Effects of Weight Loss on Norepinephrine and Insulin Levels in Obese Older Men

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Older individuals have higher plasma insulin and norepinephrine (NE) levels than the young. This may be due to biological aging; however, these changes also may be due in part to the increase in abdominal obesity that often accompanies aging. The latter possibility was tested by examining the effects of weight loss on plasma insulin and NE levels in 11 healthy men aged 52 to 72 years who had mild to moderate obesity (body mass index [BMI], 27 to 36 kg/m^2). Plasma insulin levels were measured during an oral glucose tolerance test, and on a second day NE levels were measured during supine rest and upright posture. Subjects lost 10 ± 5 kg (mean ± SD) and decreased their waist to hip ratio ([WHR] an index of the pattern of regional fat distribution) 2.8% ($P < .01$) over 9 ± 3 months through mild caloric restriction. This resulted in a 23% decrease ($P < .05$) in fasting insulin levels and a 48% decrease ($P < .01$) in 2-hour insulin levels. Weight loss also resulted in a 31% decrease ($P < .001$) in supine plasma NE levels and an 8% decrease ($P < .05$) in supine diastolic blood pressure (BP). Decreases in supine plasma NE levels correlated with changes in WHR ($r = .61$, $P < .05$), but did not correlate with changes in other measures of body composition or with changes in glucose and insulin levels. These results suggest that higher plasma NE levels are related to the distribution of body fat to upper-body or abdominal sites in obese older men.

AGING IS CHARACTERIZED by a loss of homeostatic reserve manifested by alterations in endocrine and metabolic function. The elderly tend to have higher basal and postprandial insulin levels[1] and are insulin-resistant[2,3] as compared with younger individuals. Similarly, basal plasma norepinephrine (NE) levels[4,5] and NE responses to physiologic stimuli such as upright posture,[6] exercise,[7] and glucose ingestion[6] are higher in older than in younger individuals, but adrenergically mediated tissue responses are often blunted.[8] These changes in endocrine and metabolic function have been presumed to be an effect of biological aging.

We recently showed that maximal aerobic capacity ($\dot{V}O_2$max), obesity, and particularly the pattern of regional fat distribution are more important determinants of insulin sensitivity than age.[9] These factors also may be important to the regulation of sympathetic nervous system (SNS) activity in older individuals.[10-12] Aging is typically associated with an increase in body fat[13] that tends to be distributed in upper-body sites.[14] It has been postulated that the hyperinsulinemia associated with obesity results in an increase in SNS activity.[15] Thus, the development of abdominal obesity might lead to both higher plasma insulin and NE levels in older individuals.

This study tests the hypothesis that increased plasma insulin and NE levels in older men are related to abdominal obesity by examining the effects of a weight-loss intervention on the pattern of regional body fat distribution and insulin and NE levels.

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SUBJECTS AND METHODS

Subjects

Healthy men aged 50 to 75 years were recruited and screened to select a group of sedentary, nonsmoking men with mild to moderate obesity (body mass index [BMI], 27 to 36 kg/m^2). All subjects provided written informed consent before participation according to the guidelines of the Institutional Review Board for Human Studies at Francis Scott Key Medical Center and the Joint Committee on Clinical Investigation at Johns Hopkins Hospital. Subjects underwent a thorough medical evaluation[16] including a physical examination, a fasting blood profile with lipoprotein lipids, and a graded exercise treadmill test according to the Bruce protocol.[17] Individuals with diabetes mellitus or significant abnormalities on screening were excluded, as were those taking medications that could affect glucose metabolism or SNS activity. None of the men engaged in regular aerobic exercise, and all were weight-stable ± 2.5 kg in the preceding 6 months. Of the 56 men originally recruited for a weight-loss intervention, 13 were treated with medications that could affect blood pressure (BP) or NE levels and were excluded from the study. Twenty dropped out before baseline testing due to time constraints imposed by the research testing and dietary program. Seven men failed to complete the upright-posture protocol due to technical problems associated with intravenous catheterization (n = 2) or symptomatic orthostatic BP responses (n = 5). Of the 17 men assigned to the weight-loss intervention, four subjects dropped out before completing the weight-loss intervention and one subject was excluded from analysis because he began a vigorous exercise program before reevaluation of the effects of the weight-loss program. The final study group thus consisted of 11 carefully screened, healthy men ranging in age from 52 to 72 years who successfully completed all phases of the protocol.

