes mellitus and cardiovascular diseases (1, 2). Multiple mechanisms are thought to contribute to its pathogenesis: among them, the adipose tissue excess is known to play a major role, although the molecular links between increased adiposity and insulin resistance remain unclear (3, 4).

Adipose tissue, a major regulator of the metabolic adaptation to stored energy availability (5–7), exerts these functions through the secretion of different hormone-like peptides, named adipocytokines. Adipocytokines include leptin, adipsin, TNF-α, adiponectin, and resistin (8–14): their dysregulation is known to be involved in the etiology of insulin resistance (5, 6, 15).

Leptin affects energy homeostasis by inhibiting food intake and stimulating energy expenditure (8). Both leptin synthesis and circulating levels are increased in obese patients and are correlated with the fat mass in a chronic manner (16, 17); most obese patients are leptin resistant. Adiponectin is inversely correlated with leptin (18, 19); its plasma levels are significantly reduced in obese subjects (20), in insulin-resistant subjects, and in type 2 diabetic patients (21) and increased after weight reduction (22). Two independent case-control studies in healthy Caucasians (23) and in Pima Indians (24) indicate that low plasma adiponectin levels are associated with an increased risk of type 2 diabetes.

Adiponectin has antidiabetic and antiatherogenic properties (25, 26) that are believed to be related to its inverse relationship with body fat mass and insulin resistance. Whether these parameters are necessary mediators for the metabolic effects of adiponectin, however, is not clear. Evidence in the adiponectin knockout mouse (25) and in subjects with genetic backgrounds of diabetes (27) suggest that adiponectin's biological effect may be independent of fat mass and insulin resistance.

To address this issue, we first studied the relationship between plasma adiponectin concentrations, insulin sensitivity, and serum lipid parameters in a large series of unrelated nondiabetic individuals who were either nonobese (n = 107) or obese (n = 135) to evaluate the influence of body fat mass. Second, we carried out an intervention study and evaluated both these parameters and adiponectin changes in a subgroup of 95 obese patients before and after weight loss (WL). In all subjects, plasma leptin was also measured both to have an independent marker of fat mass and to compare adiponectin behavior with that of another adipocytokine with a well-established relationship with insulin resistance.

Abbreviations: BMI, Body mass index; HDL-C, high-density lipoprotein-cholesterol; $HOMA_{IR}$, homeostasis model assessment of insulin-resistance index; ISI, insulin sensitivity index; OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio; WL, weight loss.

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Subjects and Methods

Subjects

Two hundred forty-two nondiabetic (according to American Diabetes Association criteria) subjects (87 males and 155 females) were studied. One hundred seven subjects were nonobese, and 135 were obese [body mass index (BMI) $\geq$ 30 kg/m^2]. Nonobese subjects were recruited from the staff of our hospital; obese subjects were recruited from both hospital staff and the outpatient Obesity and Metabolic Clinic of our institute. Clinical investigation was conducted in accordance with the guidelines in The Declaration of Helsinki. Informed consent was obtained from all participants before entering the study, which was approved by the local research ethics committee. All subjects were kept on a weight-maintaining diet and were not on medications known to interfere with the studied variables. On the day of the study, after a 10-h overnight fast, two systolic and diastolic blood pressure recordings were obtained at 5-min intervals in all subjects.

The clinical characteristics of the subjects are shown in Table 1.

A subgroup of 95 obese subjects (BMI, 32.4–65.5 kg/m^2) was studied before and after (6–12 months) WL, which was obtained either by the application of an intragastric balloon (40 patients) (BioEnterics, Carpinteria, CA) or of laparoscopic adjustable gastric banding (55 patients) (BioEnterics). These latter patients were selected according to the National Institutes of Health criteria (28). In the follow-up period (6–12 months), all these 95 obese subjects were on a hypocaloric (−500–1000 Kcal) balanced (50% carbohydrates, 30% lipids, 20% protein) diet. Their clinical characteristics and metabolic parameters are summarized in Table 2.

Insulin sensitivity assessments

Euglycemic-hyperinsulinemic clamp (29) was performed in a subgroup of 115 subjects representative of the entire cohort (47 males and 68 females; age, 38.6 ± 1.3 yr, mean ± SEM; range, 17–70 yr; BMI, 31.7 ± 0.9 kg/m^2; range, 17.5–55.9 kg/m^2; 61 nonobese and 54 obese). Clamp studies were performed with insulin infusion at a constant rate (40 mU/m^2·min) and with variable glucose infusion to maintain plasma glucose within 10% of the baseline value for 2 h, as previously described (30). The M value (the glucose metabolized, M) was calculated from the average glucose infusion rate (equivalent to metabolized glucose) between 60 and 120 min.

