SUMMARY This study examines factors modulating blood pressure reduction in obese patients undergoing weight reduction on a low calorie protein diet. Plasma norepinephrine (NE) was correlated ($r = 0.65, p < 0.01$) with blood pressure in 20 obese patients prior to weight loss. Reductions in blood pressure levels following upright posture and isometric handgrip exercise were related to reduction in NE levels after these maneuvers. While plasma epinephrine levels declined in parallel with NE levels, plasma dopamine actually increased ($p < 0.05$) during the first 2 weeks of caloric restriction. Prior to weight loss the obese patients demonstrated a significant rise in prolactin levels following posture and exercise, but following caloric restriction this was not observed. Levels of plasma renin activity (PRA) and aldosterone obtained after posture and exercise maneuvers were reduced after 8 weeks of caloric restriction, and reductions in PRA were related to reductions in NE ($r = 0.56, p < 0.01$). Reductions in blood pressure in association with caloric restriction in these obese patients seems to result, in part, from reduced sympathetic nervous system activity as well as secondary effects of reduced adrenergic activity on renal sodium excretion and the renin-angiotensin-aldosterone axis. (Hypertension 4: 686-691, 1982)

KEY WORDS • obesity • blood pressure • catecholamines

EVIDENCE has accumulated for an increased incidence of hypertension in obese individuals. Significant reductions in body weight in moderate to severely obese individuals have been noted to be accompanied by a decline in blood pressure. Several mechanisms have been proposed to explain why obesity leads to elevated blood pressure and how weight reduction lowers blood pressure. Increases in total blood volume and cardiac output in the presence of normal peripheral vascular resistance have been reported in obese hypertensive subjects. When cardiac output and blood volume were corrected for body surface area, however, others could not find differences in these measurements between obese and nonobese hypertensive patients. Increased salt intake with overeating has been suggested to be an important factor explaining the hypertension associated with obesity. Salt restriction and not caloric reduction has been suggested as responsible for the fall in blood pressure with weight reduction. Recent studies have demonstrated, however, that weight loss reduces blood pressure independent of salt intake.

Our group recently reported significant declines in plasma renin activity (PRA) and aldosterone levels during weight reduction in obese patients and a correlation of decrements of PRA and blood pressure. Alterations in sympathetic activity have also been described during starvation and feeding. Hypocaloric protein diets have been noted to result in greater losses of body water than observed with other diets. An enhanced diuresis with hypocaloric protein diets, perhaps the result of the natriuretic effect of hyperketonemia, has been observed. Further, DeHaven et al. have observed greater orthostatic decreases in systolic blood pressure with hypocaloric protein diets than with isocaloric mixed diets. In rats, Landsberg and Young have demonstrated that a decrease in turnover of norepinephrine (NE) may be related primarily to the elimination of dietary carbohydrate. Sympathetic nervous system activity and catecholamine re-
sponses are well established determinants of blood pressure maintenance in response to posture changes, intravascular volume depletion, and stress. 21–26 Sympathetic activity also influences blood pressure by altering renal sodium excretion. 27–30 These observations suggest that obese patients receiving hypocaloric protein diets may undergo alterations in catecholamine responses to posture and exercise. The present study examines changes in blood pressure, pulse rate, plasma catecholamine, prolactin (PRL), PRA, and aldosterone responses to upright posture and isometric handgrip exercise in obese patients during 12 weeks of weight reduction on a hypocaloric protein diet.

Methods

Twenty obese patients (15 females, 5 males), aged 22 to 55 years, with a body weight at least 25% greater than the calculated ideal weight, were studied. Patients were excluded if they had insulin-dependent diabetes mellitus, cardiovascular disease, alcoholism, drug addiction, psychiatric problems, or hypertension previously necessitating drug management. All subjects had normal BUN, serum creatinine, electrolytes, liver function tests, uric acid, serum thyroxine, CBC, urinalysis, chest x-ray, and electrocardiogram.