Measurement of Body Composition

BMI was calculated as weight (kilograms) divided by height squared (meters squared). Body density was measured by hydrostatic weighing, and percent body fat was calculated using the equations reported by Siri[18] after correction for residual lung volume as determined by helium dilution on a separate visit. Fat-free mass (FFM) was calculated as the difference between

body weight and fat mass. The waist to hip ratio (WHR), an index of the pattern of regional fat distribution, was calculated by dividing the minimum circumference of the abdomen by the circumference of the buttocks at the maximal gluteal protuberance. All body composition measurements were performed by two trained individuals, and in seven of the 11 subjects the same observer performed the measurements before and after weight loss. The coefficient of duplicate determinations for WHR (a measure of the reproducibility of the measurement) is 1.3% in our laboratory.

Measurement of $\dot{V}O_2$max

To ensure that changes in $\dot{V}O_2$max did not confound the findings, subjects were instructed to maintain their usual activity level during the study, and $\dot{V}O_2$max was determined during a graded treadmill exercise test to exhaustion[16] before and after weight loss. Oxygen consumption and CO_2 production were measured at 30-second intervals during exercise using a 120-L Tissot spirometer (Warren E. Collins, Braintree, MA) and Beckman O_2 (OM11) and CO_2 (LB2) analyzers (Beckman Instruments, Fullerton, CA). Tests were repeated when necessary to ensure that criteria for a true $\dot{V}O_2$max[9] were met in all subjects.

Dietary Control

To avoid the potentially confounding effects of short-term caloric restriction and changes in diet composition, subjects were instructed to consume a diet that followed American Heart Association recommendations[19] by a research dietitian who monitored body weight and reviewed food records to verify dietary compliance. Subjects were stable on this diet for 1 month before and after weight loss, and in addition, they were provided weight-maintaining metabolic diets from the General Clinical Research Center (GCRC) metabolic kitchen for 3 days before measurement of insulin and NE levels. This diet, which was based on 7-day food records obtained from subjects after dietary stabilization, also followed American Heart Association recommendations and provided, on average, 50% to 55% of calories as carbohydrate, 25% to 30% as fat, and 20% as protein, and sodium 135 to 155 mmol/d, potassium 100 to 110 mmol/d, a polyunsaturated to saturated fat ratio of approximately 0.7 to 0.8, and cholesterol 300 to 350 mg/d.

Metabolic Testing

All testing was performed on an outpatient basis. Subjects were weight-stable ± 0.5 kg for 48 hours before testing and refrained from strenuous physical activity and caffeinated beverages for 24 hours before study. Subjects reported to the GCRC at 7 AM after a 12-hour overnight fast on the morning of each test. A 20-gauge catheter was inserted into an antecubital vein and kept patent with a slow (<60 mL/h) infusion of 0.45% NaCl to facilitate blood sampling.

Oral Glucose Tolerance Testing

Blood samples for determination of plasma glucose and insulin levels were obtained in duplicate 10 minutes apart at baseline and at 30-minute intervals for 2 hours after ingestion of a lemon-flavored solution containing glucose 40 g/m^2 body surface area. Samples were collected in chilled glass tubes containing EDTA (1 mg/mL whole blood) and immediately centrifuged at 4°C. Plasma glucose level was measured by the glucose oxidase method (Beckman Instruments). Aliquots of plasma were frozen at −70°C for subsequent analysis of insulin by radioimmunoassay.[20] Glucose and insulin responses to oral glucose tolerance testing were assessed by calculating the glucose and insulin areas above basal from 0 to 120 minutes by trapezoidal integration. In one subject, oral glucose tolerance testing could not be accomplished after weight loss due to problems with intravenous access.

