PRELIMINARY REPORT

Plasma Adiponectin Concentrations Do Not Increase in Association With Moderate Weight Loss in Insulin-Resistant, Obese Women

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Plasma adiponectin concentrations were measured before and after moderate weight loss in 20 obese women, divided at baseline into insulin-resistant (IR) and insulin-sensitive (IS) subgroups on the basis of their steady-state plasma glucose (SSPG) concentration at the end of a 180-minute infusion of octreotide, glucose, and insulin. The groups were similar in age and body weight and lost comparable amounts of weight (8 to 9 kg) during the weight loss period. Fasting plasma insulin and SSPG concentrations were significantly higher ($P < .001$) and adiponectin concentrations somewhat lower ($P = .10$) in the IR group ($P < .001$) at baseline. Both SSPG and plasma insulin concentrations decreased in IR subjects ($P < .001$), but did not change in IS individuals. Adiponectin concentrations did not change with weight loss in either group. Thus, neither weight loss, per se, nor enhanced insulin sensitivity resulted in a change in plasma adiponectin concentrations.

THERE IS evidence that plasma adiponectin concentrations are related to various measures of body fat, lower in insulin-resistant (IR) individuals and increase in association with improved insulin sensitivity following weight loss.[1-10] However, not all obese individuals are IR,[11-16] and we have presented preliminary evidence that plasma adiponectin levels were only significantly lower in obese individuals who were also IR and hyperinsulinemic.[17] Furthermore, subjects in the majority of published weight loss studies were massively obese, and only modest increases in plasma adiponectin concentrations occurred despite relatively enormous amounts of weight loss. Finally, because obesity, per se, decreases insulin clearance,[12,13] the reliability of changes in plasma insulin concentration as the surrogate estimate of improvement in insulin sensitivity in patients who have lost large amounts of weight can be questioned. The current study represents an effort to clarify and extend these findings and was initiated to see if: (1) adiponectin concentrations increase with moderate amounts of weight loss in obese individuals and (2) improvement in direct measures of insulin-mediated glucose disposal associated with moderate weight loss in IR individuals is accompanied by increases in adiponectin concentrations.

MATERIALS AND METHODS

The experimental population consisted of 20 obese women with a body mass index (BMI) between 29.0 to 36.0 kg/m^2 in good general health, with a fasting plasma glucose concentration <126 mg/dL and normal laboratory results on a chemical screening battery. The Stanford University Human Subjects Committee approved this study, and all participants gave written informed consent.

The insulin suppression test[18-20] was used to create IR and insulin-sensitive (IS) subgroups. Briefly, subjects were infused for 180 minutes with octreotide (0.27 μg/m^2 · min), insulin (32 mIU/m^2 · min), and glucose (267 mg/m^2 · min). Blood was drawn at 10-minute intervals during the final 30 minutes of the infusion to measure plasma glucose and insulin concentrations, and the mean of these values used as the steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations for each individual.

IR was defined as a SSPG value >180 mg/dL and IS as a SSPG concentration <100 mg/d; cut points that separated the upper and lower tertiles of SSPG concentrations as measured in 490 healthy volunteers.[21]

Plasma adiponectin concentrations were measured in duplicate after an overnight fast with a radioimmunoassay established by Linco Research (St Charles, MO). This assay has a sensitivity of 0.01 mg/dL and intra- and interassay coefficient of variation (CV) of less than 8%.

After collection of baseline data, subjects were instructed on a calorie- restricted diet calculated to result in weight loss of approximately 2 to 3 kg/mo plus sibutramine (15 mg/d) for the 4-month weight loss period. At the end of this period, subjects were placed on a weight maintenance diet for 14 days, during which time weight fluctuated by <1.0 kg in any individual. They were then readmitted to the General Clinical Research Center (GCRC) and baseline measurements repeated.

The results to be presented were obtained on the first 20 individuals (10 in each group) that completed the 4-month weight loss period. IR and IS subjects were compared at baseline (Student's unpaired *t* test), as well as between baseline and postweight loss changes (Student's paired *t* test).

RESULTS

Table 1 indicates that baseline SSPG and fasting plasma insulin concentrations were significantly higher ($P < .001$) in the IR group, but the 2 groups were comparable in terms of age, weight, waist circumference, and fasting plasma glucose concentrations. Fasting plasma adiponectin concentrations were lower in IR individuals, but this difference did not reach the conventional level of statistical significance ($P = .10$).

