Insulin and Blood Pressure in Obesity

CHARLES P. LUCAS, JUAN A. ESTIGARRIBIA, LINDA L. DARGA, AND GERALD M. REAVEN

SUMMARY To assess factors in overweight persons that account for a tendency toward hypertension, 33 very obese women, 26 to 77 years of age, were studied. Blood pressures in these 33 women varied from low normal to mildly hypertensive. None of them had taken medication for high blood pressure, and none had diabetes mellitus. The effect of independent variables — age, body mass index (weight/height$^2$), fasting serum glucose levels, fasting serum insulin levels, and 24-hour urinary sodium excretion — on systolic and diastolic blood pressure was assessed. There was no correlation between sodium excretion and blood pressure. Age did not correlate with diastolic blood pressure but did correlate with systolic blood pressure when body mass index, serum glucose level, and insulin level were controlled. Diastolic blood pressure correlated with body mass index and serum glucose level, but only the latter remained significant when all independent variables were considered together. Both systolic and diastolic blood pressure were found to be significantly related to fasting serum insulin level ($r = 0.47$, $p = 0.005$ and $r = 0.68$, $p < 0.001$) even when age, weight, and serum glucose level were controlled ($r = 0.41$, $p = 0.025$ and $r = 0.62$, $p < 0.001$ respectively). The relation between serum insulin and blood pressure was more pronounced in those women with a family history of hypertension. These data indicate that insulin may play a major role in the regulation of blood pressure in obesity and that the previously accepted relation of weight to blood pressure may depend on blood levels of insulin. (Hypertension 7: 702-706, 1985)

KEY WORDS • obesity • blood pressure • insulin • sodium excretion

OBESITY is often associated with elevated blood pressure.$^{1,2}$ One of the factors thought to be responsible for this tendency toward hypertension is the often-observed hyperinsulinemia of obese subjects.$^{3,4}$ This viewpoint is bolstered by observations that short-term insulin administration to normal subjects results in sodium retention,$^{5,6}$ as well as increased blood pressure and heart rate.$^7$

The present study examines the relation of age, weight, sodium intake, serum glucose level, and serum insulin level to blood pressure in markedly obese subjects. The results from this cross-sectional analysis indicate that obese persons with higher blood pressure tend to have the highest serum insulin levels and that this association is independent of age, weight, and serum glucose level.

Subjects and Methods

Thirty-three obese women, ranging in age from 26 to 77 years, who were at least 33% above calculated ideal weight, were studied in the Wayne State University Obesity and Risk Factor Program. Their weights ranged from 166 to 411 lb, and the percentage above ideal weight was calculated from Bray's adaptation of the Metropolitan Life Insurance Company tables. Twenty-five women were white and eight were black. None had fasting serum glucose levels greater than or equal to 140 mg/dl, nor had any taken medication for diabetes mellitus. Most subjects were normotensive; only three had systolic blood pressure above 140 mm Hg or diastolic blood pressure above 90 mm Hg. None had taken antihypertensive medication. All subjects had normal values for blood urea nitrogen, serum creatinine, electrolytes, thyroid function, complete blood count, and urinalysis.

Subjects were selected from a group of patients who were referred for weight reduction and asked to sign a written informed consent. At the initial visit, a history was taken and a physical examination was performed. Individual height and weight measurements permitted calculation of body mass index (BMI) by the formula weight/height$^2$ (in kg and cm$^2$). The following data were collected at weekly intervals over the next 3 weeks: duplicate measurements of sitting systolic and diastolic blood pressure employing a mercury sphygmomanometer and 48-hour urine specimens to measure sodium and creatinine excretion. At the time of each subject's third blood pressure measurement,
blood was drawn after an overnight fast to measure serum glucose and insulin levels. Samples for insulin were collected in plain tubes. Blood was allowed to clot for 30 to 60 minutes before it was separated and frozen at −20 °C until the time of assay. Insulin was measured by radioimmunoassay, and serum glucose was measured by the glucose oxidase method. To minimize variation, the insulin determinations were made in all 33 samples on the same assay. Urinary sodium was analyzed by absorption photometry, and urinary creatinine was measured by autoanalyzer.