NE and Hemodynamic Responses to Upright Posture

Subjects rested quietly in the supine position for at least 30 minutes after intravenous catheter insertion before duplicate blood samples (2.5 mL) were drawn 10 minutes apart and placed into chilled tubes containing EGTA (final concentration, 1.8 mg/mL) and reduced glutathione (final concentration, 1.2 mg/mL) for measurement of supine NE levels. Plasma was immediately separated and frozen at −70°C until analysis. After each blood sample was obtained, BP and heart rate were determined. BP was measured in the contralateral arm using a calibrated mercury sphygmomanometer with a cuff of appropriate size by trained GCRC nurses. Diastolic BP was recorded at phase V (disappearance) of Korotkoff sounds. After baseline measurements, subjects assumed the upright posture and stood unassisted for 15 minutes. Blood samples, BP, and heart rate were obtained 5, 10, and 15 minutes after standing. Initial duplicate supine measurements of BP, heart rate, and NE levels were averaged, and measurements after 10 and 15 minutes of standing were averaged to yield mean supine and upright values, respectively, which were used in subsequent statistical analyses. NE levels were measured using the single-isotope radioenzymatic method[21] with a commercial kit (Cat-A-Kit, Amersham, Arlington Heights, IL). This assay has an 8.5% intraassay coefficient of variation and a 9% interassay coefficient of variation in our laboratory. Samples obtained at baseline and after weight loss were measured in the same assay for each individual.

Weight-Loss Intervention

During the weight-loss intervention, subjects met weekly in small groups led by a research dietitian. They were taught principles of proper nutrition according to American Heart Association guidelines and behavioral techniques to reduce caloric intake. The weight-loss program was reinforced by monitoring weekly weights and reporting results of food record analyses. When necessary, individualized counseling also was provided. Subjects continued in the weight-loss program for 9 to 12 months and then were weight-stabilized for 1 month before reevaluation with a protocol identical to that used at baseline.

Statistical Analyses

All data were analyzed with a commercial statistical software package.[22] Insulin and NE levels were not normally distributed, and hence were $\log_{10}$-transformed before parametric analyses; however, the absolute levels are reported in the text. The effects of weight loss on body composition and glucose, insulin, and NE levels were tested with paired t tests. The effects of weight loss on NE and hemodynamic responses to upright posture were tested using repeated-measures ANOVA. Pearson correlation coefficients were calculated to test for associations among changes in WHR, percent body fat, kilograms of body fat, FFM, and insulin and NE levels with weight loss. Statistical significance was set at P less than .05. All results are expressed as the mean ± SD, except as noted.

RESULTS

Effects of Weight Loss on Body Composition, $\dot{V}O_2$max, and Dietary Intake

Eleven mildly to moderately obese men (body fat, 24% to 37%) lost weight over an average of 9 ± 3 months (Table 1). The mean weight loss in this group was 10 ± 5 kg

Table 1. Effects of Weight Loss on Body Composition and $\dot{V}O_2$max

	Baseline	After Weight Loss	Range of Changes
Age (yr)	63 ± 7		
Weight (kg)	92 ± 8	82 ± 8†	−21 to −3
BMI (kg/m²)	30 ± 3	26 ± 2†	−8 to −1
Body fat (%)	31 ± 4	25 ± 4†	−16 to −1
FFM (kg)	64 ± 5	61 ± 4*	−7 to 1
Waist (cm)	106.2 ± 8.4	96.8 ± 8.9†	−1.3 to −18.3
Hip (cm)	107.0 ± 4.4	100.3 ± 4.7†	−15.1 to 1.6
WHR	0.993 ± 0.075	0.965 ± 0.079*	−0.078 to 0.022
$\dot{V}O_2$max (L/min)	2.5 ± 0.5	2.6 ± 0.4	−0.3 to 0.4

NOTE. Values are the mean ± SD.
*$P < .01$.
†$P < .001$.

