Role for Aldosterone in Blood Pressure Regulation of Obese Adolescents

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To determine the role of aldosterone in the regulation of blood pressure (BP) in obese adolescents, supine and 2-hour upright plasma renin activity (PRA), and aldosterone and cortisol were measured in 10 nonobese and 30 obese adolescents before and after a 20-week weight loss program. The obese adolescents had significantly higher supine and 2-hour upright plasma aldosterone concentrations (17 ± 8 vs 6 ± 2 ng/dl [p <0.01 supine obese vs nonobese] and 30 ± 11 vs 14 ± 8 ng/dl [p <0.01 2-hour upright]). Although PRA was not significantly different between the 2 groups of children, a given increment in PRA produced a greater increment in aldosterone in the obese adolescents. In addition, obese subjects had a significantly increased mean BP (93 ± 12 vs 74 ± 8, p <0.005)

and a weak correlation between BP and plasma aldosterone concentration. Compared with an obese control group, weight loss resulted in a significant decrease in plasma aldosterone (p <0.01) without an associated decrease in PRA. After weight loss there was also a significant decrease in the slope of the posture-induced relation between PRA and aldosterone. In addition to weight loss being associated with a significant decrease in BP (p <0.01), there was a significant correlation between the change in plasma aldosterone and the change in mean BP (r = 0.538; p <0.002 change in upright aldosterone vs change in mean BP). Obese adolescents have an increased plasma aldosterone concentration that may be important in the regulation of their BP.

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S ince 1924 it has been known that body weight and arterial pressure are related. However, little is known about the mechanism of this relation.[1] One physiologic change that may be partially responsible for hypertension in the obese person is excess mineral corticoid activity. Scavo et al[2,3] reported that although obese adults have normal plasma renin activity (PRA), they have an increased plasma aldosterone concentration and an increased aldosterone secretion rate. In obese adults with essential hypertension, Hiramatsu et al[4] documented that with increasing body weight PRA

decreases and plasma aldosterone concentration remains unchanged. Tuck et al[5] demonstrated that with weight loss both PRA and plasma aldosterone concentration decrease. Although these and other observations [6,7] suggest that in obese subjects abnormalities in the renin-aldosterone axis are present, the effect of these abnormalities on blood pressure (BP) is unclear. Therefore, we evaluated the role of aldosterone in the regulation of BP in 30 obese adolescents before and after a 20-week weight loss program.

Methods

Thirty obese adolescents, mean age 12.7 years (range 10 to 15), and 10 nonobese adolescents, mean age 12.2 years (range 10 to 14), were studied. Obesity was defined as weight for height above the 75th percentile for age and sex and triceps and subscapular skin folds above the 80th percentile for age and sex. The obese subjects were randomly placed into 1 of 3 groups. Group I consisted of 10 obese adolescents placed in a weight loss program composed of diet and behavior change. The diet was a modification of the caloric exchange program and was designed to produce approximately 1 pound per week of weight loss

TABLE I   Pertinent Clinical, Hemodynamic and Electrolyte Data in 30 Obese and 10 Nonobese Adolescents

	Obese (n = 30)	Nonobese (n = 10)	p Value
Age (yr)	12.7 ± 2.2	12.2 ± 3.0	NS
Weight (kg)	75.8 ± 22	42.2 ± 13	p <0.001
% fat	40 ± 6	20 ± 7	p <0.001
Mean BP (mm Hg)	93 ± 12	74 ± 8	p <0.005
HR (beats/min)	86 ± 12	77 ± 6	p <0.05
K$^+$ (mEq/liter)	4.0 ± 0.2	4.3 ± 0.2	p <0.03
NA$^+$ (mEq/liter)	142 ± 2	138 ± 3	p <0.03
UNa (mEq/24 hr)	212 ± 77	136 ± 14	p <0.02

BP = blood pressure; HR = heart rate; NS = not significant; UNa = urinary sodium excretion.