Protocol

During the initial clinic visit the patients’ histories were taken, physical examinations were conducted, and laboratory tests performed. Two weeks later the patients underwent upright posture and isometric handgrip exercise studies as previously described. 31 Briefly, at 0800 hour subjects assumed a supine position and a needle was placed in the left antecubital vein for blood collection. The needle was maintained patent by infusion of 5% dextrose and water at 1 ml/min. At 0830 hour, basal supine blood samples were collected for determination of NE, epinephrine (E), dopamine (DA), PRL, aldosterone, and PRA. The subjects stood upright for 10 minutes and then performed maximum handgrip for 5 minutes, as previously described. 31 Blood samples were collected, and blood pressures were determined with a mercury sphygmomanometer after 10 minutes of standing and after 5 minutes of isometric handgrip exercise. The MAP was calculated as the diastolic blood pressure plus one third of the pulse pressure.

The patients were then placed on a controlled diet consisting of 320 kcal per day given as 30 g of carbohydrate, 45 g of protein, 2 g of essential fatty acids, and 40 mmole sodium. Additional supplements were 600 mg calcium, 350 mg phosphorus, 150 mg magnesium, and 100% daily allowance for iron, copper, zinc, and all vitamins. Changes in body weight, supine MAP, BUN, uric acid, and 24 hour urine electrolytes were measured at the control period and during Weeks 2, 4, 8, and 12 of the diet. Further, upright posture and isometric handgrip exercise studies were performed during these visits. The day preceding each visit, a 24-hour urine sample was collected for determination of creatinine and sodium excretion. Failure to ingest the controlled dietary supplement was indicated by low uric acid levels or the absence of urinary ketones.

Analytical Methods

Plasma NE, E, and DA were determined in duplicate samples using a single isotope radioenzymatic assay. 31 The sensitivity of this assay is 10.0 pg/ml for NE and E, and 15.0 pg/ml for DA. All blood samples for catecholamines were collected in prechilled heparinized tubes and centrifuged at 4°C within 15 minutes. Plasma samples were immediately stored at −100°C and analyzed within 2 weeks. The PRL was measured by a homologous double isotope radioimmunoassay. 32 Sensitivity of this assay is 1.0 ng/ml, and the intra-assay coefficient of variation (CV) is 5%. Samples for PRA were collected in prechilled tubes containing EDTA and centrifuged at −4°C. The PRA was quantitated by radioimmunoassay of generated angiotensin I at 37°C for 1 hour. 31 The sensitivity of this assay is 0.2 ng/ml-hr−1 and the interassay coefficient of variation is 6%. Aldosterone was extracted from plasma samples using 15-fold volumes of methylene chloride and was separated from other interfering steroids by means of a Sephadex LH-20 column. The extracted aldosterone was measured by radioimmunoassay utilizing an antisemur provided by the NIMDD. 31 Plasma and urinary sodium was measured by atomic absorption photometry. Statistical changes in various parameters were made by repeated sampling analysis of variance method33 and Dunnetts’ multivariant analysis 34 after log transformation of data when significant differences in variance existed. Multiple regression analysis was used to calculate coefficients of correlation between various parameters studied.

Results

Body weight for the 20 patients ranged from 35% to 172% (mean, 80.1% ± 9.4%) above the calculated ideal weight for age and sex. A decrease (p < 0.05) in weight was observed 2 weeks after the onset of the diet (table 1) and continued progressively through the 12-week period. Urinary sodium determinations demonstrated that the subjects maintained a 40 mmole sodium intake from Week 2 through Week 12 (table 1). A substantial decrement (p < 0.05) in MAP was observed by the second week and by Week 12 the basal supine MAP was approximately 79% that at the onset of the diet. There was a positive correlation (r = 0.61, p < 0.01) between reductions in body weight and MAP during the 12-week period. MAP following upright posture and isometric handgrip exercise were reduced (p < 0.05) from Week 2 through Week 12. A decrease (p < 0.05) in the pulse rate after assumption of upright posture was observed at Weeks 4 through 12 (table 2).