In all 242 subjects, the homeostasis model assessment of insulin-resistance index ($HOMA_{IR}$) was calculated according to the following formula: fasting glucose (mmol/liter) × fasting insulin (mU/liter)/22.5 (31). $HOMA_{IR}$ values were strongly correlated with clamp M values (r = −0.78; $P < 0.0001$; n = 115).

TABLE 1. Clinical features and metabolic parameters of the 242 subjects studied

	Mean ± SEM	Range
Nonobese/obese	107/135	
Gender	87/155	
Age (yr)	36.8 ± 0.8	17–70
BMI (kg/m^2)	34.8 ± 0.7	17.5–65.5
Waist circumference (cm)	104.2 ± 1.5	64.5–160.0
WHR	0.93 ± 0.01	0.69–1.19
SBP (mm Hg)	119.6 ± 0.8	85–160
DBP (mm Hg)	77.6 ± 0.6	50–107
FPG (mmol/liter)	5.06 ± 0.04	3.55–6.77
FIRI (pmol/liter)	93.9 ± 4.4	8.6–409.7
$HOMA_{IR}$	3.1 ± 0.1	0.2–14.5
ISI	6.7 ± 0.4	0.75–54.8
TC (mmol/liter)	5.20 ± 0.07	2.56–8.87
HDL-C (mmol/liter)	1.23 ± 0.02	0.34–2.30
TG (mmol/liter)	1.19 ± 0.04	0.32–3.80
Leptin (ng/ml)	26.8 ± 1.6	1.2–114.8
Adiponectin (μg/ml)	15.8 ± 0.5	2.5–38.5

SBP, Systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FIRI, fasting immunoreactive insulin; ISI, ISI during OGTT; TC, fasting total cholesterol; HDL-C, fasting HDL-C; TG, fasting triglycerides.

TABLE 2. Clinical features and metabolic parameters in 95 obese patients before and after WL

	Before WL	After WL
Weight (kg)	115.1 ± 1.8	96.0 ± 1.9[a]
BMI (kg/m^2)	44.1 ± 0.6	36.7 ± 0.6[a]
Waist circumference (cm)	124.5 ± 1.6	106.4 ± 1.8[a]
WHR	0.97 ± 0.01	0.91 ± 0.01[a]
SBP (mm Hg)	122.9 ± 1.3	117.0 ± 1.2[a]
DBP (mm Hg)	79.5 ± 0.9	74.9 ± 0.9[a]
FPG (mmol/liter)	5.31 ± 0.05	4.98 ± 0.05[a]
FIRI (pmol/liter)	141.7 ± 7.2	91.8 ± 4.9[a]
$HOMA_{IR}$	4.7 ± 0.3	2.9 ± 0.2[a]
ISI	3.0 ± 0.2	5.3 ± 0.3[a]
TC (mmol/liter)	5.04 ± 0.11	4.75 ± 0.10[b]
HDL-C (mmol/liter)	1.28 ± 0.04	1.34 ± 0.04
TG (mmol/liter)	1.22 ± 0.05	0.92 ± 0.04[a]
Leptin (ng/ml)	47.0 ± 2.4	25.6 ± 1.9[a]
Adiponectin (μg/ml)	13.8 ± 0.6	16.9 ± 0.7[a]

Data are mean ± SEM. SBP, Systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FIRI, fasting immunoreactive insulin; ISI, ISI during OGTT; TC, fasting total cholesterol; HDL-C, fasting HDL-C; TG, fasting triglycerides.

[a] $P < 0.0001$ and [b] $P = 0.006$ *vs.* before WL.

Plasma glucose and insulin levels were also measured in all subjects before and 60 and 120 min after a 75-g oral glucose tolerance test (OGTT) and the ISI was calculated according to the following formula: $10{,}000/\sqrt{(\text{glucose}_0 \times \text{insulin}_0 \times \text{glucose}_{\text{mean}} \times \text{insulin}_{\text{mean}})}$ (32). ISI values were strongly correlated with both M values (r = 0.84; $P < 0.0001$) and $HOMA_{IR}$ (r = −0.94; $P < 0.0001$).