($P < .001$). This produced decreases of 19.4% ($P < .001$) in body fat and 4.6% ($P < .01$) in FFM. There was a 2.8% decrease in WHR ($P < .01$) with weight loss, consistent with a shift to a more lower-body or gluteofemoral pattern of fat distribution. Before weight loss, WHR correlated with waist circumference ($r = .85$, $P < .001$) but not with hip circumference ($r = .22$, P = NS). Changes in WHR with weight loss were correlated with changes in waist circumference ($r = .60$, $P = .05$) but not with changes in hip circumference ($r = .11$, P = NS). Thus, the decrease in WHR with weight loss was primarily due to decreases in waist circumference, reflecting the preferential loss of abdominal fat in these men. There was no significant change in $\dot{V}O_2$max with weight loss.

Food records of the diet consumed before testing demonstrate that the caloric intake necessary for weight stabilization was 6% less ($P < .05$) after weight loss (Table 2). There were no significant changes in macronutrient distribution or sodium content of the diet after weight loss.

Effects of Weight Loss on Glucose and Insulin Levels

Initial fasting glucose levels ranged from 4.8 to 6.2 mmol/L, and initial 2-hour glucose levels ranged from 5.2 to 10.8 mmol/L. Six subjects had normal glucose tolerance, three had nondiagnostic tests, two were impaired, and none were diabetic.[23] There were no significant changes in fasting glucose levels (5.3 ± 0.3 *v* 5.2 ± 0.2 mmol/L), glucose levels 2 hours after glucose ingestion (7.6 ± 1.9 *v* 6.7 ± 1.4 mmol/L), or integrated glucose areas (1,017 ± 133 *v* 939 ± 134 mmol · min/L) with weight loss. Fasting plasma insulin levels, which ranged initially from 36 to 186 pmol/L, decreased 23% (88 ± 46 *v* 68 ± 30 pmol/L, $P < .05$). Insulin levels 2 hours after glucose ingestion were 48% lower after weight loss (762 ± 852 *v* 396 ± 198 pmol/L, $P < .02$), and the insulin area was 35% lower (75.2 ± 67.7 *v* 49.1 ± 21.2 nmol · min/L, $P < .05$).

Table 2. Effects of Weight Loss on Energy Intake and Dietary Composition

	Baseline	After Weight Loss
Energy (mJ/24 h)	9.8 ± 1.1	9.2 ± 1.3*
Carbohydrate (%)	54.0 ± 2.9	54.6 ± 2.5
Protein (%)	19.4 ± 0.8	19.4 ± 1.1
Fat (%)	25.6 ± 2.3	25.6 ± 1.5
Sodium (mmol/24 h)	147 ± 18	139 ± 27

NOTE. Values are the mean ± SD.
*$P < .05$.

Initial fasting and 2-hour insulin levels and insulin areas were not related to body composition, WHR, or $\dot{V}O_2$max in these subjects. After weight loss, changes in the 2-hour insulin value correlated with decreases in percent body fat ($r = .75$, $P < .02$), but changes in fasting insulin levels and insulin areas did not correlate with changes in body fat, FFM, WHR, or $\dot{V}O_2$max.

Effects of Weight Loss on NE and Hemodynamic Responses to Upright Posture

Mean supine plasma NE levels decreased by 31% ($P < .001$) after weight loss. Plasma NE levels increased threefold to fourfold with standing both before and after weight loss (Fig 1). Mean upright plasma NE levels were 19% lower after weight loss, although this did not reach statistical significance. The effects of weight loss on the NE response to upright posture were analyzed using a two-factor (posture and weight loss) repeated-measures ANOVA model. In this model, the effects of upright posture to increase plasma NE levels ($F = 190$, $P < .0001$) and of weight loss to decrease plasma NE levels ($F = 6.8$, $P < .02$) were significant, but there was no interaction between factors.