Figure 1 demonstrates that supine plasma NE (225 ± 20 pg/ml), the plasma NE levels after assumption of upright posture (380 ± 34 pg/ml), and isometric exer-
cise (440 ± 40 pg/ml) at 4 weeks, were less (p < 0.05) than the Week 0 basal (312 ± 34 pg/ml), posture (495 ± 45 pg/ml) and exercise (562 ± 48 pg/ml) levels. Basal supine plasma NE at Week 8 (192 ± 18 pg/ml) was less (p < 0.05) than at Week 2 and considerably less (p < 0.01) than at Week 0. Although plasma NE levels following upright posture and isometric exercise at Weeks 8 and 12 were less (p < 0.01) than the levels during the control period, they were not significantly different from those at Weeks 2 through 4. Supine plasma NE at Week 0 correlated (r = 0.65, p < 0.01) with MAP. Decrements in supine plasma NE and decrements in supine MAP were correlated (r = 0.58, p < 0.01) as were decrements in NE and MAP levels following posture and exercise (r = 0.63, p < 0.01) at Weeks 2 through 12 after onset of the diet. Supine plasma E at Week 4 (31 ± 2.6 pg/ml) was less than at Week 0 (37 ± 2.8 pg/ml) (fig. 2). There was a continued progressive decrement in basal supine plasma E so that levels at Week 12 (22 ± 2.2 pg/ml) were considerably (p < 0.001) less than those at the onset of the diet. There was not a significant E increase after posture and isometric exercise maneuvers throughout the 12-week study period.

Figure 3 demonstrates the DA levels after posture and exercise throughout the study. At 2 weeks after onset of the diet, basal supine plasma DA (74 ± 10 pg/ml), DA after 10 minutes upright posture (86 ± 14 pg/ml)...

**Table 1. Mean (± SEM) Changes in Body Weight and Urinary Sodium Excretion, During 12 Weeks on a Controlled Diet in 20 Obese Patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>114.6 ± 6.2</td>
<td>107.5 ± 5.4</td>
<td>104.8 ± 4.6*</td>
<td>98.6 ± 4.0†</td>
<td>93.6 ± 3.9†</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/24 hr)</td>
<td>196.4 ± 29</td>
<td>41.8 ± 5.6‡</td>
<td>40.5 ± 5.0‡</td>
<td>40.1 ± 5.0‡</td>
<td>41.5 ± 5.5‡</td>
</tr>
</tbody>
</table>

* p < 0.05.
† p < 0.01.
‡ p < 0.001 from control.

**Table 2. Mean (± SEM) Arterial Blood Pressure (MAP) (mm Hg), Pulse/Min, PRA (ng/mill/hr), Plasma Aldosterone (ng/dl), and Prolactin (ng/ml) Levels in the Basal Supine Position (0 min), after 10 Minutes of Upright Posture (10 min), and Handgrip Exercise (HG) during 12 Weeks on a Controlled Diet in 20 Obese Patients**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>102.0 ± 3.8</td>
<td>103.2 ± 3.8</td>
<td>104.3 ± 3.8</td>
<td>87.1 ± 4.8*</td>
<td>86.8 ± 3.9</td>
</tr>
<tr>
<td>Pulse</td>
<td>80.7 ± 3.0</td>
<td>82.4 ± 3.0</td>
<td>82.8 ± 3.0</td>
<td>66.2 ± 3.0</td>
<td>79.0 ± 3.0</td>
</tr>
<tr>
<td>PRA</td>
<td>3.8 ± 0.8</td>
<td>5.8 ± 0.8</td>
<td>6.0 ± 0.8</td>
<td>3.2 ± 0.8</td>
<td>4.6 ± 0.8</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>12.9 ± 1.4</td>
<td>16.8 ± 1.4</td>
<td>18.1 ± 1.4</td>
<td>12.0 ± 1.4</td>
<td>14.1 ± 1.4</td>
</tr>
<tr>
<td>Prolactin</td>
<td>11.2 ± 1.2</td>
<td>13.5 ± 1.1</td>
<td>14.3 ± 1.1</td>
<td>10.7 ± 1.1</td>
<td>11.2 ± 1.1</td>
</tr>
</tbody>
</table>

* p < 0.05.
† p < 0.01.
BLOOD PRESSURE CONTROL IN OBESITY/Sowers et al. 689

Figure 2. Mean (± sem) plasma E responses to 10 minutes of upright posture and 5 minutes of isometric handgrip exercise in 20 obese patients during 12 weeks on a low calorie protein diet.

