SUMMARY The role of insulin in the regulation of blood pressure was evaluated in 50 obese adolescents before and after a 20-week weight loss program. When compared with 10 nonobese adolescents, the obese subjects had significantly higher systolic, diastolic, and mean arterial pressures (p = 0.005), an elevated 24-hour urinary sodium excretion (p = 0.002), an elevated fasting insulin concentration (p = 0.001), and an abnormal insulin response to an oral glucose tolerance test (sum of the insulins at 0, 1, and 2 hours post-oral glucose load; p = 0.001). We also observed a significant correlation between systolic and diastolic blood pressure (age and sex normalized) and body weight (r = 0.57, p<0.01 and r = 0.7, p<0.01), fasting insulin (r = 0.49, p<0.01 and r = 0.54, p<0.01), and sum of insulins (r = 0.42, p<0.01 and r = 0.46, p<0.01). To study the effect of weight loss on the relationship between blood pressure and insulin, the obese subjects were randomly assigned to three groups: 15 to a diet and behavior change group, 18 to a diet, behavior change, and exercise group, and 17 to an obese control group. Compared with the obese control group, the two weight loss groups each experienced a significant decrease in insulin (p<0.01), sum of the insulins (p<0.01), and blood pressure (p<0.01). The decrease in blood pressure during the weight loss program significantly correlated with the change in both insulin and body weight. However, when we statistically adjusted for the effect that the change in insulin had on the change in blood pressure, a significant relationship between the change in blood pressure and the change in body weight remained only in the diet group. Conversely, when we similarly corrected for the effect that the change in body weight had on the change in blood pressure, a significant relationship between the change in blood pressure and the change in insulin remained only in the diet and exercise group. Thus, these data suggest that the presence or absence of exercise was critical in determining the role of insulin in the regulation of blood pressure during weight loss. (Hypertension 10: 267–273, 1987)

KEY WORDS • exercise • obesity • hypertension • insulin • weight loss

DESPITE the strong association between obesity and hypertension, the etiological basis of the hypertension is poorly understood. Sodium retention is one of the major physiological changes that may in part be responsible for the elevated blood pressure that is observed in many obese persons. Hyperinsulinemia is one of the hormonal abnormalities of obesity that may be linked to sodium retention. Miller and Bogdonoff have demonstrated that insulin can reduce sodium excretion independently of changes in plasma glucose concentration. DeFronzo et al. have used euglycemic hyperinsulinemia to demonstrate that a highly significant decrease in urinary sodium excretion occurs in normal subjects within 60 minutes of beginning an insulin infusion. Rowe et al. have also observed that euglycemic hyperinsulinemia acutely increases blood pressure, heart rate, and pulse pressure in normal subjects. More recently, Lucus et al., Manicardi et al., and Rose et al. have demonstrated a significant relationship between serum insulin activity and blood pressure in obesity.

The present study was undertaken to determine if a relationship exists between fasting serum insulin and blood pressure in obese adolescents and what effect weight loss might have on this relationship.
Subjects and Methods

Fifty obese adolescents with a mean age of 12.4 years (age range, 10–16 years) and 10 nonobese adolescents with a mean age of 12.2 years (age range, 10–14 years) were studied. All of the 10 nonobese adolescents were included in our previous report, while only 15 of 50 obese adolescents were part of the previous study.9 Obesity was defined as weight for height greater than the 75th percentile for age and sex and triceps and subscapular skinfolds greater than the 80th percentile for age and sex.10 To study the effect of weight loss on blood pressure, the obese subjects were randomly placed into one of three groups. Fifteen obese adolescents were placed in and completed a 20-week weight loss program consisting of diet and behavior change (diet group). The diet was a modification of the caloric exchange program and was designed to produce a weight loss of approximately 1 lb (0.45 kg)/wk. The behavior change component consisted of a 1-hour class each week for 20 weeks that centered on record keeping, stimulus control, changing eating typography, and reinforcement of altered behavior. Eighteen obese adolescents were placed in and completed a 20-week weight loss program consisting of diet, behavior change, and exercise (diet and exercise group). The diet and behavior change were as already described. The exercise program consisted of three 1-hour exercise classes per week for 20 weeks that centered around total body activities designed to maintain heart rate for at least 40 minutes at greater than 70 to 75% of maximal exercise heart rate. Seventeen obese adolescents were placed in a control group and received no weight loss program for 20 weeks. All 50 obese subjects were tested before and after the 20 weeks. The 10 nonobese adolescents were tested only once.

