Relationship Between Insulin Resistance, Weight Loss, and Coronary Heart Disease Risk in Healthy, Obese Women

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Several popular books have recently been published stating that being insulin-resistant favors weight gain and/or prevents weight loss. Because this view seems to have gained widespread support in the general population, we thought it important to perform the current study testing the hypothesis that differences in insulin-mediated glucose disposal do not affect weight loss in response to calorie-restricted diets. For this purpose, we studied the change in weight and risk factors for coronary heart disease (CHD) in healthy women volunteers, defined as being obese on the basis of a body mass index (BMI) greater than 30.0 kg/m^2. The insulin suppression test was used to stratify obese women at baseline into insulin-resistant and insulin-sensitive subgroups on the basis of their steady-state plasma glucose (SSPG) concentration at the end of a 180-minute infusion of octreotide, exogenous insulin, and glucose. They were then instructed on a calorie-restricted diet plus sibutramine (15 mg/day) for a total period of 4 months. Baseline measurements also included determination of fasting lipid and lipoprotein concentrations, and hourly (8 AM to 4 PM) determinations of plasma glucose and insulin concentrations before and after breakfast and lunch. Twenty-four women completed the 4-month period of calorie restriction: 13 classified as insulin-resistant (SSPG = 219 ± 7 mg/dL) and 11 as insulin-sensitive (SSPG = 69 ± 6 mg/dL). The insulin-resistant group also had higher (P = .03) plasma triglyceride (TG) concentrations and a higher ratio of total to high-density lipoprotein (HDL) cholesterol concentration (P = .02) at baseline. Both groups lost a significant amount of weight during the study, and there was no difference between the weight loss in the insulin-resistant (8.6 ± 1.3 kg) and insulin-sensitive (7.9 ± 1.4 kg) groups. Weight loss in the insulin-resistant group was also associated with a significant decrease in SSPG concentration (219 ± 7 to 144 ± 14 mg/dL), associated with significantly lower fasting TG concentrations (P < .001) and day-long concentrations of plasma glucose and insulin (P < .005). None of these variables changed in the insulin-sensitive group. These results indicate that: (1) CHD risk factors in obese women vary as a function of being insulin-resistant or insulin-sensitive; (2) dramatic variations in insulin-mediated glucose disposal do not modulate weight loss in response to calorie-restricted diets, and (3) weight loss is effective in reducing CHD risk in insulin-resistant, obese women. Given these data, it seems obvious that attempts to reduce CHD risk factors by weight loss should focus on obese individuals who are also insulin-resistant.

WE HAVE RECENTLY shown that weight loss in response to a calorie-restricted diet was essentially identical in women divided at baseline into 2 dichotomous groups: insulin-resistant and insulin-sensitive.[1] Although these results indicated that the ability to lose weight was not impaired in insulin-resistant and hyperinsulinemic women, this conclusion could be criticized on 2 counts. In the first place, the study duration was only 60 days. Because obesity usually results from slow, but cumulative, weight gain over years, the clinical significance of our study could be questioned. Second, our weight loss protocol was highly controlled, relying primarily on a liquid nutritional formula rather than real food. Thus, while this approach was useful in that it attempted to eliminate the possible confounding effect of varied caloric intake between subjects, its relevance to the manner in which weight loss programs are usually initiated could be questioned. The current study was initiated to extend our earlier study, and the protocol amended to address the 2 potential problems outlined above. Consequently, we extended the period of observation to 4 months, and the diet intervention was limited to nutritional advice, with all meals prepared at home. To maximize potential for weight loss, the diet was supplemented with the appetite suppressant drug, sibutramine.

Although the primary goal of this study was to compare the amount of weight loss in insulin-resistant versus insulin-sensitive women when advised on calorie-restricted diet, the experimental protocol was also designed to: (1) evaluate the separate effects of obesity, per se, from those of insulin resistance on coronary heart disease (CHD) risk factors, and (2) to define the effects of weight loss on these same CHD risk factors.

The results to be presented provide further support for the view that the ability to lose weight in response to a calorie-restricted diet is not impaired in obese, insulin-resistant and hyperinsulinemic women. Furthermore, it was shown that baseline CHD risk factors are significantly accentuated in obese, insulin-resistant women as compared with equally obese, insulin-sensitive women, and significant improvement in CHD increase with weight loss is limited to those who are insulin-resistant at baseline.

