Is Insulin the Link Between Hypertension and Obesity?

A. Richard Christlieb, Andrzej S. Krolewski, James H. Warram, and J. Stuart Soeldner

SUMMARY Oral glucose tolerance tests with plasma glucose and insulin determinations were performed on 195 patients with impaired glucose tolerance. Patients were divided into three groups according to blood pressure levels: normal, below 140/90 mm Hg; diastolic hypertension, diastolic pressure above 90 mm Hg; and systolic hypertension, systolic pressure above 140 and diastolic pressure below 90 mm Hg. Sex, age, and glucose levels were similar among the groups. By contrast, serum insulin levels were significantly elevated for the patients with diastolic hypertension (p < 0.01). This difference persisted after correction for body weight. These results suggest a causal relationship between the level of circulating insulin and diastolic blood pressure, and support the concept that hyperinsulinemia may be the common link in the clustering of hypertension, diabetes, and obesity.

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KEY WORDS • impaired glucose tolerance • blood pressure • hyperinsulinemia

Hypertension appears to be more prevalent in patients with diabetes mellitus than in the general population. The association cannot be entirely secondary to nephropathy since it is present even in patients with recent onset of diabetes and before the development of nephropathy. Moreover, an association between blood glucose and blood pressure was demonstrated in chemical diabetes, a term that corresponds approximately to impaired glucose tolerance (IGT) in the newer nomenclature. It is unlikely that this association can be explained by hyperglycemia. Hyperinsulinemia is a common feature of IGT, and because insulin increases renal tubular reabsorption of sodium, it may contribute to the hypertension.

The present study, showing an association between insulin levels and blood pressure in a population of patients with IGT, provides evidence that insulin may be involved in the pathogenesis of hypertension in patients with diabetes mellitus.

Materials and Methods

The study group consisted of 195 patients aged 30 to 69 years who were referred to the Joslin Clinic between 1965 and 1971 and had chemical diabetes (asymptomatic, fasting blood glucose below 120 mg/dl, but abnormal oral glucose tolerance. The oral glucose tolerance test (OGTT) was judged abnormal if any one blood glucose value at a given time interval exceeded the following: fasting, 100 mg/dl; 30 minutes, 160 mg/dl; 60 minutes, 160 mg/dl; 120 minutes, 120 mg/dl; and 180 minutes, 110 mg/dl. The patients agreed to participate in a random clinical trial on the effects of long-term therapy with oral glucose-lowering agents on the dynamics of OGTTs. Some results of the study were reported previously.

During the second study visit to the clinic (before any treatment was initiated), these patients had an OGTT and a standard physical examination that included measurements of height, weight, and blood pressure. In preparation for the OGTT, the patients consumed their usual diet, which contained at least 100 to 200 g carbohydrate for 3 or more days. Between 0800 and 0900 hours, after an overnight fast, a blood sample was obtained. Dextrose (100 g) was administered orally, and venous blood samples were obtained at 30, 60, 120, and 180 minutes. Glucose was measured in whole blood by the Technicon (Tarrytown, NY, USA) autoanalyzer modification of the method of Hoffman, and serum insulin was measured by the double antibody method of Soeldner and Slone.

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less than 90 mm Hg; and normal blood pressure if systolic pressure was below 140 and diastolic below 90 mm Hg. Table 1 shows the number of patients and the frequency of each type of hypertension according to age. Percentage of ideal body weight was calculated by a conversion formula from body mass index. After completion of the initial test, patients were randomly assigned to five therapeutic subgroups, and measurements similar to the initial test were repeated every year.

### Table 1. Frequency of Hypertension in the Study Group According to Age at Examination

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>No. of patients</th>
<th>Systolic hypertension (%)</th>
<th>Diastolic hypertension (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>32</td>
<td>12.5</td>
<td>15.6</td>
</tr>
<tr>
<td>40-49</td>
<td>78</td>
<td>6.4</td>
<td>28.2</td>
</tr>
<tr>
<td>50-59</td>
<td>65</td>
<td>26.1</td>
<td>26.1</td>
</tr>
<tr>
<td>60-69</td>
<td>20</td>
<td>45.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Totals</td>
<td>195*</td>
<td>17.9</td>
<td>25.1</td>
</tr>
</tbody>
</table>

*Men 138, women 57.

In the present report, only data from the initial and the first-year follow-up examination are used. In the analysis, each type of hypertension was compared independently with the nonhypertensive group. Statistical significance was assessed by using two-tailed t tests for means from two independent samples. Analysis of covariance was used to adjust fasting insulin levels for confounding by other differences among groups.

### Results

Table 2 compares several characteristics of the hypertensive groups with the non-hypertensive group. By design, patients in both hypertensive groups had higher systolic blood pressures than those in the non-hypertensive group, and the patients with diastolic hypertension had higher mean diastolic blood pressure as well. The proportion of female patients and the mean age were also higher among hypertensive patients than individuals with normal blood pressure. The 2-hour blood glucose levels were slightly higher in both hypertensive groups, but the differences were not statistically significant. Only patients with diastolic hypertension had significantly higher mean fasting insulin levels and significantly higher percentages of ideal body weight.

Mean blood glucose and serum insulin levels at each time point of the OGGT are plotted in Figure 1 for each group separately. While there were no significant differences in the blood glucose levels at any time point, serum insulin levels in patients with diastolic hypertension were elevated, and at fasting, 2 hours, and 3 hours the differences were statistically significant (p < 0.01).

