Discrimination Between Obesity and Insulin Resistance in the Relationship With Adiponectin

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Insulin resistance and obesity are both associated with lower plasma adiponectin concentrations. Since insulin resistance and obesity are related, the extent to which the association of adiponectin with insulin resistance is dependent on its relationship with obesity is unclear. To address this issue, fasting plasma adiponectin concentrations were measured in 60 nondiabetic subjects, stratified into four equal groups on the basis of both their degree of adiposity and insulin resistance. Insulin resistance was quantified by determining the steady-state plasma glucose (SSPG) concentration in response to an infusion of octreotide, glucose, and insulin, and degree of adiposity was assessed by BMI. Subjects were defined as obese (BMI ≥30.0 kg/m^2) or nonobese (<27.0 kg/m^2) and as either insulin sensitive (SSPG <100 mg/dl) or insulin resistant (>190 mg/dl). Insulin-resistant subjects had significantly ($P < 0.001$) lower (mean ± SD) adiponectin concentrations, whether they were obese (17.1 ± 5.9 μg/ml) or nonobese (16.3 ± 7.5 μg/ml) as compared with either obese, insulin-sensitive (34.3 ± 13.1 μg/ml) or nonobese, insulin-sensitive (29.8 ± 15.3 μg/ml) subjects. Finally, adiponectin levels in insulin-sensitive subjects varied to a significantly greater degree than in insulin-resistant subjects. These results suggest that adiponectin concentrations are more closely related to differences in insulin-mediated glucose disposal than obesity. *Diabetes* 53:585–590, 2004

An association between adipokines and insulin resistance has been noted in both diabetic and nondiabetic states (1–3). Of particular interest have been the recent demonstrations that adiponectin may play a direct role in determining insulin-mediated glucose uptake (3–7). However, since adiponectin is the major adipokine secreted by fat cells and is closely linked to obesity (8,9), it is unclear to what extent the association of adiponectin with insulin resistance is independent of its relationship with obesity. Understanding this association is of importance because it may clarify mechanisms of insulin resistance and influence our understanding and use of therapeutic modalities, such as weight loss or exercise to enhance insulin sensitivity.

Studies have documented that adiponectin concentrations are significantly related to various measures of body fat (8–11) and that significant weight loss leads to a rise in adiponectin levels (9,10). However, it is possible that the relationship between obesity and adiponectin is due in part to metabolic changes frequently associated with obesity. For example, insulin resistance and hyperinsulinemia are frequently associated with obesity, and both decline with weight loss (12–14). Importantly, both in vitro and in vivo studies (15,16) have demonstrated that insulin itself may lead to downregulation of adiponectin secretion from fat cells. Moreover, several studies (15–17) have reported that improving insulin resistance and reducing insulin levels with an insulin-sensitizing agent markedly increases adiponectin concentrations, even in the absence of or after adjustment of changes in weight. One way to determine whether insulin resistance is associated with adiponectin independently of obesity is to take advantage of the fact that both obese and nonobese individuals can be insulin sensitive as well as insulin resistant (12–14,18). We have used this approach in this study and have compared plasma adiponectin levels in nonobese and obese individuals, stratified at baseline into insulin-sensitive and insulin-resistant groups.

RESEARCH DESIGN AND METHODS

Subjects included 20 men and 40 women volunteers from the San Francisco Bay Area who had participated in studies conducted at Stanford University within the past 3 years to investigate relationships of insulin resistance and weight. The Stanford Human Subjects Committee had approved all studies, and written informed consent had been obtained from all subjects. In each study, blood was drawn after an overnight fast, plasma was separated, and aliquots prepared for determination of glucose, free fatty acid (FFA), insulin, lipid, and lipoprotein concentrations as previously described (13,14) or frozen for additional assays. In each of the studies, insulin-mediated glucose disposal was also quantified by a modification (19) of the insulin suppression test as originally described and validated (20). Briefly, subjects were infused for 180 min with octreotide acetate (0.27 $\mu g \cdot m^{-2} \cdot min^{-1}$), insulin (32 $mU \cdot m^{-2} \cdot min^{-1}$), and glucose (267 $mg \cdot m^{-2} \cdot min^{-1}$). Blood was drawn at 10-min intervals from 150–180 min of the infusion to measure plasma glucose and insulin concentrations, and the mean of these four values was used as the steady-state plasma insulin and glucose (SSPG) concentration for each individual. As steady-state plasma insulin concentrations were similar in all subjects during these tests, the SSPG concentration provided a direct measure of the ability of insulin to mediate disposal of an infused glucose load; the higher the SSPG concentration, the more insulin resistant the individual.