MATERIALS AND METHODS

Subjects included 53 obese, women volunteers from the San Francisco Bay area who had responded to advertisements placed in local newspapers. Participants were required to have a body mass index (BMI) between 30 and 36 kg/m^2 and nondiabetic according to the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[2] The BMI values were selected to make sure that all volunteers included were considered to be obese (>30kg/m^2), and the arbitrary assumption that subjects with a BMI greater than 36 kg/m^2 would be unlikely to be compliant to the diet. Exclusions included psychiatric instability, history of gastrointestinal surgery for weight reduction, recent change in exercise pattern, history of hypertension,

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cardiac arrhythmia, coronary artery disease, seizures, use of monoamine-oxidase inhibitors, and pregnancy. Potential subjects were screened at the General Clinical Research Center (GCRC) at Stanford Medical Center. Blood pressure was measured with the patient sitting, after resting quietly for at least 5 minutes, with an automatic vital sign monitor, equipped with an appropriately sized blood pressure cuff. Weight was measured with subjects wearing light clothing and BMI calculated as weight (kilograms) divided by height (square meters). The study was approved by the Stanford University Human Subjects Committee, and all participants gave informed, written consent.

To create an insulin-sensitive and an insulin-resistant group, insulin-mediated glucose disposal was quantified in those who met the general inclusion criteria by a modification[3] of the insulin suppression test as originally described.[4] Briefly, subjects were infused for 180 minutes with octreotide (0.27 $\mu g/m^2 \cdot min$), insulin (25 $mU/m^2 \cdot min$), and glucose (240 $mg/m^2 \cdot min$). Blood was drawn at 10-minute intervals from 150 to 180 minutes of the infusion to measure plasma glucose[5] and insulin[6] concentrations, and the mean of these 4 values used as the steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations for each individual. As SSPI concentrations were similar in all subjects, 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.

Following the insulin suppression test, subjects were stratified into 2 groups on the basis of their SSPG values as follows: insulin resistance was defined as a SSPG value greater than 160 mg/dL and insulin sensitivity as a SSPG value less than 100 mg/dL. These values represent the upper and lower 40% percentiles of insulin resistance as measured in 490 healthy volunteers.[7] Volunteers with SSPG concentrations between these 2 cut-points (n = 8) were discharged from the study, whereas those defined as being either insulin-resistant (n = 26) or insulin-sensitive (n = 18) remained eligible for further study. Of the 44 subjects who qualified to enter the weight loss period, 5 individuals declined to be studied further; thus, 39 of the 53 individuals screened were scheduled for admission to the GCRC to begin the study.

Before starting the period of weight loss, blood was drawn after an overnight fast for determination of plasma glucose, insulin, triglyceride (TG), and total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol concentrations as described previously.[1] In addition, plasma glucose and insulin concentrations were measured for 8 hours following a standard test meal containing as percent of total calories, 15% protein, 43% carbohydrate, and 42% fat. Meals were given at 8 AM h and 12 PM, with breakfast comprising 20% and lunch 40% of estimated daily caloric requirement. Glucose and insulin concentrations were measured fasting and every hour for a total of 8 hours and daylong glucose and insulin responses compared.

Following these baseline measurements, subjects were placed on a hypocaloric diet and given sibutramine, 15 mg/day. The Harris-Benedict equation[8] was used to estimate each volunteer's basal energy expenditure, and an activity factor was added to estimate total caloric requirement (basal energy expenditure $\times$ 1.3 to 1.5). Daily caloric intake for each subject during the study was their estimated total caloric intake, minus 500 kcal, which over a 1-week period should lead to weight loss of approximately 1 lb. To maximize compliance with prescribed caloric intake, subjects were required to maintain a daily food diary, which was reviewed biweekly with study dietitians. Body weight and blood pressure were determined at baseline and weekly thereafter as described above. For purposes of analyses, 2 or more blood pressure readings were averaged before and after weight loss. The weight loss period was 4 months in duration, after which time, subjects were instructed on a weight maintenance diet. They were readmitted to the GCRC 2 weeks later, and all the baseline measures repeated.

All data are expressed as the mean $\pm$ SEM. Student's unpaired *t* test was used to compare the insulin-resistant versus insulin-sensitive groups with respect to baseline variables, weight loss, change in insulin sensitivity after weight loss, and changes in fasting plasma glucose, insulin, lipid, and lipoprotein concentrations with weight loss. Student's paired *t* test and 2-way analysis of variance were used to determine if variables changed significantly following weight loss. Finally, to ensure that subjects who completed the study were not different from those who did not complete the study, baseline characteristics were compared in the 2 groups according to insulin-resistant or insulin-sensitive group assignment.