(1,200 to 1,800 calories/day). The behavior change component consisted of a 1-hour class each week for 20 weeks that centered around record keeping, stimulus control, changing eating typography, and reinforcement of altered behavior. Group II consisted of 10 obese adolescents placed in a weight loss program consisting of diet, behavior change and exercise. The diet and behavior change were the same as in group I. The exercise program consisted of three 1-hour classes per week for 20 weeks, centering around activities designed to maintain heart rate for at least 40 minutes at more than 50% of maximal exercise rate. Group III consisted of 10 obese adolescents placed in a control group who received no weight loss program for 20

weeks. All 30 obese subjects were tested before and after the 20 weeks. The 10 nonobese adolescents were tested only once.

Experimental protocol: All patients were admitted overnight to the Clinical Research Center. BP was measured every 5 minutes for 30 minutes in a quiet room using a Critikon pressure monitor (model 1165) and an appropriate-size cuff. Mean BP was calculated as diastolic pressure plus one-third pulse pressure. All patients fasted after 10 PM of the evening preceding the study and were maintained in a supine position after 4 AM on the morning of the study. A heparin lock was placed at 7:30 AM, and with the patient in the supine position, blood was obtained for PRA, plasma aldosterone, plasma cortisol, serum sodium and potassium. After being upright and ambulating for 2 hours, repeat blood samples were obtained. Dietary sodium intake was assessed in all patients by measuring the 24-hour urinary sodium excretion the day before the study.

Laboratory procedures: Weight was measured using a beam balance scale and height was measured to the nearest 0.1 cm using a stabilometer. Body composition (percent fat and lean body weight) was measured by hydrostatic weighing.[8] Sodium concentration was determined by flame photometry. Aldosterone, cortisol and PRA were measured by radioimmunoassay.[9-11]

Statistical analysis: Statistical analysis was performed using analysis of variance to compare differences between the nonobese and obese adolescents. To compare differences between the 3 obese groups before and after 20 weeks of weight loss, we used a 2 ×
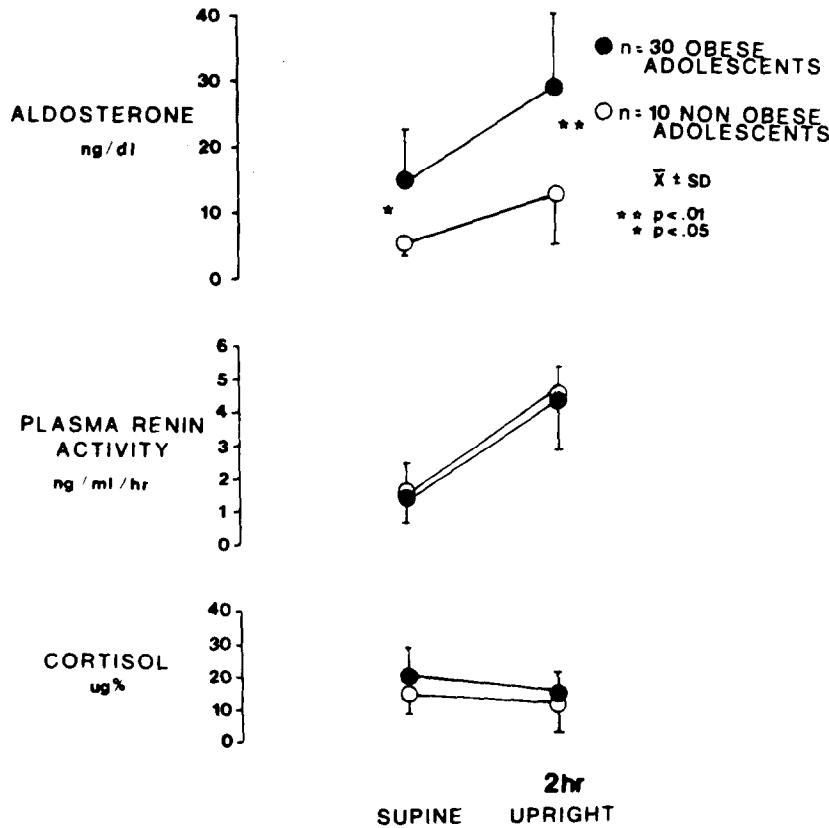

FIGURE 1. Supine and 2-hour upright plasma aldosterone concentration, plasma renin activity and plasma cortisol concentration in 30 obese and 10 nonobese adolescents. SD = standard deviation.