Experimental Protocol

All subjects were admitted overnight to the Clinical Research Center at the University of Michigan Hospitals. All adolescents fasted after 2200 of the evening preceding the study and were maintained in a supine position after 0400 on the morning of the study. A heparin lock was placed at 0730 while the adolescents were supine. Arterial pressure and heart rate were measured every 5 minutes for 30 minutes using a Critikon pressure monitor (Model 1165; Tampa, FL, USA) and an appropriate-sized cuff. The mean of the values of heart rate and blood pressure during the 30-minute rest period were used as the adolescents' blood pressure and heart rate. Mean arterial pressure also was calculated as diastolic pressure plus one third pulse pressure. At 0930, all adolescents had blood drawn for fasting insulin, fasting glucose, and serum electrolytes. All adolescents then received 100 g of oral glucose, and blood was drawn for glucose and insulin at 1030 and 1130. All adolescents then performed a multistaged discontinuous exercise test in the sitting position using an electronically braked bicycle ergometer. The first two stages were 15 and 30 W; subsequent work stages were increased by 30 W increments until the adolescent could no longer turn the pedals at 60 rpm. Each work rate was performed for 5 minutes, and there was a 3-minute rest period between every other work stage. The following parameters were measured during each stage of exercise: blood pressure, heart rate, tidal volume, oxygen uptake, and carbon dioxide production. Gas exchange was monitored continuously with an on-line measurement of ventilation rate (pneumotach; Validyne, Hampton, VA, USA), percentage of carbon dioxide (carbon dioxide analyzer; Beckman, Fullerton, CA, USA), and percentage of oxygen (oxygen analyzer; Applied Electrochemistry, Sunnyvale, CA, USA). Following the exercise test all adolescents were given lunch and then had body composition (percentage of fat) measured by hydrostatic weighing, as described by Katch et al.11 Dietary sodium intake was assessed on all adolescents by measuring the 24-hour urinary sodium excretion the day before the study.

Laboratory Procedures

Weight was measured in kilograms using a beam balance scale, and height was measured to the nearest 0.1 cm using a stadiometer. Sodium concentration was determined by flame photometry using lithium as an internal standard. Insulin was measured by radioimmunoassay, and serum glucose was measured by the glucose oxidase method.

Statistical Analysis

Statistical analysis was performed using Student's t test to compare differences between the nonobese and obese adolescents. To compare differences between the three obese groups at the end of the randomized 20-week treatment, a one-way analysis of variance with the Scheffe procedure for multiple comparisons on the pretest minus posttest values was employed. Systolic and diastolic blood pressures were adjusted for age and sex by use of the standard deviation score (Z) calculated according to the formula: Z = (X – X̄)/SD, where X = measured blood pressure; X̄ = mean of the expected blood pressure for age and sex (data from second National Health and Nutrition Examination Survey [NHANES II]); and SD = standard deviation of the expected blood pressure for age and sex. Linear regression analyses were performed before the weight loss programs using Z score systolic and diastolic blood pressures as the dependent variables, with fasting insulin, fasting glucose, sum of the insulins during an oral glucose tolerance test, 24-hour urinary sodium excretion, body weight, and percentage of fat as independent variables. The contribution of fasting insulin and body weight to the variance in Z score blood pressure was evaluated using partial correlation analysis. Linear regression analyses also were performed using the change (pretest minus posttest) in systolic, diastolic, mean, and Z score blood pressures as the dependent variables, with change in fasting insulin, change in fasting glucose, change in the sum of the insulins during an oral glucose tolerance test, change in body weight, and change in percentage of fat as the
Results
As can be seen in Table 1, we observed that when compared with the 10 nonobese adolescents, the 50 obese adolescents had significantly higher systolic, diastolic, and mean arterial pressures ($p = 0.001$). In addition to having elevated blood pressure, the obese adolescents had an increased 24-hour urinary sodium excretion ($p = 0.002$), an elevated fasting insulin concentration ($p = 0.001$), and an abnormal insulin response to a standard oral glucose tolerance test (sum of the insulins at 0, 1, and 2 hours post–oral glucose load; $p = 0.001$).