Initial supine plasma NE levels were directly related to WHR ($r = .73$, $P < .02$; Fig 2A), but were not related to percent body fat ($r = .31$, P = NS), absolute amount of body fat in kilograms ($r = .16$, P = NS), or $\dot{V}O_2$max ($r = -.43$, P = NS). With weight loss, decreases in supine plasma NE levels were related to changes in WHR ($r = .65$, $P < .05$; Fig 2B), but were not related to changes in percent body fat ($r = .53$, P = NS) or absolute amount of fat ($r = .34$, P = NS). Changes in NE levels and responses to upright posture with weight loss were not related to subjects' age or to changes in weight or FFM, nor did they correlate with changes in glucose or insulin levels.

Initial systolic and diastolic BPs were normal in all

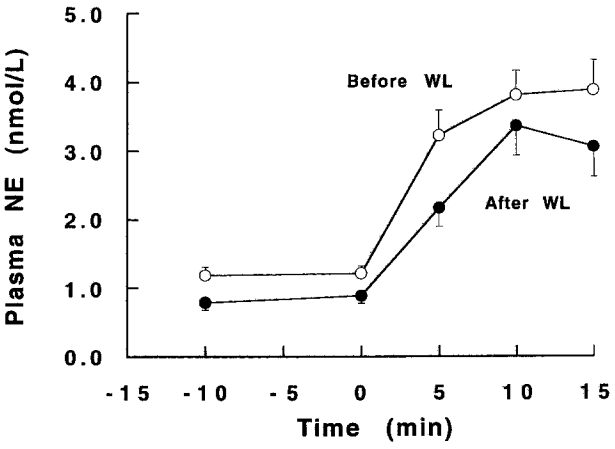

Fig 1. Plasma NE response to upright posture before (○) and after (●) weight loss (WL). Basal measurements were obtained during supine rest. Subjects stood at time 0 and remained standing for 15 minutes.

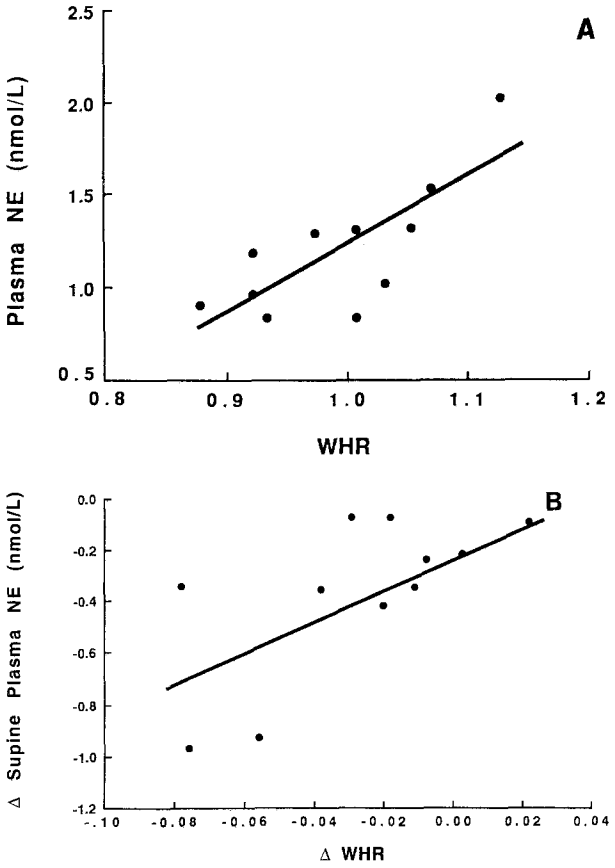

Fig 2. Relationship between initial supine plasma NE levels and WHR ($r = .73$, $P < .02$, A). The change in supine plasma NE levels correlated with the change in WHR with weight loss ($r = .65$, $P < .05$, B).

subjects. After weight loss, supine systolic BP was not significantly decreased; however, supine diastolic BP and supine heart rate both decreased by 8% ($P < .05$ for both). BP and heart rate responses to upright posture and weight loss also were analyzed using a repeated-measures ANOVA model. Systolic BP decreased with upright posture ($F = 9.5$, $P < .01$), but there was no effect of weight loss ($F = 3.8$, P = NS) on systolic BP. There was no change in diastolic BP with upright posture ($F = 0.06$, P = NS); however, levels after weight loss were decreased ($F = 6.3$, $P < .05$). Heart rate increased with upright posture ($F = 20.3$, $P < .001$), but there was no significant effect of weight loss on heart rate during the upright-posture protocol ($F = 0.5$, P = NS) (Table 3).

