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# Insulin Resistance, Glucose Intolerance and Hyperinsulinemia in Patients with Hypertension

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**Plasma glucose and insulin responses to an oral glucose challenge and insulin-stimulated glucose uptake were measured in 47 age-, weight-, and sex-matched lean white men (16 with normal blood pressure, 14 with untreated hypertension, nine treated with a thiazide diuretic only, and eight treated with combined diuretic and β-adrenergic antagonist drugs). Following a 75-g glucose dose, plasma glucose and insulin were measured for a three-hour period. In separate studies, insulin-stimulated glucose uptake was estimated by measuring the steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations achieved during the last 30 minutes of a 180-minute continuous infusion of somatostatin, insulin, and glucose (insulin suppression test). Under these conditions endogenous insulin secretion was suppressed, and differences in SSPG concentration allowed comparisons of the abilty of exogenous insulin to stimulate disposal of an identical glucose load in different individuals. The results indicated that men with untreated hypertension had significantly elevated plasma glucose ($P < .001$) and insulin concentrations ($P < .001$) after an oral challenge compared to normal volunteers. Mean SSPG concentrations were also higher ($P < .05$) than normal in patients with untreated hypertension. Furthermore, plasma glucose and insulin concentrations after the oral glucose challenge and SSPG concentration during the insulin suppression test were higher in treated than in untreated patients with hypertension. These results confirm earlier observations that untreated patients with hypertension are insulin resistant, hyperglycemic, and hyperinsulinemic compared to a well-matched normotensive control group, and suggest that conventional treatment programs for lowering blood pressure many exaggerate these metabolic defects. Am J Hypertens 1989;2:419–423**

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During the past few years several reports have been published showing that glucose intolerance and/or hyperinsulinemia are commonly seen in patients with high blood pressure.[1–5] More recently it has also been demonstrated that resistance to insulin-stimulated glucose uptake is present in patients with hypertension.[4,5] The majority of the available data are derived from measurements of subjects with untreated hypertension, and what happens to these metabolic abnormalities when efforts are made to lower blood pressure with antihypertensive drugs is not well understood. Given current emphasis on the vigorous treatment of hypertension, it is important to know what happens to glucose and insulin metabolism when this goal is accomplished. In this regard we are only aware of one relevant publication,[4] which suggested that both hyperinsulinemia and insulin resistance persisted in patients whose blood pressure had been controlled with antihypertensive drugs. However, a variety of different drugs were used in this study, making it

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difficult to differentiate between the effect of decreasing blood pressure, per se, from that of the drugs used to accomplish this task. The present study was initiated to address this issue, and involved measurement of the plasma glucose and insulin response to an oral glucose challenge, as well as the ability of insulin to promote disposal of a glucose load in a normal control population, individuals with untreated hypertension, and patients with hypertension, treated with either a thiazide diuretic alone, or diuretic plus a $\beta$-adrenergic antagonist. The results of this study provide further evidence that abnormalities of glucose and insulin metabolism are present in patients with hypertension, and indicate that these changes do not necessarily disappear when blood pressure is lowered. Indeed, the data are compatible with the hypothesis that certain drugs frequently used to control hypertension may actually accentuate these metabolic abnormalities.

## MATERIALS AND METHODS

**Subject Selection** Forty-seven white men were recruited from the Hypertension Clinic at the Palo Alto Veterans Administration Medical Center and also from the surrounding community. The protocol was approved by the Stanford University Committee for the Protection of Human Subjects, and written informed consent was obtained from all subjects. The volunteers were instructed to maintain their usual diet and activities before admission. With the exception of hypertension, all volunteers were in good general health, as determined by a history, physical examination, and screening routine laboratory analyses. The clinical characteristics of the subjects are shown in Table 1. The subjects were well-matched for age and body mass index (BMI), an index of obesity. The untreated hypertensive individuals either had never been treated or had been withdrawn from their usual medication for a period of at least eight weeks. Aside from antihypertension medication, no individuals were taking drugs known to interfere with carbohydrate or lipid metabolism. Following admission to the Palo Alto Veterans Administration Medical Center, individuals underwent an overnight fast (14 hours) and at 8:00 AM the next morning intravenous access was obtained and studies commenced. Blood pressure was measured in the sitting position following a 15-minute rest. All values represent the mean of determinations obtained on at least two separate occasions.

**Oral Glucose Tolerance Test** After an overnight fast, blood was drawn for measurement of plasma glucose and insulin, before and 30, 60, 120, and 180 minutes after the ingestion of a 75-g oral glucose challenge.

**Insulin Suppression Test** After an overnight fast, intravenous catheters were placed in each arm. Blood was sampled from one arm for plasma glucose and insulin concentration and the contralateral arm used for administration of test substances. In a modification of our previously described technique,[6] somatostatin (purchased from Peninsula Labs, Belmont, CA) was administered at 250 $\mu$g/h in a solution containing 2½% (w/v) human serum albumin by Harvard infusion pump to suppress endogenous insulin secretion. Simultaneously, insulin and glucose were infused at 25 mU/m$^2$/min and 320 mg/m$^2$/min, respectively. Blood was sampled every half hour until 150 minutes into the study, and then every ten minutes until 180 minutes had elapsed. Insulin concentrations typically plateaued after 30 minutes, whereas glucose concentrations plateaued after 120 minutes. The four values obtained from 150 to 180 minutes were averaged and considered to represent the steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations achieved during the infusion.