From the cohort of subjects studied during the past 3 years, we selected a subset of individuals who both met the criteria described below and had plasma that had been carefully frozen at −80°C for <3 years and was available for measurement of adiponectin. Participants were required to be in good general health as determined by a complete medical history and physical

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FFA, free fatty acid; SSPG, steady-state plasma glucose.

TABLE 1
Demographic and clinical characteristics of the nonobese and obese volunteers divided into insulin-sensitive and insulin-resistant groups

Characteristic	Nonobese		Obese		*P**
	Insulin sensitive	Insulin resistant	Insulin sensitive	Insulin resistant	
n	15	15	15	15	
SSPG (mg/dl)	71 ± 14	242 ± 32†	74 ± 14	241 ± 27†	<0.001
Age (years)	52 ± 9	47 ± 12	48 ± 9	49 ± 12	0.51
Sex (male/female)	5/10	5/10	4/11	6/9	0.90
BMI (kg/m^2)	24.5 ± 0.7	25.2 ± 1.5	31.7 ± 1.2‡	31.8 ± 1.4‡	<0.001
Weight (kg)	69.0 ± 8.5	70.5 ± 10.3	90.8 ± 8.4‡	94.1 ± 10.9‡	<0.001
Systolic blood pressure (mmHg)	119 ± 14	125 ± 12	122 ± 12	122 ± 16	0.69
Diastolic blood pressure (mmHg)	70 ± 10	74 ± 9	72 ± 10	74 ± 10	0.54
Total cholesterol (mg/dl)	199 ± 25	220 ± 38	199 ± 34	208 ± 35	0.26
LDL cholesterol (mg/dl)	122 ± 22	129 ± 33	121 ± 32	125 ± 27	0.86
HDL cholesterol (mg/dl)	56 ± 11	44 ± 12§	57 ± 20	43 ± 12‖	0.004
Triglycerides (mg/dl)	102 ± 50	235 ± 114‖	104 ± 41	199 ± 140‖	<0.001
Glucose (mg/dl)	91 ± 11	97 ± 10	92 ± 9	100 ± 8	0.07
FFA (μEq/l)	663 ± 265	759 ± 225	675 ± 229	781 ± 140	0.22
Insulin (μIU/ml)	5 ± 1	11 ± 6‖	7 ± 3	15 ± 10‖	<0.001

Data are means ± SD. *P values are for the differences among the four groups by one-way ANOVA; †$P < 0.001$; ‡$P < 0.001$ for pairwise comparisons, nonobese versus obese within each insulin action category; §$P \leq 0.06$ for pairwise comparisons, insulin sensitive versus insulin resistant within each category; ‖$P < 0.05$.

examination and a normal blood count and chemistry screening battery. Four equal groups of volunteers meeting these general criteria were then created on the basis of both BMI and SSPG concentration. Subjects were classified as being either obese or nonobese on the basis of BMI. The BMI cut points chosen to make this distinction were values of ≥30.0 or <27.0 kg/m^2, respectively, to correspond to suggested criteria for classifying individuals as being either obese or not heavy enough to merit the use of U.S. Food and Drug Administration–approved weight loss drugs (21). Subjects were classified as insulin resistant or insulin sensitive on the basis of having an SSPG concentration in the upper (>190 mg/dl) or lower (<100 mg/dl) tertile, respectively, of measurements of insulin-mediated glucose disposal in 490 healthy volunteers (22). Tertiles of SSPG concentrations were used to make this distinction on the basis of results of prospective studies (23,24) showing that individuals in the upper tertile of SSPG concentration developed a variety of adverse outcomes, none of which occurred in those in the lowest SSPG tertile. In additional analyses, the Adult Treatment Panel III waist circumference criteria (25) were also used to classify subjects with measurements of waist circumference ($n = 33$) into those with and without visceral obesity.

Plasma adiponectin was measured with a radioimmunoassay established by Linco Research (St. Charles, MO). This assay has a sensitivity of 0.01 mg/dl and intra- and interassay coefficients of variation (CVs) of <8%.