Figure 3. Mean (± sem) plasma DA responses to 10 minutes of upright posture and 5 minutes of isometric handgrip exercise in 20 obese patients during 12 weeks on a low calorie protein diet.

ml), and 5 minutes isometric handgrip exercise, were greater (p < 0.05) than Week 0 supine DA (55 ± 7 pg/ml), postural DA (64 ± 9 pg/ml), and DA, after isometric exercise (65 ± 9 pg/ml). At Weeks 4 through 12 of the diet, however, DA levels were not different from those at Week 0. The increments in DA at Week 2 were inversely related (r = 0.56, p < 0.01) to the decrements in urinary sodium.

Table 2 demonstrates the PRL levels through the 12-week study period. Prior to onset of the diet PRL levels after isometric exercise (14.3 ± 1.9 ng/ml) were greater (p < 0.05) than the supine PRL levels (11.2 ± 1.2 ng/ml). Supine plasma PRL levels did not change significantly throughout the 12-week period. Upright PRL levels were less (p < 0.05) at Weeks 8 and 12, however, and exercise-related PRL levels were less (p < 0.05) at Weeks 2 through 12 than at Week 0. There were no significant correlations between basal levels of, or changes in, PRL concentrations and MAP or catecholamines during the 12 weeks.

Basal supine PRA and the PRA levels following upright posture and isometric exercise were less (p < 0.05) after 8 weeks on the diet than at Week 0 (table 2). Similarly, basal supine plasma aldosterone and the aldosterone levels following upright posture and isometric exercise maneuvers were less (p < 0.05) after 8 weeks of dieting than prior to the onset of the diet (table 2). During the 12-week period of weight loss, reductions in supine PRA and supine plasma NE showed a correlation (r = 0.56, p < 0.01). Reductions in supine PRA and plasma aldosterone at Weeks 8 and 12 were also correlated (r = 0.50, p < 0.05).

Discussion

Results of the present study suggest that reductions in blood pressure in obese patients associated with caloric restriction and associated weight loss are related to a reduction in sympathetic nervous system activity. There was a correlation between blood pressure and plasma NE concentration in our obese patients prior to caloric restriction. Reductions in blood pressure during the 12 weeks of the hypocaloric protein diet were also related to reductions in plasma NE levels. Although plasma E and plasma DA levels were not related to blood pressure levels, there was a reduction in supine plasma E that paralleled the decline in supine NE levels. In contrast, plasma DA levels were actually increased at 2 weeks after implementation of the diet and subsequently did not differ from those prior to the onset of the diet.

In individuals who are not undergoing caloric restriction, alterations in sodium intake dramatically affect catecholamine secretion.21-26,35 A marked reduction in sodium intake, as experienced by our obese patients during the first two weeks on the hypocaloric 40 mmole sodium diet, has been observed to increase supine plasma NE levels as well as NE levels follow-
ing posture and exercise maneuvers. A decrease in plasma DA concentration has been observed during the course of dietary sodium restriction in individuals receiving 2680 cal/day. Sodium restriction, however, was not associated with increases in plasma NE and decreases in DA in our patients also undergoing marked caloric deprivation. These observations suggest that caloric restriction in obese patients overrides the effects of reduced sodium intake. Reduction in sodium intake may have accounted, in part, for decreases in blood pressure during the early phases of weight reduction in the present study. However, two recent reports demonstrated that blood pressure fell with long-term weight reduction independent of sodium intake.