Creatinine was measured in each 48-hour urine sample to determine if collection instructions were followed correctly, and 48-hour urine collections with variations of more than 25% were discarded. The six sitting blood pressures were also averaged. These overall means for sodium excretion and blood pressure were used in the analysis of data.

Simple and multiple regression analyses were performed using the systolic and diastolic blood pressure for each subject as the dependent variable, with age, BMI, 24-hour urinary sodium excretion, fasting serum glucose level, and fasting serum insulin level as independent variables. The contributions of each of the independent variables to the variance in blood pressure was evaluated using partial correlation analysis. Mean group differences were assessed by Student's ttest. A p value of 0.05 or less was considered statistically significant.

Results

The 33 subjects had a mean age of 41.3 ± 12.3 years (range, 26-77 yr). (Values are reported here as means ± sd.) The average weight was 233 ± 50.4 lb (range, 166-411 lb), 33 to 190% above ideal weight according to Bray's adaptation of the Metropolitan Life Insurance Company tables. Average BMI was 39.5 ± 8.3 kg/m² (range, 28.1-70.7 kg/m²). Urinary sodium excretion averaged 161 ± 51.2 mEq/24 hours (range, 61-280 mEq/24 hr), while mean 24-hour creatinine excretion was 1.13 ± 0.32 g/24 hours (range, 0.60 to 1.77 g/24 hr). Mean fasting serum insulin level equaled 17 ± 10.7 μU/ml (range, 4-52 μU/ml). The normal value for fasting serum insulin for nonobese subjects in our laboratory is 8 μU/ml ± 2 SEM. Mean serum glucose was 95 ± 7.6 mg/dl (range, 76-112 mg/dl). Mean systolic and diastolic blood pressures were 124 ± 11.2 mm Hg (range, 102-158 mm Hg) and 81 ± 8.8 mm Hg (range, 70-107 mm Hg) respectively.

Table 1 contains the simple correlations, using Pearson's r between systolic or diastolic blood pressure and 24-hour sodium excretion, age, BMI, fasting serum glucose level, fasting serum insulin level, and the serum insulin/glucose ratio, calculated for all 33 obese women and for the 21 with a family history of hypertension. Neither systolic nor diastolic blood pressures were significantly related to sodium excretion or age. Diastolic, but not systolic, blood pressure showed a significant relation to BMI (r = 0.45, p = 0.008 in all 33 women; r = 0.45, p = 0.041 in the 21 with a reported family history of hypertension). Serum glucose level did not correlate with systolic blood pressure in the 33 women, but correlated negatively in the 21 who reported a family history of hypertension (r = −0.48, p = 0.026). Serum glucose level was negatively correlated with diastolic blood pressure in all 33 subjects (r = −0.36, p = 0.042) as well as in the 21 with a family history of hypertension (r = 0.60, p = 0.004). Both systolic and diastolic blood pressure were significantly correlated with fasting serum insulin level in all 33 subjects (r = 0.47, p = 0.005 for systolic; r = 0.68, p < 0.001 for diastolic blood pressure); and these relationships were slightly more pronounced in those 21 women who reported a family history of hypertension (r = 0.67, p < 0.001 for systolic; r = 0.79, p < 0.001 for diastolic blood pressure). The correlations that were found between the insulin/glucose ratio and systolic and diastolic blood pressure were also significant in all 33 women (r = 0.48, p = 0.005 for systolic; r = 0.72, p < 0.001 for diastolic blood pressure) as well as in the 21 with a family history of hypertension (r = 0.68, p < 0.001 for systolic; r = 0.82, p < 0.001 for diastolic blood pressure).