Methods

Blood samples for adipocytokines, hormone, and metabolic parameter measurements were drawn after an overnight fast. Plasma glucose was measured by the glucose oxidase method on a Beckman Glucose Analyzer 2 (Beckman Coulter, Inc., Fullerton, CA) and plasma insulin by microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL). Total cholesterol and triglycerides were evaluated by enzymatic methods (Instrumentation Laboratory, Milan, Italy). High-density lipoprotein cholesterol (HDL-C) fraction was separated by the use of Mg^{2+} and the dextran sulfate method (Sclavo Diagnostics, Siena, Italy).

Adiponectin and leptin were measured by RIA (Linco Research, Inc., St. Charles, MO) in plasma samples immediately frozen and stored at −20 C.

Statistical analyses

Values are given as mean ± SEM. Mean values from two different groups were compared by unpaired Student's *t* test or Mann-Whitney test, as appropriate. Mean value differences between groups, after adjusting for several covariates, were evaluated by analysis of covariance test. Simple and multiple regression analyses were used to test the relationships between plasma adiponectin and leptin concentrations and the other measured variables. Clinical features, metabolic parameters, and plasma adiponectin and leptin levels before and after WL were compared by paired Student's *t* test.

Results

Effects of age, gender, and body weight on adiponectin and leptin levels

Plasma adiponectin ($P < 0.01$) and plasma leptin ($P < 0.0001$) levels were significantly higher in females (adiponectin, 16.7 ± 0.6 μg/ml; leptin, 36.5 ± 1.9 ng/ml) than in males (14.2 ± 0.6 μg/ml and 10.0 ± 1.4 ng/ml, respectively). These differences remained significant also after data adjustment for both age ($P = 0.001$ for both adiponectin and leptin) or age and BMI ($P < 0.0001$ for both).

Plasma adiponectin levels were significantly higher in nonobese (18.3 ± 0.7 μg/ml) than in obese subjects (13.8 ± 0.5 μg/ml; $P < 0.0001$). This difference remained significant also after data adjustment for age ($P < 0.0001$) or age and gender ($P < 0.0001$).

Plasma leptin levels, as expected, were significantly higher in obese (41.7 ± 1.9 ng/ml) than in nonobese (8.4 ± 0.7 ng/ml; $P < 0.0001$) subjects. This difference remained significant also after data adjustment for age ($P < 0.0001$) or age and gender ($P < 0.0001$).

Cross-sectional study

Simple and multiple correlations in all subjects studied. Plasma adiponectin and leptin levels were inversely correlated (r = −0.16; $P = 0.01$), also after adjusting data for age and gender ($P < 0.001$) (Fig. 1). However, when data were corrected also for BMI, this correlation was lost ($P = 0.3$).

Plasma adiponectin and plasma leptin concentrations were correlated with several clinical and metabolic variables of the subjects studied. Plasma adiponectin was negatively correlated with BMI (r = −0.29; $P < 0.0001$), waist circumference (r = −0.38; $P < 0.0001$), waist-to-hip ratio (WHR) (r = −0.44; $P < 0.0001$), systolic (r = −0.24; $P = 0.0004$) and diastolic blood pressures (r = −0.14; $P = 0.03$), fasting plasma glucose (r = −0.22; $P = 0.0007$) and insulin (r = −0.37; $P < 0.0001$), $HOMA_{IR}$ (r = −0.36; $P < 0.0001$), total cholesterol/HDL-C ratio (r = −0.18; $P = 0.005$), and triglycerides (r = −0.33; $P < 0.0001$), whereas it was positively correlated with age (r = 0.17; $P = 0.007$), ISI (r = 0.49; $P < 0.0001$), and HDL-C (r = 0.28; $P < 0.0001$). All these correlations, except for diastolic blood pressure, remained significant after adjustment for age, gender, and BMI ($P < 0.05$–0.0001 for all). When data were adjusted either for age, gender, and leptin levels or for age, gender, and waist circumference, the relationship between plasma adiponectin and insulin sensitivity ($HOMA_{IR}$ and ISI) or serum lipids (HDL-C, total cholesterol/HDL-C ratio, and triglycerides) remained significant ($P < 0.01$–0.001 for all), confirming that these relationships are independent of both the amount of body fat mass (as indicated by plasma leptin levels) and body fat distribution (as indicated by waist circumference). In addition, the relationship between plasma adiponectin and serum lipids was also independent of insulin sensitivity ($P < 0.01$–0.0005 for all lipid parameters, after data adjustment for age, gender, ISI, and either BMI or leptin or waist circumference).