Since blood pressure in childhood is affected by both age and sex, to evaluate the relationship between arterial pressure and fasting serum insulin, fasting serum glucose, body weight, percentage of fat, and 24-hour urinary sodium excretion, Z scores for systolic and diastolic blood pressures were determined for the obese adolescents using data from the NHANES II. Table 2 contains the simple and partial correlations between Z scores for systolic and diastolic blood pressures and these variables. Both systolic and diastolic Z score blood pressures demonstrated moderate, significant correlations with fasting serum insulin, 24-hour urinary sodium excretion, body weight, and percentage of fat. When we controlled for fasting insulin activity there were significant partial correlations of Z score blood pressures only with body weight ($p < 0.01$) and percentage of fat ($p < 0.01$). Conversely, when we controlled for body weight, there were significant partial correlations of Z score blood pressures only with fasting insulin ($p < 0.01$) and sum of insulins after an oral glucose tolerance test ($p = 0.04$; see Table 2).

The effect of weight loss on these variables was evaluated by comparing the changes that occurred after 20 weeks of weight loss, induced either by diet and behavior change alone or in combination with exercise, with changes occurring after a 20-week control period (Table 3). No significant differences were noted between the three groups of obese adolescents before the weight loss program. Since the adolescents ranged in age from 10 to 16 years and varied in sex, there were large variations in body weight and height between adolescents. However, obesity, as assessed by body composition analysis (percentage of fat), exhibited much less variability between groups. When compared with the obese control group, the two 20-week weight loss groups (the treatment groups) each experienced a modest but significant decrease in body weight ($p = 0.001$). In fact, 31 of 33 weight loss subjects experienced some weight loss, whereas 16 of 17 obese control subjects gained weight. The modest decrease in body weight observed in the two weight loss groups was associated with marked changes in body composition since, regardless of weight loss, all of the subjects (both obese controls and weight loss groups) experienced a 3- to 4-cm increase in height. Percentage of fat, as determined by hydrostatic weighing, decreased from 42 ± 6 to 39 ± 6% ($p = 0.01$) in the diet group and from 40 ± 5 to 34 ± 4% ($p = 0.001$) in the diet and exercise group, whereas it remained unchanged in the obese control group.

Figure 1 demonstrates the change in cardiovascular fitness following the weight loss program. Only the diet and exercise group experienced a decrease in resting heart rate and a decrease in the heart rate and oxygen consumption at the 60-W submaximal exercise stage. These changes in heart rate and submaximal oxygen consumption were taken to mean that a training effect on the circulation had occurred in the diet and exercise group.

When compared with the obese control group, the two weight loss groups each experienced a significant decrease in fasting serum insulin ($p = 0.008$, diet group; $p = 0.001$, diet and exercise group). In addition, fasting insulin tended to decrease more in the diet and exercise group than in the diet-alone group ($p = 0.052$). Both weight loss programs also were associated with a significant improvement in the insulin response to an oral glucose tolerance test. The sum of the insulin values during an oral glucose tolerance test decreased in both weight loss groups (diet group: from 282 ± 165 to 204 ± 122 μU/ml, $p < 0.01$; diet and exercise group: from 255 ± 121 to 149 ± 155 μU/ml, $p < 0.001$) and remained unchanged in the obese control group (from 305 ± 177 to 342 ± 167 μU/ml; see Table 3). Other than improved cardiovascular fitness in the diet, behavior change, and exercise group (see