Weight loss was similar in the IS (8.5 ± 4.2 kg) and IR (8.9 ± 5.1 kg) groups. Figure 1 indicates that plasma SSPG concentration decreased by 40% ($P < .001$) with moderate weight loss in the IR group, whereas it did not change in the IS individuals. However, plasma adiponectin concentrations were the same before and after weight loss in both groups.

Figure 1 also demonstrates that there was little variance in

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Table 1. Baseline Demographic and Metabolic Characteristics

Variable	Insulin-Sensitive	Insulin-Resistant	*P* Value
SSPG (mg/dL)	64 ± 15	214 ± 23	<.001
Age (yr)	45 ± 8	48 ± 9	.44
Weight (kg)	86.9 ± 7.5	84.1 ± 5.8	.36
Waist (cm)	94 ± 6	96 ± 8	.52
Fasting glucose (mg/dL)	93 ± 7	98 ± 8	.21
Fasting insulin (μIU/mL)	7 ± 2	13 ± 4	<.001
Fasting adiponectin (μg/mL)	25.9 ± 12.5	17.0 ± 7.4	.10

NOTE. Data are means ± SD.

SSPG concentrations at baseline in either IS or IR individuals, whereas adiponectin concentrations varied more than 5-fold in both groups.

DISCUSSION

The results presented demonstrate that moderate weight loss (8 to 9 kg) did not result in a change in plasma adiponectin concentrations in the 20 obese women we studied. There was no suggestion of an increase in adiponectin concentration with weight loss in either group or when the IS and IR groups were combined. Furthermore, repeat measurement of all samples yielded nearly identical values for all individuals. Thus, it seems unlikely that failure to demonstrate an increase in adiponectin concentrations with weight loss was due to sample size or assay variation.

Failure to see a change in plasma adiponectin concentrations with weight loss in this study is most likely due to major differences between our protocol and those of studies that have demonstrated this association.[6-10] The magnitude of obesity of patients in these studies was much greater, and in 4 instances,[6-9] surgical intervention resulted in relatively massive amounts of weight loss, ie, 23 kg to almost 57 kg. This approach is quite different from ours, in which moderate calorie restriction was instituted to bring about weight loss of 8 to 9 kg. The study most resembling ours is that of Esposito et al,[10] who reported that adiponectin concentrations increased by 2.7 μg/mL in overweight individuals who had lost 14 kg as compared with an increase of 0.5 μg/mL in subjects who had lost 3 kg. These data