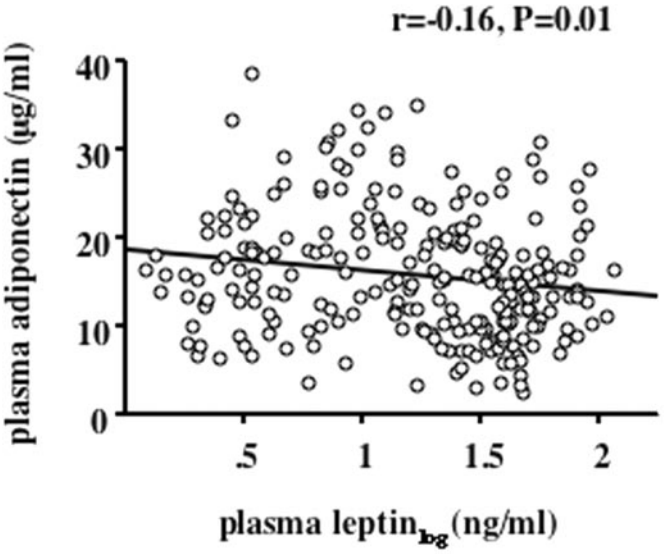

FIG. 1. Correlation between plasma adiponectin and leptin (log-transformed values) concentrations. A significant negative linear correlation is present.

Plasma leptin levels were positively correlated with BMI (r = 0.75; $P < 0.0001$), waist circumference (r = 0.70; $P < 0.0001$), WHR (r = 0.25; $P = 0.0003$), fasting plasma glucose (r = 0.33; $P < 0.0001$) and insulin (r = 0.44; $P < 0.0001$), $HOMA_{IR}$ (r = 0.43; $P < 0.0001$), and HDL-C (r = 0.28; $P < 0.0001$) and negatively correlated with age (r = −0.20; $P = 0.003$), ISI (r = −0.53; $P < 0.0001$), and total cholesterol/HDL-C (r = −0.24; $P = 0.0003$). However, at variance with adiponectin, all these leptin correlations were no longer significant (except WHR, $P < 0.05$) after adjustment for age, gender, and BMI, thus confirming that plasma leptin reflects mainly the effect of body fat mass on these parameters.

Insulin sensitivity, as measured by euglycemic clamp in a subgroup of 115 subjects, was strongly correlated with both plasma adiponectin (r = 0.44; $P < 0.0001$) and leptin (r = −0.59; $P < 0.0001$) concentrations. Again, after adjustment for age, gender, and BMI or waist circumference, only plasma adiponectin, but not leptin, was still correlated with the M values ($P < 0.001$).

Obese vs. nonobese subjects

When subjects were grouped according to BMI into nonobese (BMI < 30 kg/m^2; n = 107) and obese (BMI ≥ 30 kg/m^2; n = 135) groups, plasma adiponectin was correlated with BMI in nonobese subjects (r = −0.27, $P < 0.005$ and $P = 0.001$ after adjustment for age and gender) (Fig. 2A), but not in obese subjects (Fig. 2B). Plasma adiponectin, in contrast, was significantly correlated with insulin sensitivity (evaluated by both clamp M and ISI value, Fig. 3, A and B, respectively) and lipid parameters (HDL-C and triglycerides, Fig 3, C and D, respectively) in both nonobese and obese subjects, also after adjustment for age and gender ($P < 0.05$–0.0001 for all).

In contrast to adiponectin, plasma leptin was correlated with BMI in both nonobese (r = 0.36; $P < 0.0001$) (Fig. 2C) and obese subjects (r = 0.45; $P < 0.0001$) (Fig. 2D), also after adjustment for age and gender ($P < 0.0001$ for both). As far as insulin sensitivity is concerned, in both nonobese and obese subjects, plasma leptin was not correlated with M or ISI (except for the relationship in nonobese subjects with the ISI value, r = −0.22; $P < 0.05$). Also, no significant correlations, after adjustment for age and gender, were observed between plasma leptin and lipid parameters in both nonobese and obese subjects.