### Table 1. Anthropomorphic, Hemodynamic, and Biochemical Data for 10 Nonobese and 50 Obese Adolescents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonobese (n = 10)</th>
<th>Obese (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>12.2 ± 3.0</td>
<td>12.4 ± 3.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>42.2 ± 13</td>
<td>72.5 ± 13*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>148.2 ± 10.4</td>
<td>158 ± 9*</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>20 ± 7</td>
<td>41 ± 6*</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>104 ± 6</td>
<td>126 ± 13*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>60 ± 7</td>
<td>77 ± 11*</td>
</tr>
<tr>
<td>Mean</td>
<td>74 ± 8</td>
<td>95 ± 11*</td>
</tr>
<tr>
<td>Z systolic</td>
<td>−0.20 ± 0.54</td>
<td>1.2 ± 1.1*</td>
</tr>
<tr>
<td>Z diastolic</td>
<td>−0.58 ± 0.78</td>
<td>0.91 ± 1.1*</td>
</tr>
<tr>
<td>Fasting insulin (μU/ml)</td>
<td>5.5 ± 3.5</td>
<td>23 ± 8*</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>92 ± 7</td>
<td>95 ± 10</td>
</tr>
<tr>
<td>Sum insulins (μU/ml)</td>
<td>99 ± 59</td>
<td>272 ± 135*</td>
</tr>
<tr>
<td>Sum glucose (mg/dl)</td>
<td>317 ± 25</td>
<td>323 ± 69</td>
</tr>
<tr>
<td>UNa* (mEq/24 hr)</td>
<td>136 ± 14</td>
<td>214 ± 68*</td>
</tr>
</tbody>
</table>

Values are means ± SD. Some of the data from the 10 nonobese and 15 of the 50 obese adolescents was previously reported by use.  

Z = Z score; Sum insulins = sum of the insulin values during an oral glucose tolerance test; Sum glucose = sum of the glucose values during an oral glucose tolerance test; UNa* = 24-hour urinary sodium excretion.

*p < 0.01, †p < 0.05, compared with values in nonobese adolescents.
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improved insulin response to an oral glucose tolerance test; the diet and exercise group had a significantly
relationship existed between the change in blood pressure and the change that also occurred in each of the following measured variables: fasting insulin, body weight, percentage of fat, and sum of the insulins during an oral glucose tolerance test. The decrease in systolic, diastolic, and mean pressures during the 20-week program significantly correlated with the change in all of these variables (Table 4). However, when we statistically adjusted for the effect that the change in fasting serum insulin had on the change in blood pressure, a significant relationship between the change in blood pressure and the change in body weight and percentage of fat remained only in the diet group. Conversely, when we statistically corrected for the effect that change in body weight or percentage of fat, or both,
and blood pressure exists in both adults\textsuperscript{1,2} and children.\textsuperscript{14-15} In the present study, we have demonstrated that, when compared with our nonobese control group and the adolescents in NHANES II, our obese adolescents had a significantly elevated blood pressure (both systolic and diastolic; see Table 1). We have also demonstrated that weight loss resulted in a significant decrease in systolic (10 ± 10 mm Hg, \(p = 0.001\)), diastolic (6 ± 12 mm Hg, \(p = 0.001\)), and mean arterial pressures (8 ± 10 mm Hg, \(p = 0.001\)). In both of our weight loss groups (diet and behavior change alone or in combination with exercise) blood pressure decreased by the same magnitude (see Table 3). The decrease in blood pressure that we observed in our two weight loss groups was similar to that reported by Brownell et al.\textsuperscript{15}

Not only did our study demonstrate that weight loss results in a significant decrease in blood pressure in obese adolescents, but it also provided new information about the possible mechanism by which body weight and arterial pressure may be related. As can be seen in Table 2, the variables that significantly correlated with blood pressure (age and sex normalized) in our obese adolescents before weight loss were body weight, percentage of fat, fasting serum insulin, the sum of the insulins following an oral glucose tolerance test, and 24-hour urinary sodium excretion. However, when we controlled for either body weight or fasting serum insulin, 24-hour urinary sodium excretion was no longer significantly correlated to blood pressure.