TABLE II   Change in Body Composition, Blood Pressure, Aldosterone, Plasma Renin Activity and Electrolytes After Either a 20-Week Weight Loss Program or Control Period

	Obese Control (n = 10)		Obese Diet (n = 10)		Obese Diet + Exercise (n = 10)	
	Pre	Post	Pre	Post	Pre	Post
Weight (kg)	67.6 ± 30	71.9 ± 25	72.4 ± 20	69.9 ± 17‡	71 ± 8	69 ± 9†‡
% fat	39 ± 6	41 ± 9	41 ± 7	36 ± 7†‡	40 ± 6	34 ± 5†‡
Height (cm)	157 ± 9	161 ± 10†	157 ± 10	161 ± 9†	157 ± 6	162 ± 6†
BP (mm Hg)	88 ± 10	93 ± 13	92 ± 12	81 ± 7†‡	90 ± 8	82 ± 4†‡
Aldo (ng/dl)						
supine	21 ± 15	18 ± 6	15 ± 8	10 ± 6†‡	17 ± 8	9 ± 4†‡
2-hr upright	29 ± 8	31 ± 7	28 ± 8	19 ± 6†‡	38 ± 12	19 ± 4†‡
PRA (ngAl/ml/hr)						
Supine	1.9 ± 1.2	1.7 ± 1.1	1.4 ± 0.8	1.6 ± 0.9	1.6 ± 0.95	2.4 ± 0.9
2-hr upright	4.9 ± 1.7	3.8 ± 1.3	3.8 ± 1.8	4.9 ± 1.5	5.1 ± 2.1	4.9 ± 1.6
Cortisol (μg/dl)						
Supine	19 ± 4	19 ± 4	19 ± 5	15 ± 3*§	18 ± 4	15 ± 2*§
2-hr upright	14 ± 4	14 ± 4	15 ± 3	12 ± 3*§	16 ± 3	12 ± 2*§
Serum Na⁺ (mEq/liter)	142 ± 2	142 ± 2*‡	142 ± 3	140 ± 2*§	142 ± 2	140 ± 2*§
Serum K⁺ (mEq/liter)	4.0 ± 0.2	3.9 ± 0.2	3.9 ± 0.25	4.2 ± 0.2*§	3.9 ± 0.2	4.2 ± 0.3*§
UNa⁺ (mEq/24 hr)	211 ± 74	194 ± 62	212 ± 57	184 ± 33	208 ± 78	195 ± 77
24-hr urine creat. (g/day)	1.1 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.2	1.2 ± 0.3

Pre vs post: * p <0.05; † p <0.01; obese control vs obese diet or diet + exercise; ‡ p <0.01; § p <0.05.

Aldo = aldosterone; BP = mean blood pressure; Creat. = creatinine; UNa = urinary sodium excretion; K⁺ = potassium; Na⁺ = sodium; pre = before weight loss; post = after 20-week weight loss program or control period; PRA = plasma renin activity.

3 analysis of variance and the Scheffe[12] procedure for multiple comparisons.

Systolic and diastolic BPs were adjusted for age and sex by use of the standard deviation score (z) calculated according to the formula $z = x-x/SDx$, where x = measured BP, x = mean of the expected BP for age and sex (Hanes II data[13]), and SDx = standard deviation x. Linear regression analysis was used to determine the correlation between posture-induced changes in PRA and plasma aldosterone in nonobese and obese adolescents before and after weight loss. Comparisons between regression slopes were made using analysis of variance. The homogeneity of variance was assessed by Bartlett's test.[14] All results are expressed as mean ± standard deviation.

Results

Compared with the 10 nonobese adolescents, the 30 obese adolescents had a higher mean BP (p <0.005) (Table I). They also had an increased 24-hour urinary sodium excretion rate (p <0.02) and serum sodium concentration (p <0.03) and a decreased serum potassium concentration (p <0.03). The association of an elevated mean BP, a mildly decreased serum potassium concentration and a mildly increased serum sodium concentration in our obese adolescents is consistent with the possibility of an excess in mineral corticoid activity.

