Insulin Resistance in Patients With Essential Hypertension Can Occur in the Absence of Microalbuminuria

Jeannie W. Yip, Clare Jones, Francesco Facchini, Ida Chen, and Gerald M. Reaven

This study was initiated to see if the presence of resistance to insulin-mediated glucose disposal, glucose intolerance, and hyperinsulinemia in healthy patients with hypertension was dependent upon the coexistence of microalbuminuria. For this purpose we compared these variables in 68 individuals: 34 patients with hypertension and 34 normal volunteers. The two groups were similar in terms of age, gender distribution, body mass index, and ratio of waist to hip girth. Furthermore, although four patients with hypertension satisfied the criteria for microalbuminuria, as compared to one normal volunteer, the urinary albumin excretion (UAE) rates were similar in the two groups (8.07 ± 1.08 vs 7.67 ± 1.12 µg/min). Despite the similarities, both the plasma glucose and insulin responses to a 75 g oral glucose challenge were significantly higher (P < .01) in those with high blood pressure. In addition, the steady-state plasma glucose (SSPG) concentrations at the end of a 180 min continuous infusion of somatostatin, insulin, and glucose was significantly higher in those with hypertension (156 ± 13 vs 107 ± 10 mg/dL, P < .01). Since the steady-state plasma insulin levels were also somewhat higher in those with hypertension, the higher SSPG values indicate that these individuals were relatively insulin resistant as compared to the control population. Finally, UAE rates were not correlated with either the plasma glucose or insulin responses to oral glucose or to the SSPG concentrations—either in the entire group of 68, or when the 34 patients in each group were considered separately. These results demonstrate that insulin resistance, glucose intolerance, and hyperinsulinemia can occur independently of microalbuminuria in patients with hypertension. Am J Hypertens 1996;9:959-963

KEY WORDS: Insulin, hyperinsulinemia, microalbuminuria, glucose intolerance.

Patients with hypertension, as a group, tend to be resistant to insulin-mediated glucose disposal, glucose intolerant, hyperinsulemic, and dyslipidemic—with higher plasma triglyceride (TG) and lower high density lipoprotein (HDL)-cholesterol concentrations.1-3 Since all of these changes have been shown4-7 to increase risk of coronary heart disease (CHD), it seems likely that they contribute to the increased prevalence of CHD in patients with high blood pressure.8 In this context, recent demonstrations from longitudinal studies in both diabetic and nondiabetic populations that micro-
albuninuria is associated with similar metabolic changes, as well as with CHD, is of great interest.9-14 Although both insulin resistance and microalbuminuria appear to be associated with increased risk for CHD, the relationship between the two variables in question is not well-understood. For example, results of some studies have suggested that insulin resistance in patients with non-insulin-dependent diabetes mellitus (NIDDM) is dependent upon the coexistence of microalbuminuria,15,16 whereas other investigators have found the two variables to be independent of each other.17,18 Since microalbuminuria has been reported to be present in 20% to 40% of patients with high blood pressure,19-24 it seemed important to define the relationship, if any, between insulin resistance and microalbuminuria in patients with uncomplicated essential hypertension. More specifically, we wished to see if the existence of insulin resistance in patients with high blood pressure could occur in the absence of microalbuminuria. The present study was initiated to accomplish this task.

MATERIALS AND METHODS

Nonobese (body mass index ≤ 30 kg/m²), nondiabetic, patients with essential hypertension were recruited from local medical clinics and the surrounding community. Essential hypertension was defined as either a blood pressure > 140/90 mm Hg or receiving treatment with at least two antihypertensive medications, in the absence of evidence of secondary hypertension. Healthy volunteers with normal blood pressure who responded to newspaper advertisements calling for human subjects to participate in metabolic research studies served as controls. All the participants were in good general health as determined by history and physical examination (with the exception of hypertension), and had complete blood count, serum electrolytes and liver function tests within the normal limits, with a urinalysis negative for protein and blood. Patients with a past history of angina, myocardial infarction or cerebral vascular disease were excluded. The experimental protocol was approved by the Institutional Review Board of the Stanford University Medical Center and written informed consent was obtained before initiation of any study. Thirty-four subjects were recruited in each group, and their baseline clinical characteristics are shown in Table 1. It can be seen from these data that the two groups were reasonably comparable in terms of gender distribution, age, body mass index (BMI), and ratio of waist to hip girth (WHR). In contrast, systolic and diastolic blood pressure were higher in the hypertensive group, despite the fact that antihypertensive drugs were being used by 20 of the patients.

Experimental measurements were performed during two admissions to the Stanford University General Clin-
compared to one normal volunteer, satisfied the criteria for the designation of microalbuminuria.

Total integrated plasma glucose and insulin responses following the 75 g oral glucose challenge are shown in the left panel of Figure 1. These results demonstrate that patients with high blood pressure had significantly higher ($P < .01$) plasma glucose and insulin responses than did the normal volunteers.

The results of the insulin suppression test are displayed in the right panel of Figure 1. These data indicate that the SSPG values were higher in those with hypertension ($P < .01$), despite somewhat higher SSPI concentrations. Although these data make it clear that normotensive individuals, as a group, were less insulin resistant than patients with hypertension, this was not true of all normal subjects. A frequency distribution of SSPG values is given in Table 2, and demonstrates that the greatest differences between the two groups were seen at the extremes. Thus, approximately five times as many normotensive individuals could be classified as being insulin sensitive on the basis of an SSPG value $< 60$ mg/dL (29% vs 6%). In contrast, approximately 3 times as many patients with hypertension had an SSPG value $> 180$ mg/dL (41% vs 14%) and were at the extreme end of the insulin resistance scale.