**Table 1. Simple Correlations of Sitting Systolic and Diastolic Blood Pressure with Urinary Sodium Excretion, Age, Body Mass Index, Serum Glucose Level, Serum Insulin Level, and Insulin/Glucose Ratio in all 33 Subjects and in 21 with a Family History of Hypertension**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All 33 women</th>
<th>21 with family history of hypertension</th>
<th>All 33 women</th>
<th>21 with family history of hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Urinary sodium excretion</td>
<td>−0.05</td>
<td>0.793</td>
<td>−0.19</td>
<td>0.674</td>
</tr>
<tr>
<td>Age</td>
<td>0.28</td>
<td>0.108</td>
<td>0.20</td>
<td>0.40</td>
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<tr>
<td>Body mass index</td>
<td>0.33</td>
<td>0.059</td>
<td>0.43</td>
<td>0.053</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>−0.18</td>
<td>0.329</td>
<td>−0.48</td>
<td>0.026*</td>
</tr>
<tr>
<td>Fasting serum insulin</td>
<td>0.47</td>
<td>0.005*</td>
<td>0.67</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Serum insulin/glucose ratio</td>
<td>0.48</td>
<td>0.005*</td>
<td>0.68</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Statistically significant at p < 0.05.
Average insulin levels were higher in those with a family history of hypertension than in those with no family history of hypertension (18.7 ± 2.3 vs 12.8 ± 5 μU/ml), but this difference was not statistically significant. Average systolic and diastolic blood pressures were similar in these two groups (123.3 ± 11.2 vs 126.5 ± 11.3 mm Hg for systolic and 82.5 ± 6.5 vs 80.0 ± 7.7 mm Hg for diastolic blood pressure).

Table 2 contains the partial correlations between blood pressure and age, BMI, serum glucose level, and serum insulin level in all 33 women and in the 21 who reported a family history of hypertension (24-hr sodium excretion was excluded from this analysis because it did not correlate with blood pressure). When we controlled for all other variables in the 33 women, there was a partial correlation of age with systolic (r = 0.41, p = 0.023), but not diastolic, blood pressure. While the simple correlation of BMI with diastolic blood pressure was significant, the partial correlation of BMI with either systolic or diastolic blood pressure was not. The simple negative correlation between serum glucose level and systolic blood pressure also disappeared in the partial correlation analysis, while that between serum glucose level and diastolic blood pressure remained significant in all 33 women as well as in the 21 who reported a family history of hypertension (r = −0.44, p = 0.015 and r = −0.48, p = 0.045 respectively). The correlation between serum insulin level and systolic blood pressure remained significant when the other factors were controlled (r = 0.41, p = 0.025 in all 33 women and r = 0.58, p = 0.011 in the 21 with a reported family history of hypertension). Similarly, the partial correlation of serum insulin level with diastolic blood pressure remained significant in all 33 women (r = 0.62, p < 0.001) and in the 21 who reported a family history of hypertension (r = 0.75, p < 0.001).

Discussion

Obese persons have a higher likelihood of becoming hypertensive than do the nonobese, and this finding agrees with the observation of higher morbidity and mortality in the overweight owing to cardiovascular disease. To explain this increase in blood pressure, Dahl and colleagues and, later, others found increased sodium intake in their obese subjects. Dahl and his co-workers also observed that salt restriction normalized arterial pressure in their group of subjects, while a low calorie intake had no effect on blood pressure when a diet high in sodium was maintained. Other investigators, however, have demonstrated that weight loss is associated with a reduction of blood pressure that is independent of sodium intake and accompanied by a decrement in norepinephrine and plasma renin activity.

Using the average of three 48-hour urine collections, we could find no significant relation between sodium excretion and either systolic or diastolic blood pressure. The relationship between 24-hour sodium excretion and blood pressure has been examined by numerous investigators, and our findings are in accord with most but not all studies. Altschul and Grommet, who studied a group of lean, normotensive subjects, also found that urinary sodium excretion did not correlate significantly with blood pressure. When they reexamined their data in a subgroup with a family history of hypertension, however, they observed a highly significant correlation between blood pressure and urinary sodium excretion, a finding not present in their subgroup with no family history of hypertension. We failed to obtain an association between sodium excretion and blood pressure in our group of subjects even when we examined the data of those who reported a family history of hypertension. This disparity between our findings and those of Altschul and Grommet suggests that a different mechanism might control blood pressure in lean and obese persons. While our findings also appear to contradict those of Dahl and colleagues, it should be noted that our study was cross-sectional while that of Dahl and co-workers was interactive. Thus, while sodium intake would not appear to explain differences in blood pressure in our obese and essentially normotensive subjects, "excessive" sodium intake superimposed on other more fundamental mechanisms could still influence the level of blood pressure in obesity.