To evaluate the renin-angiotensin-aldosterone axis in adolescent obesity, we compared the changes in PRA and aldosterone concentration that occurred with acute postural change. Compared with nonobese adolescents, the obese adolescents had an elevated plasma aldosterone concentration in both the supine (17 ± 8 vs 6 ± 2 ng/dl, p <0.01) and upright (30 ± 11 vs 14 ± 8

ng/dl, p <0.01) positions (Fig. 1). However, despite the observed increase in plasma aldosterone, the 2 groups of children had similar changes in PRA.

Because BP in childhood is affected by both age and sex, in order to evaluate the relation between plasma aldosterone concentration and BP, a Z score BP was determined for each adolescent. In the obese adolescents, there were correlations between both Z score systolic and diastolic BP and 2-hour upright plasma aldosterone concentration (r = 0.35 and 0.56, respectively, p <0.05), fat weight (r = 0.35 and 0.56, respectively, p <0.05) and plasma potassium concentration (r = 0.42, p <0.05 for diastolic BP). The effect of weight loss on these variables was evaluated by comparing the changes in plasma aldosterone, PRA, plasma cortisol, serum sodium and potassium, body weight, fat weight and BP that occurred in 2 groups of obese adolescents after 20 weeks of weight loss vs that which occurred in a group of obese adolescents after a 20-week control period.

The two 20-week weight loss groups showed modest but significant decreases in body weight (p <0.01). In fact, all patients in the weight loss programs lost some weight, whereas all of the obese control patients gained weight. Since both the obese control group and weight loss groups had a significant 4-cm increase in height (p <0.01), the modest decrease in body weight observed in the 2 weight loss groups was associated with marked changes in body composition (Table II). In addition, compared with the obese control subjects, the 2 weight loss groups had a significant decrease in fat weight (p <0.01), mean BP (p <0.01), supine and upright plasma aldosterone (p <0.01), plasma cortisol (p <0.03) and serum sodium concentration (p <0.02), and a small but significant increase in serum potassi-

um concentration (p <0.02) (Table II). The decrease in mean BP during the 20-week program significantly correlated with the change in plasma aldosterone (r = 0.38, p <0.03 supine and r = 0.54, p <0.002 upright) (Fig. 2), fat weight (r = 0.73, p <0.001), and body weight (r = 0.60, p <0.01). The changes in plasma aldosterone and changes in body weight and fat weight were significantly correlated (r = 0.421, p <0.05 and r = 0.61, p <0.01, respectively). There was also a significant correlation between change in mean BP and plasma aldo-

sterone independent of the effect of body weight (p = 0.05).

Although weight loss was associated with a significant decrease in plasma aldosterone concentration, we observed no significant change in PRA. However, weight loss markedly affected the relation between the posture-induced changes in PRA and plasma aldosterone. Before weight loss, the increment in plasma aldosterone between supine and upright posture divided by the increment in PRA was significantly in-
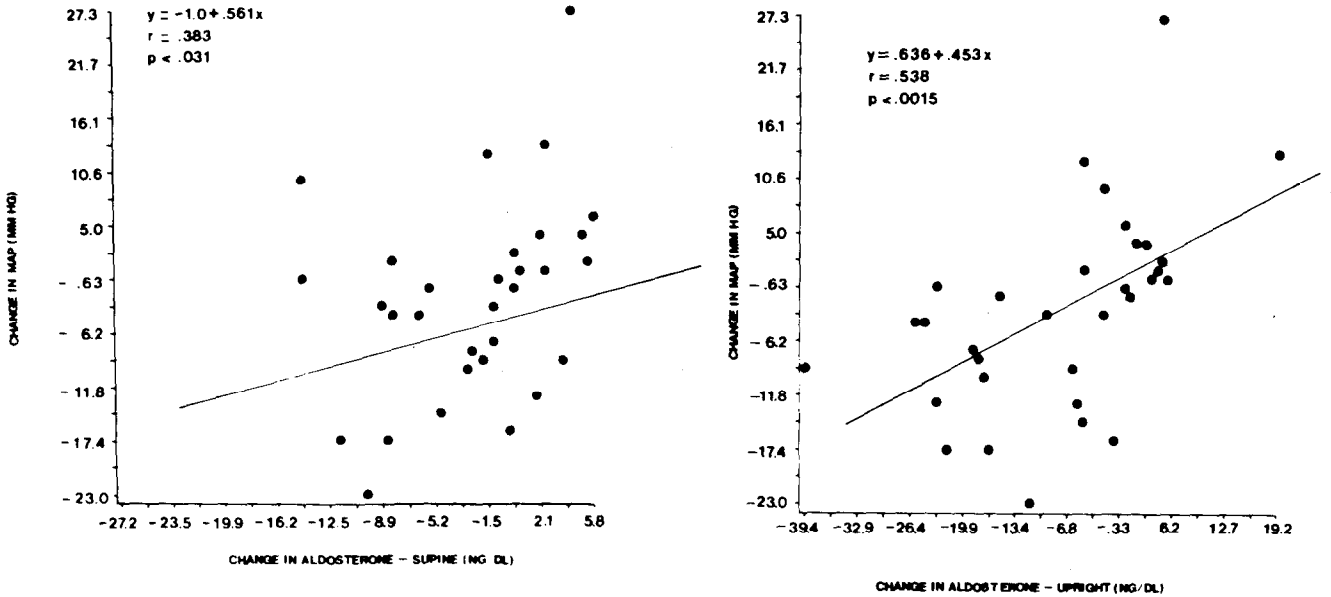