The results presented demonstrate that although UAE rates were similar in the two groups, patients with high blood pressure were relatively insulin resistant, glucose intolerant, and hyperinsulinemic. In an effort to further explore the possibility of a relationship between UAE and the metabolic variables in question, Pearson correlation coefficients were calculated. The results of this analysis (data not shown) indicated that UAE rates were not correlated with either the glucose or the insulin responses to oral glucose or to the SSPG values. This observation was true when the 68 subjects were considered as a whole, as well as when the two groups of 34 were considered separately.

**DISCUSSION**

The results of this study have shown that patients with hypertension were relatively insulin resistant, glucose intolerant, and hyperinsulinemic as compared to a matched group of normal individuals. Furthermore, all of the observed metabolic changes appeared to be independent of variations in UAE. Consequently, we can conclude that insulin resistance does occur in patients with uncomplicated high blood pressure in the absence of microalbuminuria. However, it should be emphasized that our results do not negate the possibility that the degree of insulin resistance in any given individual with hypertension might not be greater if they also were microalbuminuric. Indeed, the SSPG values in two of the four hypertensive subjects with microalbuminuria were $> 180$ mg/dL, and between 120 and 180 mg/dL in the other two. Thus, based upon the results in Table 2, it is obvious that these four subjects were in the upper distribution of SSPG values in the entire group of patients with high blood pressure; an observation consistent with the view that magnitude of insulin resistance will be greater in individuals who are both hypertensive and microalbuminuric. Alternatively, it could be argued that although microalbuminuria may not cause insulin resistance, insulin resistance predisposes an individual to develop albuminuria. This is obviously an important issue, and one not addressed by our study. However, relevant to this question are the observa-

**FIGURE 1.** Mean (± SEM) total integrated plasma glucose and insulin response to a 75 g oral glucose challenge and the steady-state insulin (SSPI) and glucose (SSPG) responses during the insulin suppression test (IST).
patients with hypertension or 34 normal volunteers.

over a wide range of blood pressure, or in either 34

between insulin resistance and UAE rate in 68 subjects

SSPG values were similar in the treated and untreated

patients. This seems most unlikely in that the

majority of patients were being treated with ei-

other angiotensin converting enzyme inhibitors or cal-

cium channel blockers, or both; drugs which have

been associated with either no change, or actually an

increase in insulin sensitivity.27,28 Furthermore, mean

insulinemic microalbuminuria. A new risk indicator for


Kuusisto J, Mykkanen L, Pyorala K, Laakso M: Hyper-

The possibility that this discrepancy was due to

our inclusion of patients with treated hypertension

seems unlikely in light of published data reporting a

prevalence of microalbuminuria in 23% of a group of

92 treated patients with high blood pressure23 versus

26% in 95 untreated patients.24 Furthermore, the UAE

rates were comparable in the treated (6.4 ± 1 µg/min)

versus the untreated (9.4 ± 1 µg/min) patients

with hypertension. Finally, UAE rates in those treated

only with a calcium channel blocker (n = 3) were

relatively similar compared to patients (n = 6) receiv-

ing only angiotensin converting enzyme inhibitors

(7.3 ± 1 v 5.2 ± 1 µg/min).

It could also be argued that the insulin resistance

present in the patients with hypertension was due to

the fact that 20 of the 34 were receiving antihyper-

tensive treatment. This seems most unlikely in that the

vast majority of patients were being treated with ei-

ither angiotensin converting enzyme inhibitors or cal-

cium channel blockers, or both; drugs which have

been associated with either no change, or actually an

increase in insulin sensitivity.27,28 Furthermore, mean

SSPG values were similar in the treated and untreated

patients.

In conclusion, we could not detect any correlation

between insulin resistance and UAE rate in 68 subjects

over a wide range of blood pressure, or in either 34

patients with hypertension or 34 normal volunteers.

However, the 34 patients with hypertension were in-

sulin resistant, glucose intolerant, and hyperinsuleni-

mic when compared to 34 normotensive individuals. Since

estimates of both total body (BMI) and regional adiposity (WHR) were similar in the two groups, these data
demonstrate that the insulin resistance in patients with
hypertension is not dependent upon the coexistence of microalbuminuria.

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mediated glucose uptake by extrahepatic tissue is a

TABLE 2. FREQUENCY DISTRIBUTION
OF SSPG VALUES

<table>
<thead>
<tr>
<th>SSPG Value</th>
<th>Normotensive (n [%])</th>
<th>Hypertensive (n [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 mg/dL</td>
<td>10 (29)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>60-120 mg/dL</td>
<td>13 (38)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>120-180 mg/dL</td>
<td>6 (18)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>&gt;180 mg/dL</td>
<td>5 (15)</td>
<td>14 (41)</td>
</tr>
</tbody>
</table>

SSPG, steady-state plasma glucose.
hallmark of NIDDM patients who have or will develop hypertension and microalbuminuria. Diabetes 1994; 43:491–499.