Epidemiological studies have demonstrated that age is positively correlated with blood pressure, which is partly related to the increasing adiposity associated with aging. Weight gain alone, however, does not completely account for the rise in blood pressure seen in older persons. In our subjects, the partial correlation of systolic blood pressure with age was significant and may have been due to the loss of arterial compliance that occurs with aging. On the other hand, there was no significant relationship in this group of obese

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<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>With systolic BP</td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>0.41</td>
<td>0.023*</td>
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<tr>
<td>Body mass index</td>
<td>0.16</td>
<td>0.406</td>
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<tr>
<td>Serum glucose</td>
<td>-0.28</td>
<td>0.131</td>
</tr>
<tr>
<td>Serum insulin</td>
<td>0.41</td>
<td>0.025*</td>
</tr>
<tr>
<td>With diastolic BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.19</td>
<td>0.321</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.22</td>
<td>0.241</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>-0.44</td>
<td>0.015*</td>
</tr>
<tr>
<td>Serum insulin</td>
<td>0.62</td>
<td>&lt;0.001*</td>
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</tbody>
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*Statistically significant at p < 0.05.
women between age and diastolic blood pressure using simple or partial correlations.

We did find that BMI was significantly related to diastolic blood pressure, which agrees with the findings of investigators describing a positive relation between blood pressure and either weight or total fat mass. In our group of 33 women, however, weight was not significantly related to blood pressure when the correlation was adjusted for age, serum glucose level, and serum insulin level. Thus, these results suggest that obesity's effect on blood pressure operates through other factors.

An association between insulin and blood pressure was suggested in 1976 by Berglund et al., who observed that 50-year-old, untreated hypertensive men had greater fat mass, more glucose intolerance, and higher fasting serum insulin levels than did normotensive controls. When a subgroup of their hypertensive men was compared with a subgroup of normotensive controls with similar BMI values, a higher mean serum insulin level was still apparent in the hypertensive group. Our results both confirm and extend these observations. Berglund et al. controlled for the effect of age by observing people near the age of 50; our study controlled for the effect of age on blood pressure by examining partial correlations that included age as a variable.

DeFronzo's studies suggest an important role for insulin in blood pressure control based on the sodium-retaining property of the hormone. He demonstrated this effect in isolated dog and intact human kidneys at concentrations of insulin within the physiological range. Insulin has also been shown to affect sodium transport across isolated membranes of amphibia. Therefore, the hyperinsulinemia of some obese subjects could contribute to the higher blood pressure of obesity by its direct sodium-retaining action on the kidney.

Another mechanism by which insulin could elevate blood pressure has been suggested by Rowe et al., who observed the effect of insulin infusions on blood pressure of normal subjects. Keeping serum glucose level constant, they observed that insulin not only increased blood pressure, but also elevated serum norepinephrine and other indices of sympathetic nervous system activity, such as pulse and pulse pressure. These findings suggest that insulin may control blood pressure in obese subjects by its direct effect on renal sodium retention or by releasing norepinephrine, the latter resulting in arterial smooth muscle contraction and renal sodium retention. Obese persons are known to have increased levels of insulin and norepinephrine. Simultaneous measurements of insulin and norepinephrine are needed to strengthen this hypothesis.

The relation between serum glucose level and blood pressure was of low order and not constant. However, the significant negative simple and partial correlations of serum glucose level and diastolic blood pressure suggest an independent, currently unaccounted for, effect of glucose on blood pressure. The highly positive and significant relation between blood pressure and the insulin/glucose ratio indicates that an interaction of insulin and glucose may have special importance. While these data of insulin and blood pressure do not prove cause and effect, they provide insight into support for the concept that blood pressure regulation in obesity may be controlled in part by the tendency of some overweight persons to secrete increased amounts of insulin and to have a higher degree of insulin resistance.

References


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