Intervention study: plasma adiponectin and leptin and WL

In a subgroup of 95 obese patients, plasma adiponectin and leptin levels were measured before (baseline value) and after WL. WL (−16.8 ± 0.8% of basal weight, range −3.5 to −37.1%) was associated with a significant increase of plasma

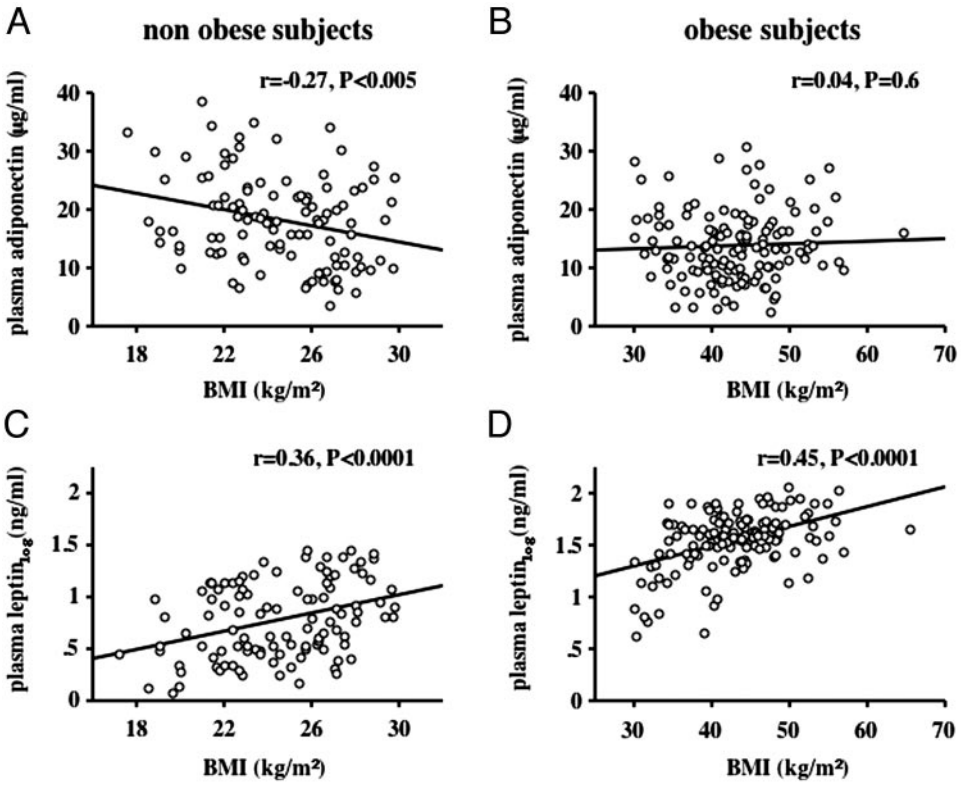

FIG. 2. Correlations between plasma adiponectin (A and B) and leptin (log-transformed values, C and D) concentrations and BMI in nonobese (A and C) and obese subjects (B and D). A significant negative linear correlation is present between adiponectin and BMI only in nonobese subjects, whereas leptin is correlated with BMI in both nonobese and obese subjects.