Summary statistics are expressed as mean ± SD. Adiponectin, HDL cholesterol, triglyceride, insulin, and FFA concentrations were log transformed to obtain a more normal distribution for statistical tests. Demographic and metabolic characteristics of the four study groups were compared by one-way ANOVA, except for sex distribution, which was compared by χ^2 test. Post hoc Bonferroni pairwise comparisons were performed for variables that were significantly different ($P < 0.05$) by one-way ANOVA. Variation of adiponectin levels in both the insulin-sensitive and the insulin-resistant groups was assessed by calculating each group's variance and 95% CIs. Spearman correlation coefficients (r_s) were calculated to evaluate the relationship of adiponectin levels with BMI and SSPG concentrations in the whole study group. Pearson (r) correlation coefficients were calculated to explore the relationships between plasma adiponectin concentrations and the demographic and metabolic characteristics of the study subjects. As several of these parameters, including adiponectin, vary between the sexes, the Pearson correlation coefficients were sex adjusted. Standardized regression coefficients (β) were calculated using multiple regression analysis to further quantify the strengths of associations between plasma adiponectin and the variables of interest, specifically, age, sex, BMI, blood pressure, lipids, glucose, FFA, insulin, and SSPG concentrations.

RESULTS

Demographic and clinical characteristics for all four groups are presented in Table 1. SSPG concentration was significantly higher (and similar), by selection, in the insulin-resistant groups (242 ± 32 and 241 ± 27 mg/dl) than in the insulin-sensitive groups (71 ± 14 and 74 ± 14 mg/dl, $P < 0.001$ for ANOVA and post hoc comparisons). In contrast, no significant differences in age, blood pressure, total cholesterol, LDL cholesterol, FFA, and fasting glucose concentrations were present across all four groups. Neither BMI nor weight significantly differed between insulin-sensitive and insulin-resistant individuals within each category of obesity. On the other hand, obese subjects were heavier and had higher BMI than nonobese subjects, regardless of their category of insulin action ($P < 0.01$ for all comparisons). Insulin-resistant subjects (both nonobese and obese) had higher insulin and triglyceride levels and significantly lower HDL cholesterol levels than their insulin-sensitive counterparts.

Adiponectin concentrations were not similar across all four groups, as shown in Fig. 1 (ANOVA, $P < 0.001$). Although adiponectin concentrations were essentially equal in both nonobese and obese insulin-resistant subjects (16.3 ± 7.5 and 17.1 ± 5.9 μg/ml, respectively), they were significantly lower than in either of the insulin-sensitive groups (29.8 ± 15.3 and 34.3 ± 13.1 μg/ml, $P \leq 0.01$ compared with each insulin-resistant group). There were no differences in adiponectin levels between nonobese and obese individuals within the insulin-sensitive or insulin-resistant groups. In the subset of 33 individuals with waist circumference measurements, plasma adiponectin levels were also similar in the obese and nonobese individuals within each insulin-sensitive or insulin-resistant group when the subjects were classified using the Adult Treatment Panel III criteria for visceral obesity.

Figure 2 graphically depicts the relationship of fasting adiponectin levels with BMI (*A*) and SSPG concentrations (*B*) in the entire study sample. It can be seen that there was no correlation between adiponectin levels and BMI (Spearman correlation coefficient, $r_s = 0.01$, $P = 0.96$), whereas plasma adiponectin levels were inversely correlated ($r_s = -0.44$, $P < 0.001$) with SSPG concentrations.