**Methods of Analysis** Glucose was measured by a previously described enzymatic spectrophotometric technique,[7] whereas insulin was measured by radioimmunoassay.[8] Data are expressed as means ± SE, and results were analyzed by either one-way or two-way analysis of variance,[9,10] as appropriate.

## RESULTS

Figure 1 (left panel) shows the time course of the glucose response during the oral glucose tolerance test. By two-way ANOVA, each of the hypertensive groups had a significantly higher ($P < .05$) glucose response during the test than the control subjects. In addition, patients on combined $\beta$-blocker and diuretic therapy had a significantly higher glucose response than either the diuretic-treated or untreated hypertensive patients. The insulin response is shown in the right panel of Figure 1. Similarly, by two-way ANOVA, each of the hypertensive groups had higher ($P < .05$) insulin concentrations

TABLE 1. CLINICAL CHARACTERISTICS (MEAN ± SEM)

| Group | N | Age (yr) | BMI (kg/m$^2$) | Systolic BP (mm Hg) | Diastolic BP (mm Hg) |
|---|---|---|---|---|---|
| Control | 16 | 54 ± 10 | 25.7 ± 2.2 | 125 ± 13 | 75 ± 9 |
| Hypertension-untreated | 14 | 50 ± 11 | 25.9 ± 1.9 | 144 ± 1 | 97 ± 2 |
| Diuretic-treated hypertensive | 9 | 53 ± 11 | 26.2 ± 1.1 | 134 ± 9 | 83 ± 6 |
| Diuretic + $\beta$-blocker-treated hypertensive | 8 | 55 ± 12 | 26.2 ± 2.5 | 138 ± 11 | 85 ± 7 |

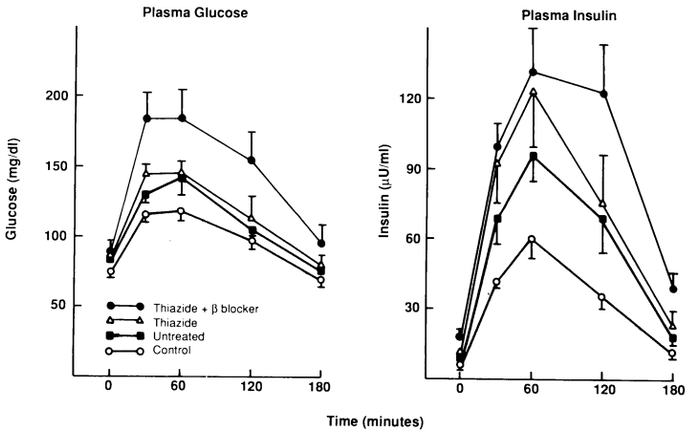


**FIGURE 1.** *Mean (± SEM) plasma glucose and insulin concentrations before and after the 75 oral glucose challenge in the four experimental groups.*

than the normal controls. Within the hypertensive groups there is a significant difference only between the untreated hypertensive patients and those on combination therapy, with the latter having higher plasma insulin concentrations throughout.

Steady-state plasma insulin concentrations during the insulin suppression test are shown in the left panel of Figure 2. The mean value in patients with hypertension treated with combined diuretic plus $\beta$-receptor antagonist was significantly higher ($P < .05$) than either the untreated group with hypertension or the controls when compared by one-way ANOVA. Furthermore, the diuretic-treated patients with hypertension had significantly higher SSPI levels than did the control population.

Despite having the highest SSPI concentrations during the insulin suppression test, hypertensive patients treated with diuretic plus $\beta$-receptor antagonist also had the highest SSPG value, and it was significantly higher ($P < .05$) than in the other three groups (one-way ANOVA) (Figure 2, right panel). The other two groups with hypertension also had significantly ($P < .05$) higher SSPG concentrations than did the control group (one-way ANOVA).

## DISCUSSION

The results presented confirm previous reports that patients with hypertension, as a group, are glucose intolerant and hyperinsulinemic.[1-5,11-13] In addition, we have shown that the changes in plasma glucose and insulin response that occur in patients with hypertension are most likely secondary to a defect in the ability of insulin to stimulate glucose uptake in these individuals. Insulin resistance in patients with hypertension has been previously described in Chinese males[4] and in Italian males and females.[5] Thus, it seems reasonable to conclude that the relationship between insulin resistance, hyperinsulinemia, and hypertension is not a function of gender, race, or ethnic background.