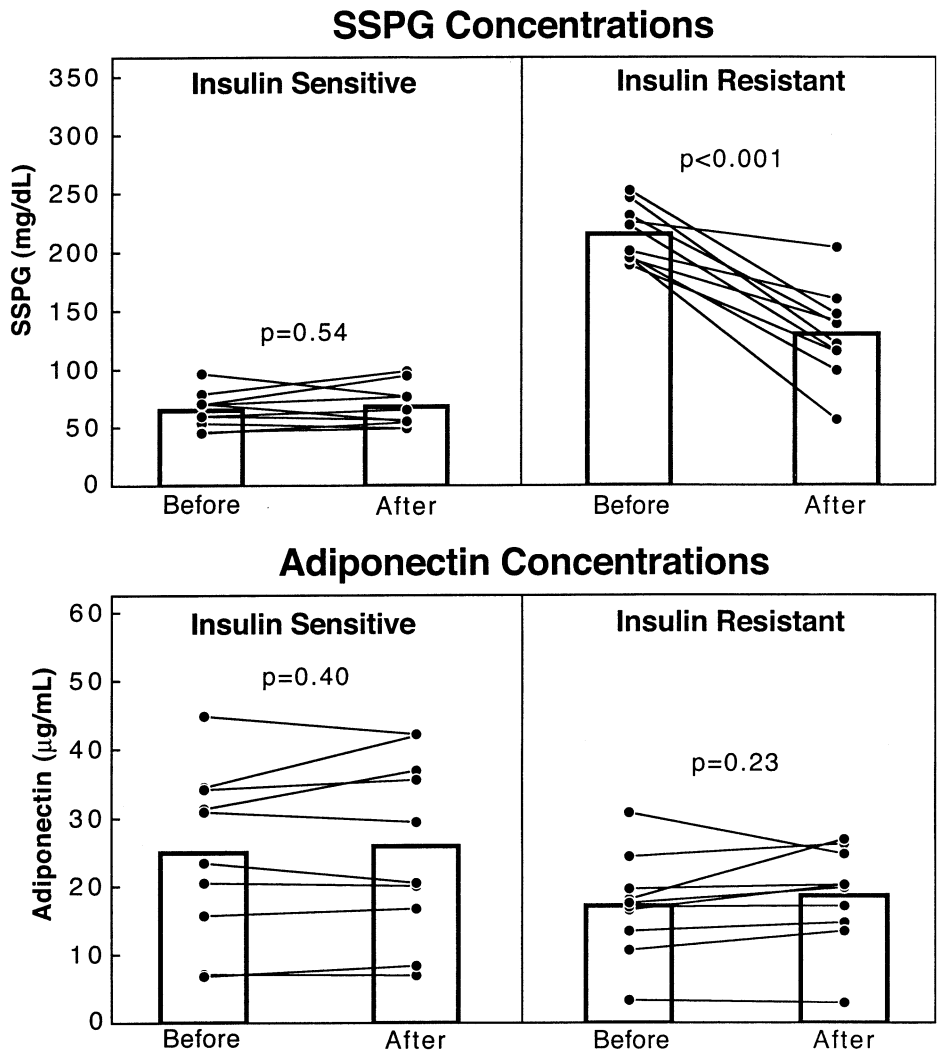

Fig 1. SSPG and adiponectin concentrations before and after weight loss in IS and IR individuals. The height of the bars indicates the mean value, and the solid lines connect the individual data points before and after weight loss.

suggest that changes in plasma adiponectin do not become apparent until substantial amounts of weight have been shed.

Our results also indicated that substantial improvements in insulin sensitivity after moderate weight loss in IR subjects were not associated with an increase in plasma adiponectin concentration. Because there is ample evidence that insulin resistance is attenuated with this degree of weight loss,[11,13,15,16] our findings imply that changes in circulating adiponectin may not mediate weight loss-induced improvements in insulin sensitivity. These data differ from those when much greater amounts of weight are lost,[6-10] but are consistent with preliminary results of a study[22] that seems quite similar to ours as regards both experimental protocol and results. Furthermore, there are several potential explanations to account for the disparate findings. In addition to the obvious differences in experimental protocol described above, surrogate measures based on changes in plasma insulin concentration were used to assess insulin sensitivity in all of these studies. Although these estimates of insulin action are correlated with specific measures of insulin-meditated glucose disposal, they account for less than 40% of the variability from person to person when insulin-mediated glucose disposal is measured directly.[21] The limitation of insulin concentrations as indicators of insulin action is accentuated in obese individuals because obesity, per se, results in decreased insulin clearance.[12,13] Thus, large amounts of weight loss will lead to lower insulin concentrations, independent of any change in insulin sensitivity, and their use in this situation cannot provide reliable estimates of insulin action. In addition, there is evidence that insulin acts on adipose tissue to decrease adiponectin synthesis and secretion,[23-25] and it is possible that higher adiponectin levels after large amounts of weight loss are a simple consequence of the greater decreases in insulin concentration, unrelated to a change in insulin sensitivity.

Although our results are straightforward, important caveats must be made. Firstly, circulating adiponectin levels may not be as important in regulation of insulin action as changes in adiponectin concentration at the tissue level. Secondly, there is evidence that different forms of adiponectin may vary in their metabolic effects.[26] Thus, plasma adiponectin concentrations may not increase with moderate weight loss, but changes in adiponectin may contribute to improvement in insulin sensitivity because its biologic effects may be more closely related to differences in tissue levels of adiponectin and/or the ratio of the globular to the full-length form of adiponectin. These possibilities deserve further evaluation and could alter interpretation of our study, as well as many of the previous publications in this field.

In conclusion, our results indicate that moderate amounts of weight loss in obese women were not associated with an increase in plasma adiponectin concentration, not even when insulin sensitivity improved in IR individuals. It should be noted that there is also evidence that adiponectin concentrations do not change when insulin sensitivity improves with exercise training.[7] The fact that there are 2 instances in which improvements in insulin sensitivity occur without any change in plasma adiponectin concentrations demonstrates that there is still much to learn about the role that adiponectin plays in modulation of insulin-mediated glucose disposal.

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