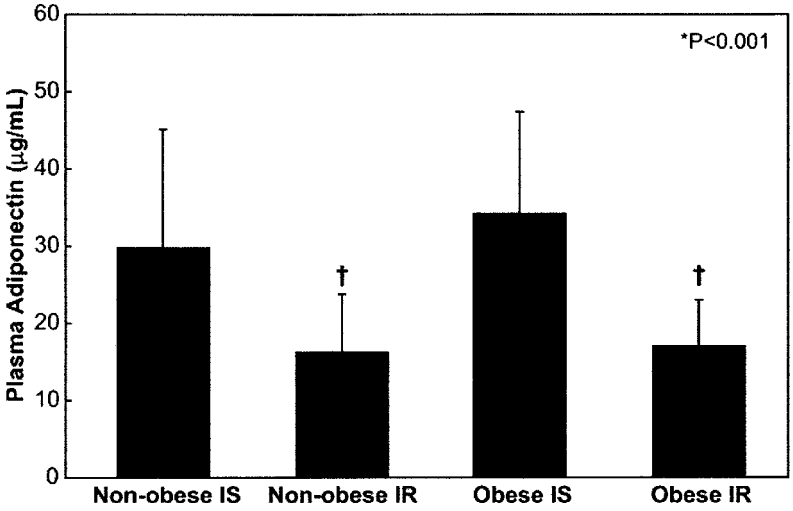

FIG. 1. Comparison of plasma adiponectin concentrations in the four experimental groups. Vertical bars represent the mean adiponectin concentrations, and error bars represent the SD. IS, insulin sensitive; IR, insulin resistant. *Mean adiponectin levels were not similar across the four groups as compared by one-way ANOVA ($P < 0.001$); †post hoc pairwise comparisons showed that adiponectin levels were significantly different ($P \leq 0.01$) between insulin-sensitive and insulin-resistant groups within each obesity category, whereas there were no significant differences ($P = 1.0$) between the nonobese and obese groups within each insulin action category.

Correlation between SSPG and adiponectin concentrations was essentially identical in the 33 individuals with measurements of waist circumference ($r_s = -0.438$, $P = 0.01$). Moreover, the SSPG-adiponectin relationship only changed modestly when it was adjusted for differences in waist circumference among subjects (Spearman partial correlation coefficient, $r_s = -0.38$, $P < 0.01$). Interestingly, adiponectin levels in insulin-sensitive subjects (SSPG <100 mg/dl) ranged from very low to very high values (Fig. 2*B*) and showed significantly greater variation (variance = 201 [95% CI 127–364]) than levels in insulin-resistant (SSPG >190 mg/dl) subjects (variance = 44 [28–80]). In fact, 19 of 30 insulin-sensitive subjects had adiponectin levels that overlapped with those of insulin-resistant subjects, and several insulin-sensitive subjects had levels of adiponectin that were as low as the lowest values in the insulin-resistant group, demonstrating that there were many instances where reduced adiponectin levels were not associated with insulin resistance.

Relationships in the entire study group between adiponectin and various demographic and metabolic parameters were also evaluated. Although weight, blood pressure, total cholesterol, LDL cholesterol, glucose, and FFAs were not significantly correlated with adiponectin concentrations, insulin ($r = -0.49$, $P < 0.001$) and triglyceride ($r = -0.27$, $P = 0.04$) levels were both negatively correlated with adiponectin concentrations. As has been reported previously, HDL cholesterol levels ($r = 0.50$, $P < 0.001$) and age ($r = 0.30$, $P = 0.02$) were also significantly correlated with adiponectin levels. Interestingly, within each category of insulin action, where SSPG values were continuously distributed, adiponectin was poorly correlated with SSPG (insulin sensitive, $r = 0.02$, $P = 0.58$, and insulin resistant, $r = 0.13$, $P = 0.51$).

In multivariate regression analysis, insulin ($\beta = -0.38$) and HDL cholesterol concentrations ($\beta = 0.38$) were both strongly related to adiponectin levels. Age ($\beta = 0.21$) and BMI ($\beta = 0.15$) were also related to adiponectin levels, although with much reduced standardized regression coefficients. If SSPG concentration was entered in the model instead of insulin levels, as high collinearity prevents their simultaneous entry, it was also strongly ($\beta = -0.42$) related to adiponectin concentrations.

It should be noted that plasma insulin levels were strongly associated with SSPG concentrations ($r_s = 0.67$, $P < 0.001$) as well, indicating that in these insulin-sensitive or insulin-resistant subjects, insulin concentration is the one factor that appears to be linked to both adiponectin levels and degree of insulin resistance. To look more carefully at the potential role of insulin in modulating adiponectin levels, we compared levels of adiponectin across quintiles of fasting insulin levels for the entire study group. These results, depicted in Fig. 3, show that the mean levels of adiponectin trended lower as insulin levels increased ($P = 0.001$, by one-way ANOVA). Consistent with this notion, 11 of the 12 subjects with insulin levels in the highest quintile had adiponectin levels below the median value (19.9 μg/ml), whereas only 3 of the 12 subjects in the lowest quintile of insulin had adiponectin levels below this value.

DISCUSSION

It is apparent from these studies of obese and nonobese individuals that adiponectin levels are more tightly linked with insulin concentrations and insulin resistance than degree of obesity. Obese insulin-sensitive subjects had higher adiponectin levels than the obese insulin-resistant subjects, despite the fact that weight and BMI were equal in both groups of obese subjects. Similarly, adiponectin levels in nonobese insulin-sensitive subjects were elevated compared with those of the nonobese subjects who were classified as insulin resistant. Thus, within each category of obesity, stratification by insulin sensitivity status proved a useful indicator of adiponectin concentration. Moreover, when adiponectin levels were plotted against BMI (Fig. 2*A*), it was evident that adiponectin levels in insulin-resistant subjects were uniformly low, regardless of the obesity status of the individual subjects. These results demonstrate a clear and significant relationship between insulin resistance and plasma adiponectin concentrations.