RESULTS

A total of 44 volunteers qualified for the study; 18 defined as insulin-sensitive and 26 defined as insulin-resistant. However, 5 of these individuals also withdrew before beginning the diet. Of the 39 subjects starting the diet, 8 volunteers dropped out within the first month for a variety of personal reasons. Seven additional subjects did not complete the 4-month study: 4 for unknown reasons, 2 because they did not want to remain on sibutramine, and 1 because of vacation travel. Thus, 24 volunteers completed the entire study; 13 classified as insulin-resistant and 11 as insulin-sensitive.

Table 1 presents the demographic data and baseline clinical characteristics of those completing (completors) and not completing (noncompletors) the entire 4-month study, divided into insulin-sensitive and insulin-resistant subgroups. It is apparent

Table 1. Baseline Characteristics of Completors Versus Noncompletors

	Insulin-Sensitive		Insulin-Resistant	
Variable	Completors (n = 11)	Noncompletors (n = 7)	Completors (n = 13)	Noncompletors (n = 13)
SSPG mg/dL	69 ± 6	83 ± 8	219 ± 7	201 ± 9
Age (yr)	45 ± 2	49 ± 3	48 ± 3	46 ± 2
BMI (kg/m^2)	30.9 ± 0.4	32.6 ± 0.8	32.1 ± 0.6	32.4 ± 0.5
Weight (kg)	87 ± 2	89 ± 4	84 ± 2	86 ± 2
Systolic blood pressure (mm Hg)	120 ± 5	120 ± 4	131 ± 3	124 ± 5
Diastolic blood pressure (mm Hg)	60 ± 3	70 ± 4	76 ± 2	71 ± 2
Cholesterol (mg/dL)	195 ± 10	198 ± 14	200 ± 10	233 ± 12*
TG (mg/dL)	124 ± 20	121 ± 23	158 ± 17	193 ± 33
HDL cholesterol (mg/dL)	55 ± 4	51 ± 5	49 ± 3	46 ± 4
LDL cholesterol (mg/dL)	116 ± 9	123 ± 10	119 ± 8	149 ± 10*

* $P < .05$ for insulin-resistant completors *v* noncompletors.

Table 2. Comparison of Baseline Cardiovascular Risk Factors in Insulin-Sensitive Versus Insulin-Resistant Subjects

Variable	Insulin-Sensitive (n = 18)	Insulin-Resistant (n = 26)	Insulin-Sensitive (n = 11)	Insulin-Resistant (n = 13)
Systolic blood pressure (mm Hg)	120 ± 3	127 ± 3	120 ± 5	131 ± 3
Diastolic blood pressure (mm Hg)	69 ± 2	74 ± 2	69 ± 3	76 ± 2
Cholesterol (mg/dL)	196 ± 8	217 ± 9	195 ± 10	200 ± 10
TG (mg/dL)	123 ± 15	175 ± 19*	124 ± 20	158 ± 17
HDL cholesterol (mg/dL)	54 ± 3	48 ± 3	55 ± 4	49 ± 3
LDL cholesterol (mg/dL)	119 ± 6	133 ± 7	116 ± 9	119 ± 8

* $P < .05$ for insulin-sensitive *v* insulin-resistant subjects.

that the demographic characteristics of the completors and noncompletors were comparable in the insulin-sensitive and insulin-resistant subgroups. The only differences in the metabolic variables between the completors and noncompletors were the total and LDL cholesterol concentrations in the insulin-resistant subjects.

A comparison of baseline cardiovascular risk factors in the insulin-sensitive (n = 18) and insulin-resistant (n = 26) volunteers who qualified for entrance into the study, as well as the members of each of the 2 groups completing, appears in Table 2. These results indicate that the total group of insulin-resistant, obese women had significantly higher plasma TG concentrations. The same qualitative difference in TG concentration was seen when the completors of the 2 groups were compared, but in this case, it was no longer statistically significant.

The changes in weight and SSPG concentration in the 24 volunteers who completed the 4-month study are shown in Fig 1. Weight decreased significantly ($P < .001$) in both groups, with a loss of 8.6 ± 1.3 and 7.9 ± 1.4 kg in the insulin-resistant and insulin-sensitive groups, respectively. Thus, there was no difference in the weight loss between the 2 groups.