Fasting and hypocaloric protein diets are associated with a natriuresis during the early days of caloric deprivation. Although this natriuresis is poorly understood it has been attributed to various factors such as hyperketonemia, relative hypercarnitineemia, relative hypoinsulinemia, and mineralcorticosteroid resistance. Our results suggest that the natriuresis associated with a hypocaloric protein diet may result from alterations in catecholaminergic influences on the kidneys. Epinephrine and NE and stimulation of the renal sympathetic nerves have been demonstrated to cause reabsorption of sodium, independent of simultaneously induced changes in renal hemodynamics. The results of a number of investigations suggest a role for dopamine in the regulation of the renal excretion of sodium as dopamine has a natriuretic effect and its excretion parallels that of sodium. During the first 2 weeks of caloric deprivation, our observations that plasma dopamine levels increased while plasma NE and E levels declined suggest that these alterations in renal catecholaminergic influences may account, in part, for the natriuresis observed during the early stages of weight loss associated with caloric deprivation.

In addition to an association with sodium loss, low caloric protein diets have been observed to be associated with larger postural declines in blood pressure than have diets of isocaloric mixtures of protein and carbohydrate. In our patients maintained on a low caloric protein diet we found that upright blood pressure levels were correlated with plasma NE levels after posture and isometric exercise. These findings provide further evidence for the role of the sympathetic nervous system in the hemodynamic adaptation to upright posture and exercise. Restriction of carbohydrate intake in our obese patients may explain the reduction in NE concentrations following posture and exercise maneuvers. Turnover of NE in pancreatic, hepatic, and cardiac tissues has been observed to be reduced with starvation and reversed by sucrose feeding in rats. Pronounced carbohydrate restriction has also been shown to reduce blood pressure in spontaneously hypertensive rats consistent with a reduction in sympathetic nervous system activity. Conversely, increased plasma NE levels have been observed following glucose ingestion in man. Further, a fall in serum insulin levels that probably accompanied the low calorie diet and associated weight reduction in our obese patients may have contributed to the sodium diuresis and reduction in sympathetic nervous system activity. Thus, reduction in carbohydrate intake may have decreased sympathetic nervous system activity through hypothalamic or peripheral mechanisms.

A role for PRL in the regulation of blood pressure and blood volume has been suggested as the result of a number of studies. Stumpe et al. reported that treatment of patients with essential hypertension with the dopamine agonist bromocriptine caused parallel decreases in plasma PRL and blood pressure. Similarly, bromocriptine treatment in the spontaneously hypertensive rat model for human essential hypertension is associated with parallel lowering of PRL and blood pressure. Basal supine PRL levels have been reported to be elevated in patients with essential hypertension. An increase in PRL levels after upright posture, not present in normotensive subjects, has been observed in patients with essential hypertension. In this investigation we observed a rise in PRL levels after posture and isometric exercise maneuvers in our obese subjects prior to onset of dieting. During the 12 weeks of the low-calorie protein diet, however, no rise in PRL levels following posture and exercise maneuvers was observed. A reduction in ambulatory PRL levels during the first 2 weeks of dieting may have played a role in blood pressure reduction and natriuresis during this period. An effect of PRL on the kidney is suggested by the observation that administration of ovine PRL causes sodium retention in humans. Patients with hyperprolactinemia in association with prolactinomas have higher serum osmolalities after fluid deprivation, reflecting a decrease in urinary sodium clearance. Finally, the results of this study suggest that control of PRL secretion may be altered in obese patients and that these abnormalities are corrected with caloric deprivation and loss of weight.

The observations that supine PRA and plasma aldosterone levels were significantly reduced at 8 weeks after onset of a low caloric protein diet in obese patients confirms previous observations. In the present study we have further demonstrated a relationship between the fall in plasma NE and PRA from levels found prior to the onset of the diet. We have also demonstrated that PRA and aldosterone levels following posture and exercise maneuvers are reduced at 8 weeks of dieting. The reduction in aldosterone was related to decrements in PRA. Since the sympathetic nervous system and renal nerves are major factors in modulating renin release, particularly in response to posture, volume depletion and exercise, reductions in PRA levels associated with posture and exercise following caloric reduction probably reflect diminished sympathetic nervous system activity. Thus, reduction in blood pressure in association with caloric restriction in obese patients appears to result from direct effects on plasma catecholamines and secondary effects of reduced adrenergic activity on renal sodium excretion and the renin-angiotensin-aldosterone axis.
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