FIGURE 2. Regression relation between the change in mean arterial pressure (MAP) and the change in plasma aldosterone concentration during the 20-week study.
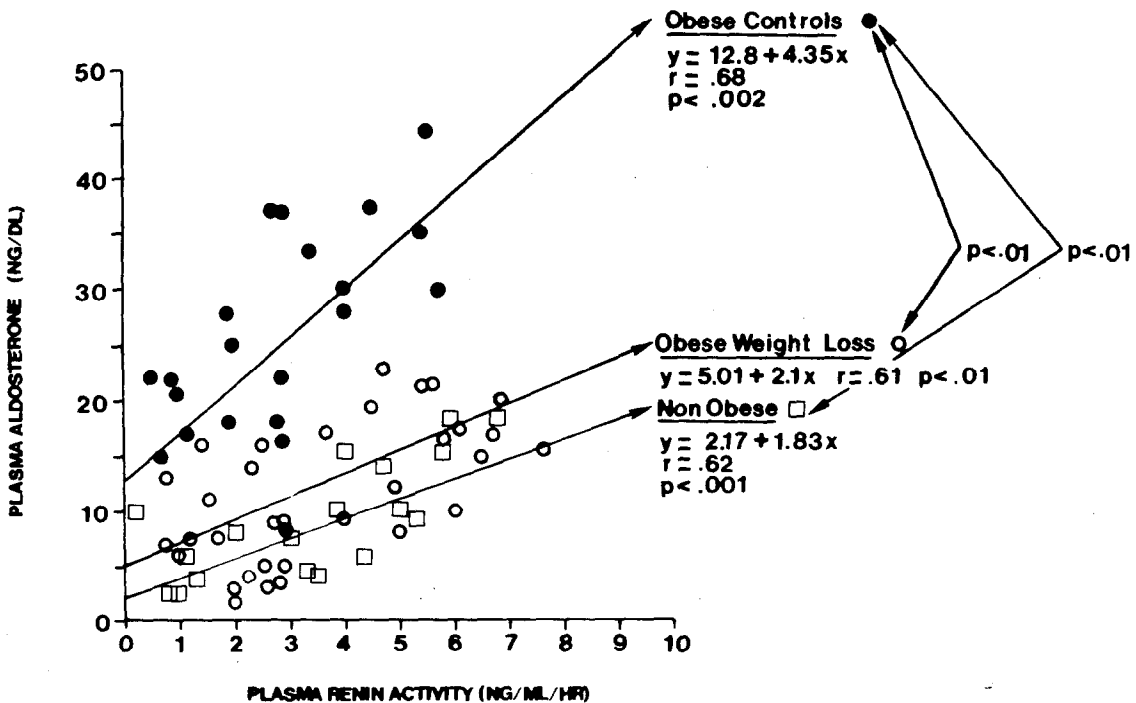

FIGURE 3. Regression relations between posture-induced changes in plasma renin activity and plasma aldosterone in 10 obese control subjects (dots), in 20 obese subjects after weight loss (circles) and in 10 nonobese subjects (squares). The 2 weight-loss groups were combined.

creased in the obese adolescents (1.8 vs 4.4 ng/dl aldosterone/ng/ml/hour AI, p <0.01 nonobese vs obese adolescents). After the weight loss program, there was a significant decrease in the slope of the relation between PRA and aldosterone to the extent that only the obese control group still had a slope that was significantly greater than the nonobese adolescents (Fig. 3).