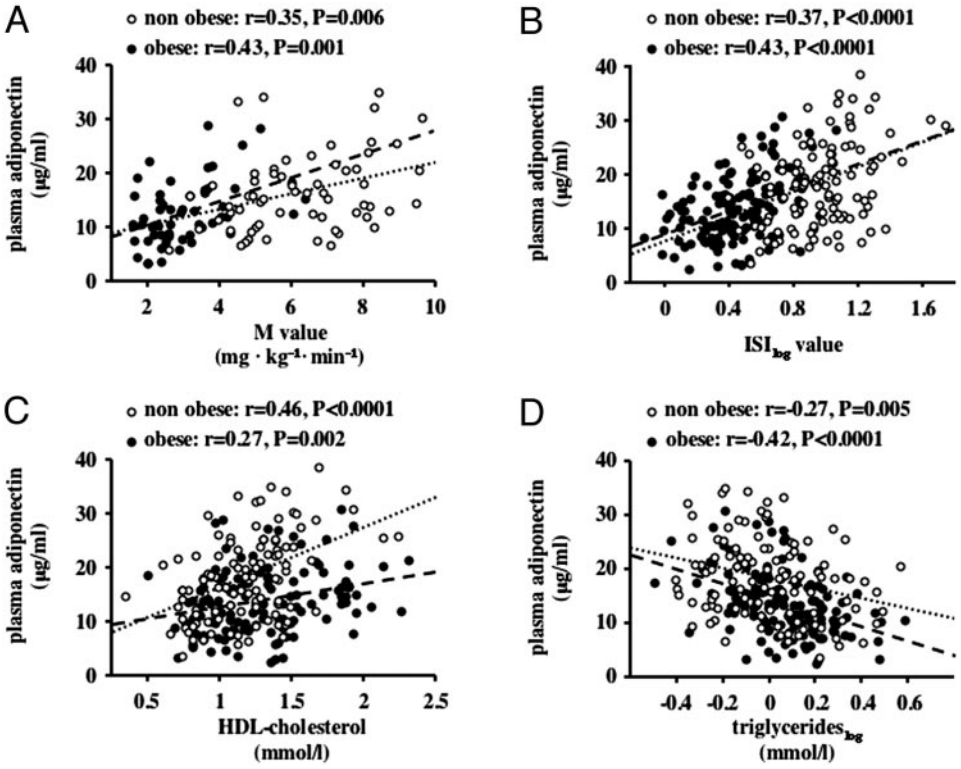

FIG. 3. Correlations between plasma adiponectin levels and insulin sensitivity (A, M value at euglycemic clamp; B, ISI_{log} at OGTT) and serum lipids (C, HDL-C; D, triglycerides) in both nonobese (○) and obese (●) subjects. Adiponectin was positively correlated with M value, ISI, and HDL-C and negatively correlated with triglycerides in both nonobese and obese subjects. At multiple regression analysis, correlations between plasma adiponectin and M value ($P = 0.01$ and $P = 0.006$ for nonobese and obese, respectively), ISI_{log} ($P < 0.0001$ for both nonobese and obese), HDL-C ($P < 0.01$ for both nonobese and obese), and triglycerides ($P < 0.05$ and $P < 0.0001$ for nonobese and obese subjects, respectively) remained significant after adjusting data for age and gender.

adiponectin and a significant decrease of leptin concentrations (Table 2). When these changes were calculated as Δ values (plasma concentration after WL minus baseline level), Δ-adiponectin was negatively correlated with baseline adiponectin ($r = -0.23$, $P < 0.05$, $P < 0.05$ after adjustment for age and gender). Furthermore, Δ-adiponectin was significantly correlated with changes in BMI ($r = -0.20$; $P < 0.05$; Fig 4A), HDL-C ($r = 0.41$; $P < 0.0001$; Fig 4C) and triglycerides ($r = -0.34$; $P < 0.001$; Fig 4E), and these relationships remained significant also after adjustment for age and gen-