The results in Fig 1 also show that weight loss in the insulin-resistant group was associated with a dramatic decrease in SSPG concentration from 219 ± 7 to 144 ± 14 mg/dL ($P < .001$). In contrast, there was no change in SSPG concentration in the insulin-sensitive group.

The plasma glucose and insulin concentrations from 8 AM to 4 PM of the 2 groups, before and after weight loss, are shown in Fig 2. Weight loss in the insulin-resistant group was associated with a significant ($P < .005$, 2-way analysis of variance) decrease in the daylong plasma glucose and insulin responses. Similar to the measure of insulin resistance, daylong plasma glucose and insulin responses of the insulin-sensitive group were essentially identical, before and after weight loss. It shall also be noted that the daylong plasma insulin concentrations were significantly higher in the obese women who were also insulin-resistant ($P < .001$).

The changes in lipid and lipoprotein concentrations with weight loss in the 2 groups are shown in Table 3. These variables did not change in insulin-sensitive individuals, but the TG concentration decreased significantly ($P < .001$) in the insulin-resistant subjects. In addition, systolic blood pressure decreased from 131 ± 3 to 125 ± 4 mm Hg ($P = .06$) in the insulin-resistant group, whereas it was somewhat higher (117 ± 4 *v* 120 ± 4, $P = .40$) after weight loss in the insulin-sensitive women.

DISCUSSION

The results of our current study are essentially identical to our previous publication showing that weight loss in response to ingestion of a calorie-restricted liquid nutritional formula was essentially identical in women stratified at baseline into insulin-resistant and insulin-sensitive groups.[1] However, in this instance, the study lasted for 4 months, rather than 2, and the diet consisted of food prepared at home, with advice from the study nutritionists. As such, we believe the results are of greater clinical relevance than our earlier observations and provide further evidence that variations in insulin-mediated glucose disposal from person to person have little, if any, effect on the ability to lose weight. On the other hand, it should be pointed out that this conclusion depends on our implicit assumption that there are no effects of sibutramine that might alter the ability of an individual to lose weight as a function of baseline degree of insulin sensitivity. We are unaware of any data to suggest this

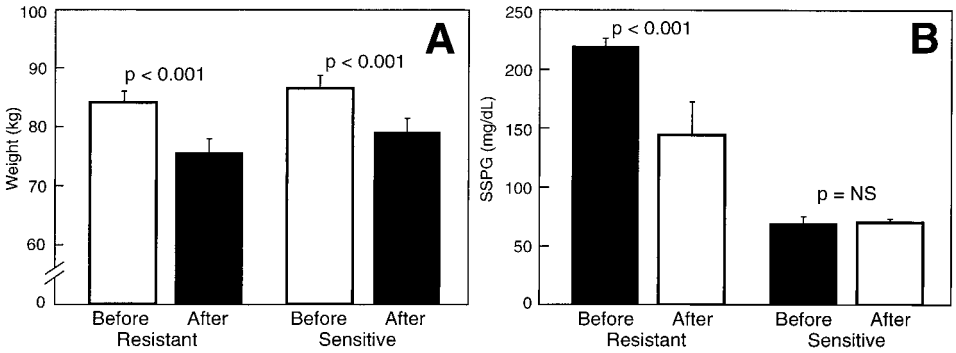

Fig 1. Effect of the calorie-restricted diet on weight loss (A) and SSPG concentration (B) in insulin-resistant and insulin-sensitive volunteers.