Shen and associates[4] had previously demonstrated that the degree of insulin resistance, glucose intolerance, and hyperinsulinemia seen in patients untreated with high blood pressure is comparable to that present in individuals receiving drug treatment for hypertension. The results we have presented provide further evidence that lowering blood pressure by pharmacological means does not necessarily improve the abnormalities of glucose and insulin metabolism seen in patients with high

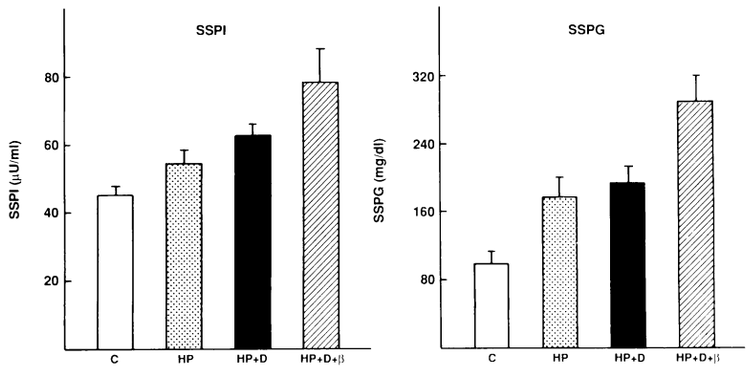


**FIGURE 2.** *Mean (± SEM) steady-state plasma insulin (SSPI) and glucose concentrations during the last 30 minutes of the infusion of somatostatin, insulin, and glucose in the control group (C), untreated patients with hypertension (HP), and in patients with hypertension treated with either diuretic alone (HP + D) or diuretic plus β-adrenergic antagonist (HP + D + β).*

blood pressure. Indeed, it could be argued that conventional forms of antihypertensive medication, the use of either a thiazide diuretic alone, or combind treatment with diuretic plus β-receptor antagonist, may actually accentuate the insulin resistance, glucose intolerance, and hyperinsulinemia associated with hypertension. On the other hand, it must be emphasized that this is a cross-sectional study, not a longitudinal one, and that the metabolic variables in question may have been more abnormal in the drug-treated patients before treatment was initiated. These preliminary results suggest the need for randomized controlled studies of the effects of these drugs on insulin resistance in patients with hypertension.

The observation that insulin resistance, glucose intolerance, and hyperinsulinemia are present in some patients with high blood pressure, and that these changes may not go away when blood pressure is lowered, is an important one for several reasons. Glucose intolerance and hyperinsulinemia have been identified as increasing the risk of developing coronary artery disease.[14-17] It is certainly possible that the presence of these metabolic abnormalities in patients with hypertension, and the fact that they may persist despite lowering of blood pressure with conventional antihypertensive treatment, may help explain why it has been difficult to demonstrate that risk of ischemic heart disease is decreased when blood pressure is lowered.[18-20] If the glucose intolerance and hyperinsulinemia that is seen in patients with high blood pressure contributes to this increased risk of coronary artery disease, it would seem more appropriate to treat hypertension with drugs that will not exacerbate these metabolic defects. Indeed, it could be argued that it would be useful to develop drugs that will both lower blood pressure and enhance insulin sensitivity, thus improving the defects in glucose and insulin metabolism in patients with hypertension. Finally, repeated demonstration of the association between hypertension and insulin resistance and hyperinsulinemia makes it necessary to consider the nature of the relationship. We have previously reviewed the circumstantial evidence suggesting that insulin resistance and hyperinsulinemia may be involved in the etiology of hypertension.[21] Furthermore, blood pressure increases in normal rats fed a fructose-enriched diet,[22] an intervention known to lead to insulin resistance and hyperinsulinemia.[23] In addition, hyperinsulinemia has been demonstrated in spontaneously hypertensive rats.[24] Given these data we feel it necessary to continue evaluation of the possibility that elevated ambient insulin concentrations may be involved in the development of high blood pressure.

Although not the focus of this study, some attention must be directed toward the possibility that high blood pressure and/or its treatment may modulate the rate of insulin catabolism. It is apparent from Figure 2 that the SSPI concentrations during the insulin suppression tests were not the same in all four groups. The fact that SSPG concentrations were higher in the three hypertensive groups than in the normotensive controls, despite higher SSPI concentrations, provides strong evidence that hypertension is associated with insulin resistance. Because the subjects were infused with insulin at the same rate, the likely explanation for the higher steady-state SSPI concentrations is a decreased clearance of insulin in the subjects with hypertension. Unfortunately, we did not measure C-peptide that would have enabled us to quantify the catabolic rate of insulin.[25] However, it should be noted that a defect in the catabolic rate of insulin seems to exist in spontaneously hypertensive rats[24] and indirect evidence has been published which suggests that a similar defect is present in patients with noninsulin-dependent diabetes mellitus who also have high blood pressure.[26]

In conclusion, evidence has been presented demonstrating that patients with hypertension, as a group, are insulin resistant, glucose intolerant, and hyperinsulinemic compared to subjects with normal blood pressure. Lowering of blood pressure does not necessarily lead to an improvement in these metabolic abnormalities, and may actually accentuate them. The role of the observed changes in glucose and insulin metabolism in both the etiology and clinical course of pateints with hypertension can only be speculated upon at this time, but available evidence supports the view that these are issues worthy of serious consideration.

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