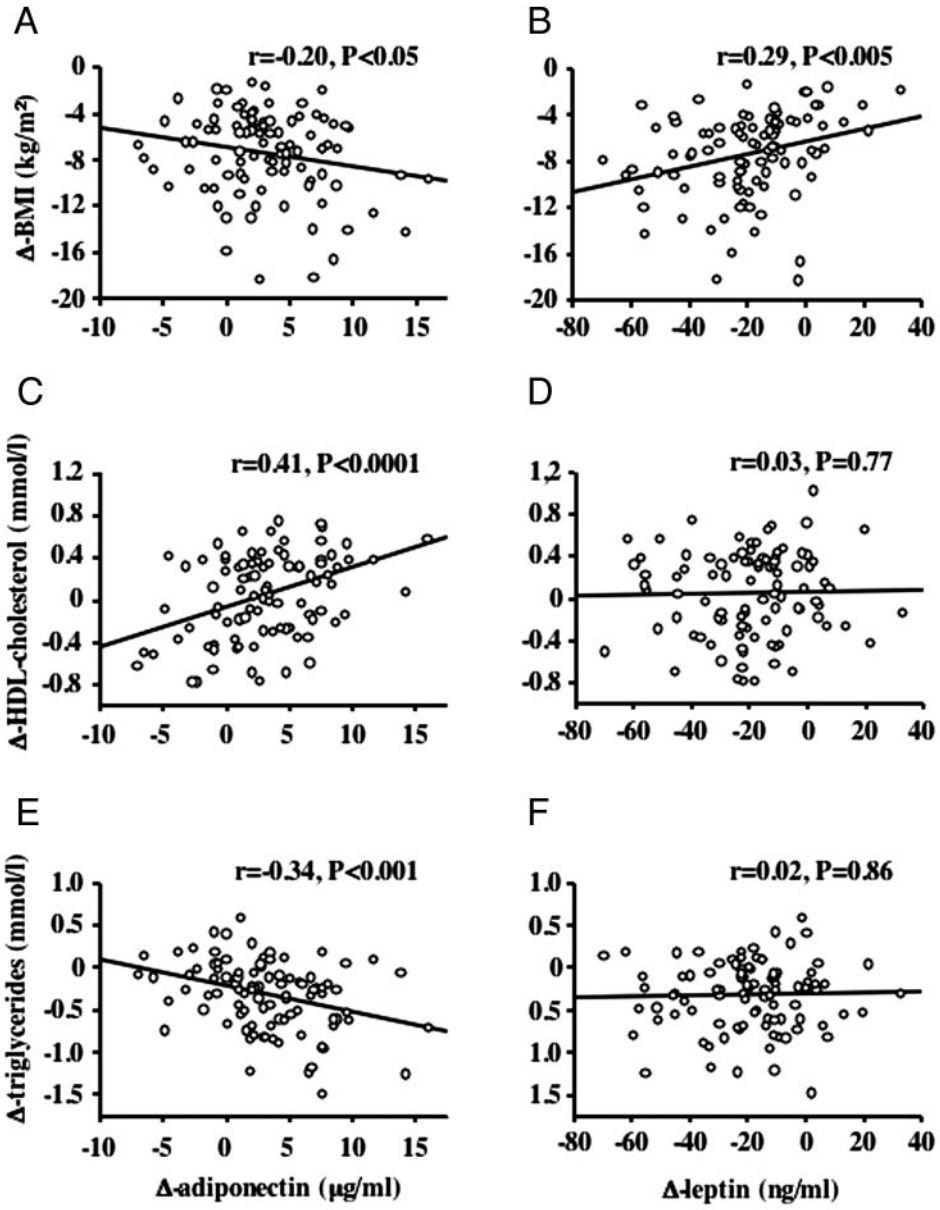

FIG. 4. Correlations between Δ-adiponectin (A, C, and E) and Δ-leptin (B, D, and F) levels and Δ-BMI (A and B), Δ-HDL-C (C and D), or Δ-triglycerides (E and F). Δ-Adiponectin was negatively correlated with Δ-BMI and Δ-triglycerides and positively correlated with Δ-HDL-C. Leptin was only positively correlated with Δ-BMI. At multiple regression analysis (adjusting data for age and gender), Δ-adiponectin remained correlated with Δ-BMI ($P < 0.05$), Δ-HDL-C ($P < 0.0001$), and Δ-triglycerides ($P < 0.001$) and Δ-leptin remained significantly correlated with Δ-BMI ($P = 0.007$).

der ($P < 0.05$–0.0001 for all). Interestingly, the relationship between Δ-adiponectin and Δ-HDL-C and Δ-triglycerides was independent of changes in adiposity ($P < 0.005$, after adjustment for age, gender and Δ-BMI or Δ-leptin) and changes in insulin sensitivity ($P < 0.001$, after adjustment for age, gender, and Δ-ISI).

Changes in leptin were also significantly correlated with baseline levels ($r = -0.68$, $P < 0.0001$, and $P < 0.0001$ after data adjustment for age and gender) and with Δ-BMI ($r = 0.3$; $P < 0.005$; Fig. 4B) but, at variance with adiponectin, no correlations were observed with Δ-HDL-C and Δ-triglycerides (Fig. 4, D and F, respectively).

Moreover, as expected, insulin sensitivity improved significantly after WL (Table 2) and was significantly correlated with Δ-BMI ($r = 0.30$, $P < 0.005$, and $P < 0.005$ after adjustment for age and gender). In contrast, no correlation was present between Δ-ISI and either Δ-adiponectin or Δ-leptin.

Discussion

The relationship between obesity, insulin resistance, and type 2 diabetes is well known. The mechanisms of this relationship, however, are still unclear. In particular, the role of adipose tissue and of the hormones it secretes in determining insulin resistance requires a better understanding.

In the present study, we have investigated the specific role of adiponectin and leptin by analyzing the correlation of their plasma levels with a variety of metabolic and clinical parameters related to the insulin resistance syndrome. Data were also corrected both for fat mass, fat distribution, and insulin sensitivity to overcome the influence of these factors.