Discussion

In the present study, we have demonstrated that compared with nonobese adolescents, obese adolescents have a significantly higher plasma aldosterone concentration. Other investigators have also demonstrated abnormal aldosterone production in obesity. Garnett et al[6] documented a mild increase in aldosterone secretion in 9 obese adults. In addition, Scavo et al[2,3] demonstrated that in obese adults aldosterone secretion is significantly increased in both absolute values as well as when indexed to body surface area, the metabolic clearance rate of aldosterone is normal and the plasma aldosterone concentration is increased. However, unlike Scavo's study, in the present study, we also evaluated both the effect of weight loss on the hyperaldosteronism of obesity and the correlation between the increased plasma aldosterone concentration and BP. We observed that weight loss, either with or without exercise, produced a significant reduction in both plasma aldosterone concentration and BP and a small but significant increase in serum potassium concentration. In addition, the decrease in plasma aldosterone concentration significantly correlated with the observed decrease in mean BP. Thus, our data suggest, but do not prove, that the hyperaldosteronism associated with obesity may have contributed, in part, to the hypertension of obesity. Tuck et al[5] demonstrated, as did we, that with weight loss, plasma aldosterone levels decrease while serum potassium concentration increases. However, unlike our study, Tuck did not demonstrate a statistically significant correlation between the decrease in aldosterone concentration and the decrease in mean BP. A possible explanation for the differences between the 2 studies may be that Tuck et al severely reduced caloric intake to 320 kcal/day (almost starvation levels), whereas in the present study, only a mild reduction in caloric intake was used. Since Spark et al[7] and Garnett et al[6] demonstrated that with fasting wide swings in both aldosterone and PRA can occur, it is possible that these starvation-induced swings in aldosterone may have obscured the correlation between changes in plasma aldosterone and changes in mean BP.

The mechanism of hyperaldosteronism of obesity is unknown. Although aldosterone metabolism was not measured in this study, on the basis of the work of Scavo et al[2,3] and Garnett et al,[6] the hyperaldosteronism observed in our obese adolescents was probably a result of increased aldosterone secretion rather than decreased metabolic clearance. Aldosterone secretion is normally regulated by the renin-angiotensin system, serum potassium,[15] sodium balance,[16] ACTH activity[17,18] and other less defined secretagogues.[19] Our data suggest that the hyperaldosteronism of obesity may be the result of an abnormality either in the renin-angio-

tensin system or in ACTH activity. With regard to the renin-angiotensin system, even though angiotensin II was not directly measured because PRA was normal and was not altered by weight loss, it is unlikely that an increase in plasma angiotensin II was present. However, based on the observation that a given increment in PRA produced a greater increment in aldosterone in the obese adolescents and that weight loss, in part, corrected this relation, adrenal sensitivity to angiotensin II may apparently be increased.[20] Hiramatsu et al[4] also observed that obese patients have an increased aldosterone/PRA ratio. Kisch et al[21] and Marks et al,[22] using a graded infusion of angiotensin II, demonstrated that some patients with essential hypertension have increased adrenal sensitivity to angiotensin II. Many of Kisch's hypertensive patients may have been mildly obese. Since Shoback et al[23] reported that a substantial subgroup of essential hypertensive patients have an abnormality in sodium-modulated renovascular and adrenal responsiveness to angiotensin II, our results suggest that a similar defect may also be present in obese adolescents. Further studies in obese adolescents before and after weight loss, using graded infusions of angiotensin II, are required to prove that obesity can produce a defect in tissue responsiveness to angiotensin II.

Finally, although we did not directly measure ACTH activity since weight loss was associated with a significant decrease in serum cortisol, it is possible that ACTH activity could have also decreased. Other investigators also demonstrated an increased cortisol excretion rate in obesity[24,25]; increased ACTH activity may also contribute to the hyperaldosteronism of obesity.

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