Regression analyses provided further evidence of a relatively robust relationship between insulin resistance or insulin levels and adiponectin. In contrast, weight, BMI, and waist circumference were less strongly related to adiponectin. Several prior studies (1,2) have also reported that insulin resistance is closely related to adiponectin levels, even after adjusting for measures of obesity. The

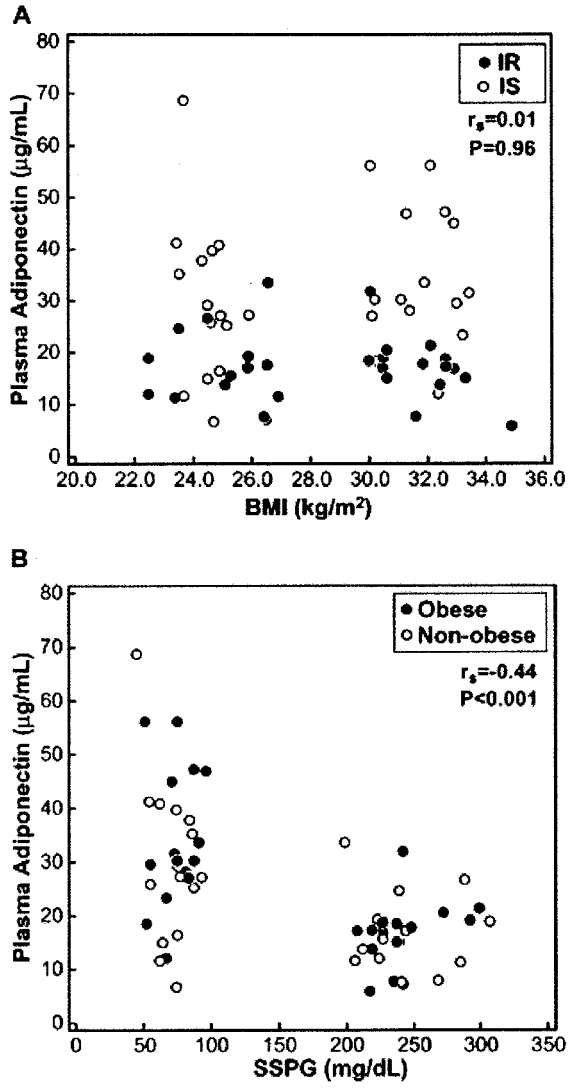

FIG. 2. Relationship between plasma adiponectin concentrations, BMI, and SSPG concentrations in 60 nondiabetic volunteers. *A*: The relationship between plasma adiponectin levels and BMI is shown, where subjects are identified by their insulin resistance status, insulin sensitive (IS, ○) and insulin resistant (IR, ●). *B*: The relationship between plasma adiponectin levels and SSPG concentrations is shown, where subjects are identified by their obesity status, either nonobese (○) or obese (●). The Spearman correlation coefficient (r_s) describes the strength of association between the graphed variables.

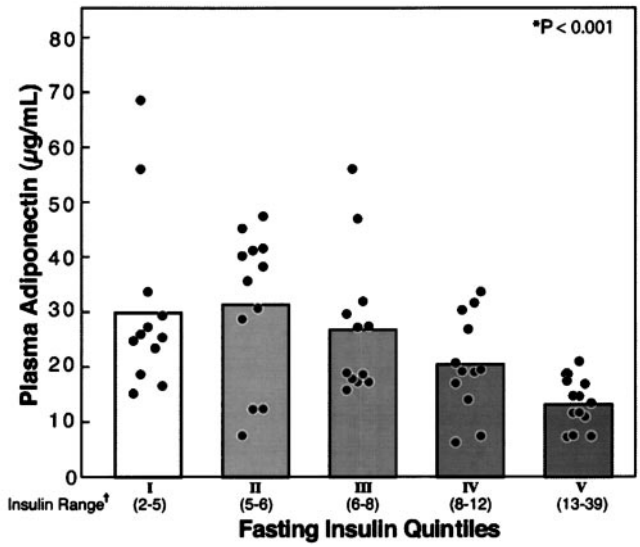

FIG. 3. Relationship between fasting plasma adiponectin and quintiles of fasting insulin concentrations. Vertical bars represent the mean adiponectin concentration for each fasting insulin quintile. *Mean adiponectin levels were not similar across quintiles as compared by one-way ANOVA (P = 0.001). Individual data points are also shown. †Insulin concentrations are given in microunits per milliliter.