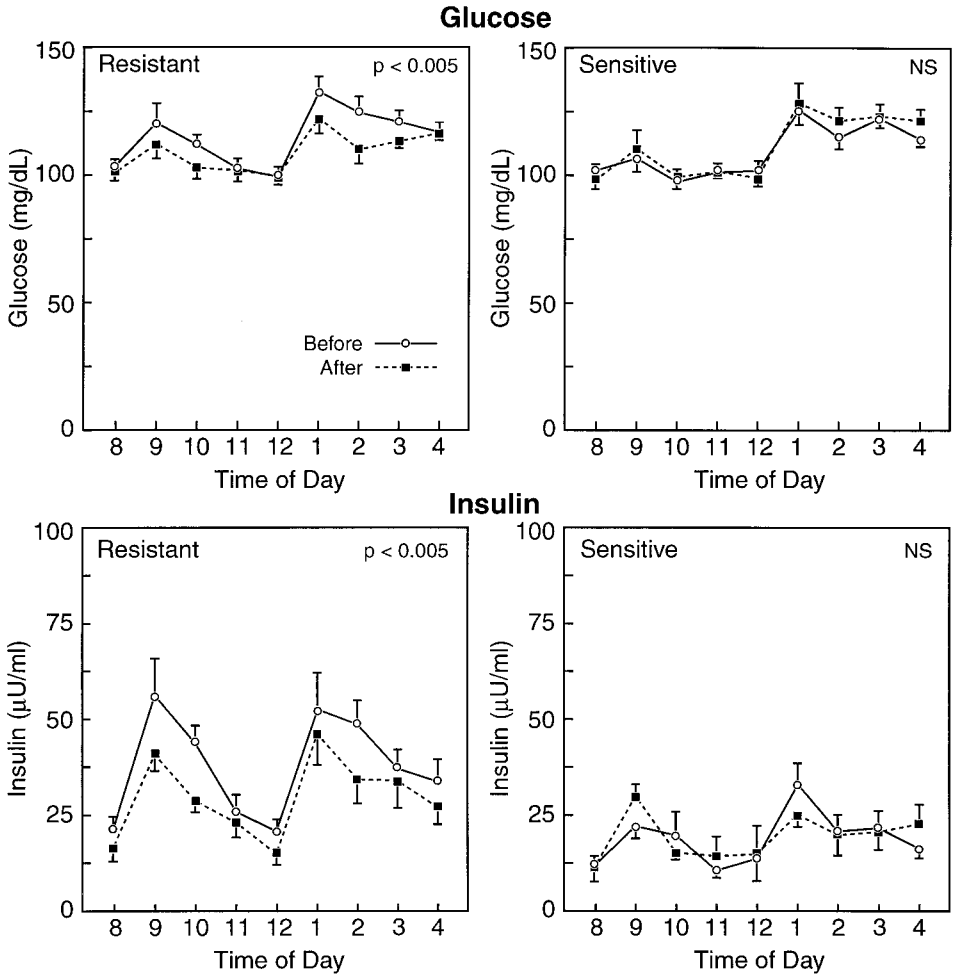

Fig 2. Daylong plasma glucose (upper panels) and insulin concentrations (lower panels) before and after weight loss in insulin-resistant and insulin-sensitive volunteers.

alternative, and it appears that the metabolic effects associated with sibutramine-assisted weight loss appear to be more a matter of how much weight is lost, without evidence of any divergent impact attributed to differences in the characteristics of the overweight patients studied.[9-11]

Evidence[12,13] that insulin-mediated glucose disposal tends to be decreased in association with obesity seems to have led to the notion that insulin resistance predisposes to weight gain and obesity. The current results provide additional evidence that this is unlikely. In 5 studies, insulin resistance or hyperinsulinemia (as a surrogate marker of insulin resistance) at baseline had either no effect on weight gain over time[1,14] or actually predicted that insulin-resistant individuals gained less,[15-17] rather than more, weight over several years of observation. However, there are 2 studies that have come to the conclusion that hyperinsulinemia predicted increased weight gain; 1 in Pima Indian children[18] and the other in nondiabetic offspring of 2 parents with type 2 diabetes.[19] The results in the Pima Indian children were in marked contrast to the results of studies of adult Pima Indians,[15] leading to the suggestion that hyperinsulinemia, and presumably insulin resistance, accentuates weight gain in Pima children, but protects against weight gain in Pima adults. This suggestion may explain why the acute insulin response to intravenous glucose predicted increased weight gain in the nondiabetic offspring of parents with type 2 diabetes.[19] However, the significance of this conclusion is weakened by the finding that acute hyperinsulinemia only predicted weight gain in individuals who were also insulin-sensitive. This is a most unusual combination of metabolic features, given the close positive correlation between insulin resistance and hyperinsulinemia.[7,20-22] Based on the totality of published findings, it does not seem likely that insulin resistance and/or hyperinsulinemia play a significant role in modulation of weight gain.