An association between insulin and blood pressure has been suggested previously.\textsuperscript{7, 8, 10-18} Fournier et al.\textsuperscript{17} demonstrated a strong association between blood pressure and factors associated with glucose metabolism in nondiabetic subjects. They suggested a physiological role for insulin in blood pressure regulation. Modan et al.\textsuperscript{18} determined in a random population study that insulin resistance or hyperinsulinemia (or both) constitutes a common pathophysiological feature of obesity, glucose intolerance, and hypertension and thus may explain their ubiquitous association. Manicardi et al.\textsuperscript{7} demonstrated that middle-aged moderately obese persons with essential hypertension have a heightened plasma insulin response to oral glucose administration. Rose et al.\textsuperscript{8} reported that insulin may be a major factor in blood pressure regulation in the maturity-onset obe-
sity that develops following traumatic leg amputation in young men. Finally, Lucus et al.4 reported that insulin appears to play a major role in the regulation of blood pressure in very obese women. Our results both confirm and extend these observations. We have shown not only that, as in obese adults, there was a significant relationship between fasting serum insulin and blood pressure in obese adolescents, but also that with weight loss the blood pressure reductions paralleled the decrease in serum insulin concentration. Furthermore, we have demonstrated that the presence or absence of exercise in the weight loss program was important in determining the role of insulin in the regulation of blood pressure during weight loss. When weight loss was produced with a diet and behavior change program that did not incorporate exercise, although there was a relationship between the decrease in blood pressure and the decrease in fasting insulin, this relationship was no longer significant when the correlation was adjusted for the concomitant decrease in body weight or percentage of fat, or both. In contrast, when weight loss was produced with a diet, behavior change, and exercise program, the decrease in blood pressure was related to the decrease in fasting serum insulin independently of the change in body weight or percentage of fat, or both. The observations in our exercise group are in agreement with the previous findings of Krotkorwski et al.19 They found that, in 27 obese women who were physically trained for 6 months while receiving an ad libitum diet, the substantial reduction in blood pressure that occurred did not correlate with either the change in body fat or the woman’s initial blood pressure, but rather with the changes that occurred in plasma insulin and triglyceride.

Thus, in obese adolescents, obesity’s effect on blood pressure seems to operate both through insulin and other factors. When the weight loss was produced by caloric restriction alone, obesity’s effect on blood pressure appeared to operate through other factors in addition to insulin. However, when caloric restriction was accompanied with physical training, the relationship between change in blood pressure and change in either body weight or percentage of fat, or both, was attenuated while the relationship between the change in blood pressure and change in insulin was amplified (see Table 4). Others have previously reported that physical training, independently of weight or fat loss, is associated with a decrease in fasting plasma insulin as well as at most points during an oral glucose tolerance test.20-22 Such was also the case in our subjects (see Table 3).

The mechanisms whereby elevations in insulin could cause hypertension were not examined directly in our study. However, others have suggested an important role for insulin in blood pressure control through its enhancement of sodium retention and sympathetic nervous system activity. Herrera et al.23 and Andre and Crabbe24 have shown that insulin enhances sodium transport across isolated amphibian membranes. DeFronzo et al.4 have demonstrated that insulin enhances sodium reabsorption in the distal tubule in humans. Short-term administration of insulin has also been reported to increase sympathetic activity.5,23,26

In summary, our data are consistent with the hypothesis that the disturbances in carbohydrate metabolism that occur in many obese persons may also significantly contribute to the hypertension that frequently occurs in obese adolescents.
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