present data extend the findings of these studies by providing a rather striking example of an obesity-independent association of insulin resistance with adiponectin levels. The observation that plasma insulin concentrations were associated with both adiponectin levels and insulin resistance raised the possibility that part of the association between these latter two variables may be explained through their mutual relationships with insulin. More specifically, plasma insulin concentrations are well recognized to be elevated in insulin-resistant nondiabetic individuals (22–24), and there is evidence that insulin may have direct effects on adiponectin concentrations. Adiponectin message and protein expression have been shown to be sensitive to insulin concentrations in vitro (15,26,27), and elevation of plasma insulin levels during hyperinsulinemic clamps has induced falls in adiponectin levels in both obese and nonobese subjects (16,28). It is therefore conceivable that the higher levels of insulin in insulin-resistant subjects may downregulate levels of adiponectin, as suggested by the data in Fig. 3. A similar role for insulin in the regulation of proteins secreted from fat cells has been previously described for the adipokine, leptin (29,30). However, the close relationship between insulin resistance and compensatory hyperinsulinemia, coupled with the standardized regression coefficients showing that both insulin levels and insulin resistance status were strongly related to adiponectin, makes it difficult to determine whether insulin resistance or hyperinsulinemia is most closely linked to adiponectin concentration.

It should be emphasized that our results are not necessarily in conflict with previous reports (8–11) that adiponectin concentrations are inversely correlated with the degree of adiposity. However, our study design permitted us to demonstrate that adiponectin concentrations are related to the degree of insulin resistance/hyperinsulinemia independent of weight, BMI, or waist circumference. On the other hand, our reliance on BMI and waist circumference as measures of obesity may have limited detection of subtle effects of adiposity on plasma adiponectin concentrations. However, our findings are consistent with reports from prior studies (1,2) indicating that adiponectin levels are related to measures of insulin resistance independent of visceral adiposity. On the other hand, we cannot exclude the possibility that differences in degree of adiposity and/or fat distribution, if measured more precisely, might also modulate adiponectin concentrations. Although these data are in agreement with recent suggestions that individuals with obesity and insulin resistance may be predisposed to develop more cardiovascular risk factors than those with obesity alone (13,31), this does not imply that obesity without insulin resistance is benign.

Finally, although our results document an association between insulin resistance and insulin levels with plasma adiponectin concentrations, they also provide some indication that adiponectin levels can also be disassociated

from insulin resistance. For example, there was extensive overlap of adiponectin levels between insulin-sensitive and insulin-resistant subjects, and levels of adiponectin in several insulin-sensitive individuals were among the lowest measured in our population. There are other reported instances of disassociation between adiponectin levels and insulin resistance. For example, increases in adiponectin levels do not accompany exercise training–associated improvements in insulin resistance or fitness (8,32). Similarly, although large reductions in weight resulting from gastric partition surgery are associated with moderate elevations in adiponectin levels (10), a more typical weight loss program utilizing simple caloric restriction does not appear to alter adiponectin levels (33). Yet, both methods of weight loss lead to substantial improvements in insulin action (10,33).

These data point out that the relationship between adiponectin and insulin resistance is probably not one of direct cause and effect in all instances. It is possible that in some situations their inverse relationship may be mediated in part by insulin levels, by other hormones such as catecholamines or androgens (15,16,34), by proinflammatory cytokines (17,35), by medications (16,17), or possibly by changes in clearance of adiponectin. Although our data indicated a less robust relationship of adiponectin with obesity, some or all of these factors may also be influenced by the extent and location of obesity. Additionally, the molecular mechanisms modulating insulin resistance may vary between individuals and in different circumstances (e.g., obesity and exercise), and thus the relevance of adiponectin in these situations may also vary. An alternative explanation may be related to the different forms of adiponectin and its receptors now identified in animals and humans and the possibility that the biological action of adiponectin may differ among these structural variants and isoforms (36,37). The results of the current study do not permit us to choose between these alternate explanations, but do indicate that sorting out the relationship between adiponectin and insulin resistance may be more complex than initially thought.

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