First, we studied a cohort of nondiabetic subjects spanning a wide range of BMI (from normal weight to severe obesity) and found that plasma levels of adiponectin and leptin were inversely correlated but that this relationship was no longer

present after data adjustment for BMI. In addition, the two adipocytokines had different behaviors: the plasma adiponectin relationship with insulin sensitivity (*i.e.* M value of glucose disposal at clamp, ISI at OGTT and $HOMA_{IR}$) and serum lipid profile (total cholesterol/HDL-C ratio, HDL-C, and triglyceride levels) was statistically independent of body fat mass, whereas the correlation between leptin and those parameters was entirely mediated by BMI. This difference between the two adipocytokines was present also when only obese patients were considered: plasma adiponectin was correlated with insulin sensitivity, triglycerides, and HDL-C concentrations but not with the degree of obesity, whereas plasma leptin was only correlated with BMI. These data indicate that also in obese patients, at variance with leptin, the relationship between plasma adiponectin and either insulin sensitivity or serum lipids is independent of body fat mass. Our studies, carried out in subjects unrelated to diabetic patients yet providing results similar to a previous study carried out in a large cohort of subjects that included more than 50% first-degree relatives of type 2 diabetics (27), exclude the influence of the diabetic genetic background on the BMI-independent relationship between plasma adiponectin and both insulin sensitivity and lipid profile.

Despite the strong correlation between adiponectin levels and insulin sensitivity, a wide variability of adiponectin levels was observed, even in subjects having similar insulin sensitivity and/or BMI. Similar observations have already been reported (20, 21, 27) and may be attributed to a number of factors that influence adiponectin synthesis and secretion (including hormones like glucocorticoid, TNF-α intracellular mediators like cAMP, and drugs like thiazolidinediones) (33). In addition, common genetic variants of the adiponectin gene may influence circulating adiponectin levels and, therefore, also adiponectin changes after WL (34, 35).

All available evidence is based on correlation studies and suggests that in human beings, adiponectin's influence on insulin sensitivity is independent of fat mass. To better identify the specific role of fat mass on this relationship, we carried out an intervention study in 95 obese patients, studied before and 6–12 months after WL. As expected, plasma adiponectin levels increased (+22% with respect to baseline levels), and plasma leptin levels decreased (−45%) after WL. Changes were correlated with the baseline levels of each adipocytokine and with the amount of body weight reduction. In these patients, adiponectin changes after WL correlated with triglyceride decrease and HDL-C increase but, surprisingly, not with insulin sensitivity changes, although insulin sensitivity improvement was directly correlated with WL. Moreover, the relationship between plasma adiponectin changes and serum lipid changes was independent from the degree of WL. These data, in concert with the results obtained at the cross-sectional study, strongly suggest that adiponectin levels directly regulate lipid metabolism and that this effect is independent from the patient fat mass, WL, and insulin sensitivity. These observations, if confirmed in larger series, may have important clinical implications. Baseline adiponectin level measurements could be useful in identifying obese patients at high risk of dyslipidemia and cardiovascular disease. The obese individuals with the highest plasma adiponectin levels may represent a subgroup of patients with a lower atherogenic risk because of a better lipid profile and the ability of adiponectin to inhibit the development of endothelial dysfunction and the atherosclerotic vascular changes (36–38). In contrast, obese individuals with the lowest adiponectin levels should be considered at high risk for cardiovascular disease: a WL program and (when available) adiponectin treatment should be highly recommended in these patients.

The observation that, after WL, changes in adiponectin levels are not related to changes in insulin sensitivity may have different explanations. It is known that adiponectin circulates as a full-length form active in the liver (39) and a globular form active in skeletal muscles (40). The two forms interact with the specific receptors AdipoR1 and AdipoR2 (41). Changes of circulating adiponectin may differently involve the two forms and, therefore, the biological effects in target tissues (42, 43). Because the present assay measures both forms, we have no insight on this issue: it is therefore possible that small changes in total plasma adiponectin levels (such as the 22% we have observed after WL) have important biological effects because these changes involve also the relative prevalence of the specific form. Because data in animal models suggest that the major biological effect of adiponectin occurs in target tissues (*i.e.* muscle, liver, and fat), where it increases the activity of molecules involved in fatty acid transport and oxidation (44, 45), the present observations suggest that adiponectin may have a direct effect in decreasing tissue fatty acid content and serum lipids and that amelioration of insulin resistance is only a secondary effect.

In conclusion, our studies indicate that in both nonobese and obese subjects, low plasma adiponectin concentrations are associated with insulin resistance, independently of the subject's BMI. In addition, adiponectin changes after WL are associated with an antiatherogenic amelioration of the lipid profile, an effect that is independent from both the degree of body weight reduction and from the changes in insulin sensitivity. This positive effect on the lipid profile may also help explain the role of adiponectin in protecting against endothelial dysfunction and atherosclerotic vascular changes (36–38).

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