DISCUSSION

The results of this study suggest that plasma NE levels are related to the pattern of regional body fat distribution in obese, middle-aged, and older men, and change in parallel to changes in abdominal fat produced by weight loss. In contrast, changes in insulin levels with weight loss correlated with changes in overall obesity but not with the regional pattern of fat distribution in these older men. Although supine plasma NE levels, insulin levels, and diastolic BP all decreased significantly with weight loss, the analyses do not indicate that these variables are directly related to one another.

An upper-body pattern of fat distribution is associated with a number of metabolic abnormalities including insulin resistance, hyperinsulinemia, and hypertension.[9,24,25] Despite this, few studies have examined the relation between the regional pattern of fat distribution and SNS activity. Troisi et al[10] reported a positive correlation between 24-hour NE excretion and WHR. A potential weakness of anthropometric measures such as WHR is their inability to distinguish abdominal obesity due to the accumulation of subcutaneous fat from that due to the accumulation of fat in visceral sites. To address this, Leonetti et al[26] measured both subcutaneous and visceral abdominal fat depots using computerized tomographic scanning and showed that 24-hour NE excretion was correlated with subcutaneous abdominal fat but not with visceral fat. In both the latter study and the former study, NE excretion was directly related to BMI, and after adjusting for BMI, neither WHR nor the amount of subcutaneous abdominal fat were independently related to NE excretion. These results differ somewhat from those of the present study in which plasma NE levels were not related to body fatness. This may be due to the restricted range of obesity in this study (due to the selection of obese subjects for the weight-loss intervention), which could have limited our ability to discern a relationship between SNS activity and body fatness. It is also possible that by restricting the range of obesity, our ability to detect a relation between NE levels and the regional pattern of body fat distribution was enhanced.

The decrease in plasma NE levels with weight loss observed in obese older men in this study is consistent with the results of studies in obese younger subjects[27-30] and in obese patients with borderline hypertension.[31] Since ours is the only study that has related changes in SNS activity to changes in body fat distribution, it is not known whether the results of the present study can be generalized to other populations studied under different conditions. Additional studies are needed to confirm these preliminary findings and to determine the reason for the association between plasma NE levels and the regional pattern of body fat distribution.

Table 3. Effects of Weight Loss on NE and Hemodynamic Responses to Upright Posture

	Baseline	After Weight Loss
NE (nmol/L)		
Supine	1.20 ± 0.36	0.83 ± 0.32*
Upright	3.97 ± 1.08	3.23 ± 1.38
Systolic BP (mm Hg)		
Supine	128 ± 12	122 ± 10
Upright	122 ± 11	111 ± 5*
Diastolic BP (mm Hg)		
Supine	79 ± 8	73 ± 6*
Upright	81 ± 7	72 ± 10
Heart rate (beats per minute)		
Supine	63 ± 7	58 ± 8*
Upright	69 ± 12	68 ± 13

NOTE. Values are the mean ± SD.
*$P < .05$

Findings in a number of studies suggest that insulin acutely increases SNS activity.[32] In addition, Troisi et al[10] found higher 24-hour NE excretion rates among subjects with hyperinsulinemia as compared with subjects with normal insulin levels. Since abdominal obesity is often accompanied by hyperinsulinemia, it is tempting to speculate that the higher plasma NE levels associated with upper-body obesity are a direct result of the higher insulin levels. However, in the present study NE levels were not related to insulin levels at baseline, nor were changes in NE related to changes in insulin with weight loss. Thus, evidence of the direct involvement of insulin in the relation between abdominal obesity and SNS activity is lacking at present. Bjorntorp[33] has suggested that the distribution of fat in an upper-body abdominal pattern might be due to hypothalamic hyperactivity. According to this hypothesis, both increased SNS activity and increased cortisol secretion are consequences of poor coping patterns in response to environmental stress. These abnormalities in hypothalamic and pituitary function secondarily lead to abdominal obesity and insulin resistance. Although animal models lend credence to this hypothesis, it remains untested in humans.