Table 3. Lipid and Lipoprotein Concentration Before and After Weight Loss in Insulin-Sensitive and Insulin-Resistant Subjects

	Insulin-Sensitive			Insulin-Resistant		
Variable	Pre	Post	*P*	Pre	Post	*P*
Cholesterol (mg/dL)	195 ± 10	184 ± 12	.07	196 ± 10	182 ± 10	.25
TG (mg/dL)	124 ± 20	102 ± 15	.12	150 ± 16	103 ± 12	.01
LDL cholesterol (mg/dL)	116 ± 9	112 ± 10	.34	115 ± 8	111 ± 9	.68
HDL cholesterol (mg/dL)	55 ± 4	54 ± 4	.46	51 ± 3	51 ± 3	.94

Although the primary goal of our study was to see if baseline differences in insulin-mediated glucose disposal modulated the response to calorie-restricted diets, there are other aspects of our results that are noteworthy. For example, current recommendations[23] for weight loss are based largely on the association of excess morbidity and mortality with being overweight (BMI, 25.0 to 29.9 kg/m^2) or obese (BMI >30.0 kg/m^2). In fact, the risk of diabetes, hypertension, and coronary artery disease begins to increase in association with increasing BMI below 25.0 kg/m^2.[23] To our knowledge, no studies have stratified these risks in overweight/obese persons with respect to insulin resistance and/or hyperinsulinemia, which have been shown to predict the development of type 2 diabetes, hypertension, and CHD.[24-36] Lack of attention to this issue is probably a reflection of the widely held view that all obese individuals are insulin-resistant. Our ability to recruit obese insulin-sensitive individuals clearly demonstrates that this is not the case. Indeed, of the 53 obese volunteers who met the general inclusion criteria, 34% were classified as being insulin-sensitive. The fact that obese individuals can also be insulin-sensitive is consistent with results of previous studies,[37,38] but it is a fact that is often overlooked.

In addition to emphasizing the fact that not all obese individuals are insulin-resistant, the results shown in Fig 2 and Table 2 clearly indicate that obese individuals, who are insulin-resistant, also have significantly higher daylong glucose and insulin concentrations and fasting plasma TG concentrations than do equally obese, but insulin-sensitive, individuals. As discussed above, these changes have been shown to increase risk of diabetes, hypertension, and CHD, emphasizing the fact that obese, insulin-sensitive individuals are at significantly reduced CHD risk as compared with their insulin-resistant counterparts. It is also apparent from Figs 1 and 2 and Table 3 that weight loss in insulin-sensitive individuals did not lead to any improvement in their already normal values for insulin-mediated glucose disposal, plasma glucose, insulin, lipid, and lipoprotein concentrations, or blood pressure.

Although weight loss does not appear to be of metabolic benefit in insulin-sensitive, obese individuals, it certainly led to an improvement in insulin-mediated glucose disposal in insulin-resistant, obese individuals. Furthermore, the decline in SSPG concentrations in these individuals was associated with a significant decrease in daylong concentrations of plasma insulin, lower fasting plasma TG concentrations, and a decline in systolic blood pressure of marginal significance ($P = .06$). This latter observation is of particular interest given the evidence that sibutramine can lead to small increments in blood pressure in an unselected overweight population.[9-11] Thus, it appears that this concern may not be applicable to overweight, insulin-resistant subjects.

It seems apparent that not all obese individuals are insulin-resistant, nor do they gain equal metabolic benefit from weight loss. Given the well-recognized difficulty in achieving weight loss in obese individuals, an obvious implication from our results is that healthcare professionals should be particularly energetic in carrying out weight loss programs in those obese individuals who are more at risk for increased morbidity and mortality, and thereby, more likely to benefit from weight loss. This conclusion is not meant to abandon efforts to urge all overweight individuals to lose weight, but to emphasize the importance for success in the subgroup of obese individuals who are insulin-resistant and at the highest risk to develop the untoward consequences related to obesity. In this context, the supplemental use of sibutramine should be considered. None of the 24 patients who took the maximum recommended dose of sibutramine experienced significant side effects, and the 2 subjects who stopped the drug did so for no apparent reason. Furthermore, there was no increase in blood pressure; in fact, blood pressure actually decreased somewhat in the insulin-resistant subgroup.

In conclusion, overweight individuals classified as being insulin-resistant lost as much weight over a 4-month period as did individuals defined as being insulin-sensitive. However, the combination of insulin resistance and compensatory hyperinsulinemia in the insulin-resistant group puts them at significantly greater risk to develop type 2 diabetes, hypertension, and CHD, and the results presented demonstrate the ability of weight loss to attenuate this risk. Consequently, it is urged that attempts should be made to identify the subgroup of overweight individuals who display the characteristics of insulin resistance and the efforts to achieve weight loss given particular emphasis in this subset.

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