Analysis of covariance was used to adjust the insulin

### Table 2. Characteristics of the Study Group According to Blood Pressure Category

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normal blood pressure (n = 111)</th>
<th>Systolic hypertension (n = 35)</th>
<th>Diastolic hypertension (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female patients (%)</td>
<td>33.3</td>
<td>42.9</td>
<td>42.9</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46±8</td>
<td>53 ±9*</td>
<td>49±8*</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>121±10</td>
<td>146 ±10*</td>
<td>150 ±19*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>76±6</td>
<td>79 ±7</td>
<td>98 ±9*</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>92±17</td>
<td>91 ±16</td>
<td>88 ±18</td>
</tr>
<tr>
<td>Blood glucose 2 hr after 100 g oral glucose challenge (mg/dl)</td>
<td>131±50</td>
<td>142 ±59</td>
<td>138 ±48</td>
</tr>
<tr>
<td>Fasting serum insulin (μU/ml)</td>
<td>17±12</td>
<td>19 ±11</td>
<td>29 ±18†</td>
</tr>
<tr>
<td>Ideal body weight (%)</td>
<td>117±21</td>
<td>114 ±25</td>
<td>137 ±32‡</td>
</tr>
</tbody>
</table>

Values expressed as means ± sd.

Probability values are in comparison with those for the group with normal blood pressure: *p < 0.001; †p < 0.05; ‡p < 0.01.

**Figure 1.** Mean blood glucose (top) and serum insulin (bottom) during oral glucose tolerance test in normotensive patients and in patients with systolic and with diastolic hypertension. Insulin levels were significantly higher in patients with diastolic hypertension at fasting, 2 hours, and 3 hours of OGGT (p < 0.01). IRI = immunoreactive insulin.
levels during OGTT for group differences in sex, age, percentage of ideal body weight, and 2-hour blood glucose (Table 3). Individuals with diastolic hypertension (who also had high systolic blood pressure; see Table 2) had higher insulin levels during OGTT than those with normal blood pressure. The difference for fasting insulin levels remained highly significant ($p < 0.0001$), whereas at 2 hours and 3 hours the differences were adjusted downward and were not quite significant.

Measurements similar to those done for the initial examination were repeated in 113 individuals 1 year later. When these patients were classified according to blood pressure values during the second examination, the patterns of insulin secretion among the categories were similar to those shown in Table 3.

To study further the association between fasting insulin levels and hypertension, the study group was stratified into nonobese and obese subjects showed that obese persons with diastolic hypertension had insulin levels that were significantly elevated compared with obese normotensive individuals. In addition, similar results were found when the subjects were restudied 1 year later.

The mechanism whereby elevations in insulin could cause hypertension were not examined in this study, but two potential mechanisms can be proposed on the basis of results from earlier reports. First, insulin-induced renal reabsorption of sodium can result in sodium-dependent hypertension by mechanisms previously reviewed. A second, as suggested by Tarazi, hyperresponsiveness of a sodium-replete vasculature to sympathetic stimulation can increase peripheral vascular resistance. Insulin was reported to increase sympathetic activity even in the absence of hypoglycemia. Therefore insulin could be a hypertensive hormone through its enhancement of sympathetic activity.

#### Discussion

An etiological association between hypertension and hyperinsulinemia was suggested, but has not been verified by any clinical or epidemiological study. While the population described here cannot provide that verification, the observed association is consistent with a causal relationship between the level of circulating insulin and diastolic blood pressure. Since the population studied all had so-called chemical diabetes (IGT), the presence of this association in the general population remains to be demonstrated.

It is unlikely that lack of adjustment of cuff size could account for these findings. The results of the separate analysis in which the study group was stratified into nonobese and obese subjects showed that obese persons with diastolic hypertension had insulin levels that were significantly elevated compared with obese normotensive individuals. In addition, similar results were found when the subjects were restudied 1 year later.

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Quite apart from these hypothetical mechanisms, the finding that elevated insulin is associated with elevated diastolic blood pressure can explain the interrelationships among hypertension, diabetes, and obesity that have been observed in various studies. In patients with glucose intolerance (but not insulin dependence),
Insulin was reported to be highest in those with IGT and remains elevated with increasing severity of glucose intolerance until the level of fasting hyperglycemia is 150 mg/dl. Reporting on blood pressure and glycemia in two populations, Jarrett et al. found in one population a stepwise increase in systolic and diastolic blood pressures from normoglycemic individuals to those with borderline diabetes and then to persons with newly diagnosed diabetes. In subjects with previously diagnosed diabetes, blood pressures were similar to those in individuals with normoglycemia. Although this latter finding was not confirmed in their second population, a reduction in blood pressure once diabetes is established can be explained if the insulin effect on blood pressure is reversible. Although insulin is elevated early in diabetes, it decreases with established diabetes, and the postprandial insulin response is small in patients with a fasting glucose of 150 mg/dl or more.

If the latent period of diabetes is short and the associated hyperinsulinemia with sodium retention disappears as overt diabetes is established, one would expect the insulin-induced elevation in blood pressure to fall. The latent period of diabetes during which insulin may be elevated can persist for many years in some patients, however. In this circumstance, the interval may be long enough to permit other hypertensive mechanisms to become established, with the result that hypertension is sustained despite the appearance of overt diabetes and a fall in insulin level.

In obese individuals, the frequency of both hypertension and non-insulin-dependent diabetes is increased. Furthermore, obesity is accompanied by insulin resistance and elevated fasting and postprandial insulin levels that fall significantly after weight reduction. These observations led DeFronzo to postulate that the hyperinsulinemia of obesity initiates the hypertensive process. The current results lend support to this hypothesis.

In summary, the results reported here support the concept that hyperinsulinemia may be the common link in the clustering of hypertension, obesity, and diabetes mellitus.

References
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