The energy content, macronutrient composition, and sodium content of the diet are all important determinants of SNS activity. Overfeeding generally increases and underfeeding decreases SNS activity.[34] Decreases in plasma NE levels were reported during very-low-energy diets of 1 to 8 weeks' duration[27,28]; however, complete fasting, particularly when combined with sodium restriction, may actually increase plasma NE levels.[29,30] Subjects in the present study were weight-stable for a minimum of 4 weeks after weight loss and therefore were in energy balance before retesting. Thus, decreases in plasma NE levels observed in this study cannot be ascribed to underfeeding, nor can they be due to changes in diet composition or sodium content, since these were maintained constant throughout the study. On the other hand, it is possible that the decrease in plasma NE levels in our study is related to the lower 24-hour energy intake in these men after weight loss. Based on studies in younger obese individuals, Schwartz et al[35] suggested that the decreased caloric intake associated with the weight-reduced state could result in decreased SNS activity. Supporting this, a direct correlation between daily caloric intake, estimated from food records, and 24-hour NE excretion has been noted that was independent of the effects of BMI.[10] In addition, the increase in the rate of NE appearance into plasma observed with aerobic exercise training in older individuals is related in part to an increase in energy intake.[36] Thus, even during periods of energy balance, caloric intake appears to be an important determinant of SNS activity. Since the caloric intake necessary for weight stabilization was decreased in these men after weight loss, it is likely that this reduction contributed to the observed decrease in supine plasma NE levels.

Until recently, it was impossible to measure SNS activity directly. Thus, investigators have relied on indirect measures of SNS activity, which may be difficult to interpret in some cases. Urinary NE excretion is an indirect measure of SNS activity that is thought to represent integrated activity of the SNS during the period of urine collection. However, measurement of urinary NE is subject to a great deal of variability due to the effects of diet, smoking, and physical activity. Plasma NE levels also are an indirect measure of SNS activity, reflecting both the spillover of NE into the plasma and its subsequent clearance. They, too, are markedly affected by diet, smoking, and physical activity; however, when these factors are carefully controlled, as they were in the present study, plasma NE levels generally correlate well with other indices of SNS activity.[36] Schwartz et al[35] demonstrated a decrease in NE appearance into plasma but no change in NE levels after weight loss in obese young men. If these findings also apply to older men, then the decrease in plasma NE levels with weight loss in the present study probably reflects an actual decrease in SNS activity.

Our finding that weight loss is associated with a decrease in WHR is consistent with the results of a number of studies in both men[14,37-42] and women.[38,41-49] However, some studies have not demonstrated a significant decrease in WHR with weight loss in all groups of subjects.[14,37,51-54] In 10 recent studies involving men, seven demonstrated significant decreases in WHR with weight loss,[14,37-42] and in another the decrease in WHR almost reached statistical significance. Those studies that did not demonstrate a decrease in WHR had fewer subjects and tended to be of shorter duration than the present study. Thus, these studies may have lacked statistical power or may have been too short in duration to demonstrate a decrease in WHR. In women, the effects of weight loss on the pattern of regional body fat distribution are less clear. Although a number of studies demonstrate significant decreases in WHR with weight loss,[41-49] others do not.[14,37,40,53,54] The reasons for these conflicting results are not readily explained by small sample sizes or interventions of short duration, nor do they seem attributable to differences in menopausal status. However, several studies suggest that women with abdominal obesity are more likely to decrease their WHR with weight loss than women with gluteofemoral obesity.[43,44,49]

In summary, the results of this study suggest that higher plasma NE levels are related to abdominal obesity in obese older men. The reason for this association is not known at present, but it does not appear to involve insulin directly. Nevertheless, the concurrent decreases in plasma NE levels, insulin levels, diastolic BP, and WHR observed in this study suggest that weight loss may decrease the risk of cardiovascular complications associated with abdominal obesity in older men.

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