Insulin Resistance and Blood Pressure in Young Black Men

Bonita Falkner, Sonia Hulman, Jaime Tannenbaum, and Harvey Kushner

Insulin resistance, independent of obesity or non-insulin-dependent diabetes mellitus, has been demonstrated to be associated with high blood pressure. To determine if insulin resistance could be an antecedent to hypertension in a high-risk population, we studied normotensive (112±12/70±10 mm Hg) and borderline hypertensive (135±8/85±5 mm Hg) lean young black men (22–26 years old) with the euglycemic hyperinsulinemic clamp technique. All subjects had clinically normal oral glucose tolerance. Body mass index and percent adipose mass were the same in both groups. Fasting plasma insulin concentration was significantly higher in the borderline hypertensive group (p<0.01). Insulin-directed exogenous glucose metabolism at the same degree of steady-state hyperinsulinemia was significantly lower in the borderline hypertensive group (5.98±2.22 versus 8.22±1.96 mg/kg/min; p<0.01). For the total population, a significant inverse correlation existed between the glucose infusion rate and systolic blood pressure (p<0.01). These data indicate that there is a relation between insulin-mediated glucose uptake and blood pressure. Furthermore, in this high-risk population insulin resistance may precede the onset of established essential hypertension. (Hypertension 1990;16:706–711)

In the United States, there is a greater prevalence of essential hypertension1–4 among the black population, with a disproportionately greater mortality from hypertensive disease occurring in blacks than whites.5,6 The morbidity of essential hypertension is related to cardiovascular consequences, which are similar to the morbid events that occur in diabetes mellitus and obesity. These three disorders not only share a common outcome but also overlap in occurrence, with blacks having a greater prevalence in all three disorders.7 Insulin resistance has been documented in the three disorders (essential hypertension, diabetes, and obesity) and may contribute to the vascular disease.

Non-insulin-dependent diabetes mellitus (NIDDM) and obesity are characterized by hyperinsulinemia and insulin resistance, defined as a suboptimal metabolic response to a given level of insulin. More recently, data are emerging that indicate hyperinsulinemia or insulin resistance correlate with essential hypertension, independent of NIDDM or obesity.8 Ferrannini et al9 used the hyperinsulinemic euglycemic clamp technique to study insulin resistance in nonobese adults having established hypertension and normal glucose tolerance. Compared with the normotensive control group, the hypertensive group exhibited pronounced impairment of glucose uptake in response to the exogenous insulin infusion. Their study provides substantial evidence of an association of insulin resistance with established essential hypertension independent of obesity and carbohydrate intolerance. This report, along with other studies, raises the possibility that insulin resistance may contribute to the pathogenesis of essential hypertension.

The purpose of our investigation was to determine if insulin resistance exists as an antecedent of established essential hypertension. We used the euglycemic hyperinsulinemic clamp technique to study insulin sensitivity in nonobese young adult black men with borderline hypertension. The borderline hypertensive young black men were matched with a similar group of young black men who were normotensive.

Methods

Subjects

Participants in this study were all young adult black men. Nonobese young men 22–26 years of age were selected from a larger population of young adult blacks that was already under study and has previously been described.10 In each subject, growth and blood pressure data was recorded from the newborn period, through childhood, adolescence, and young adulthood. Based on the average seated blood pres-
ure measurements (obtained with a mercury column sphygmomanometer) in the preceding 5 years, subjects were classified as normotensive (systolic blood pressure <135 mm Hg and diastolic blood pressure <85 mm Hg) or borderline hypertensive (systolic blood pressure ≥135 mm Hg or diastolic blood pressure ≥85 mm Hg). Normotensive and borderline hypertensive subjects were matched by age and body mass index (BMI) with exclusion of obese subjects. BMI (weight/height²) was less than 30 kg/m² in all subjects selected for the present study. No subject was taking or had ever taken antihypertensive medication. Before enrollment in this study, each subject provided written informed consent to the protocol, which had been approved by the Human Studies Committee of Hahnemann University.

All subjects had clinically normal oral glucose tolerance¹¹ confirmed by a 75 g oral glucose challenge performed at least 1 week before the hyperinsulinemic euglycemic clamp procedure.

Hyperinsulinemic Euglycemic Clamp Technique

Each subject reported to the research center after an overnight fast. All studies were begun at 9:00 AM. An angiocatheter (18 or 20 gauge) was placed in the right forearm for infusion, and a second (22 gauge) angiocatheter was placed retrograde in a vein in the left hand or wrist. The hand was warmed with a heating blanket to "arterialize" the blood sampled from this catheter. During the study, the subject either slept or was distracted with television. After venous access was established and the subject had rested, a blood sample was withdrawn for determination of fasting glucose, fasting insulin concentration, and baseline catecholamine level.

Sensitivity to insulin was determined by the hyperinsulinemic euglycemic clamp technique.¹² An insulin "prime" was infused over a 10-minute period followed by a constant infusion of 60 milliunits/m²/min for 120 minutes. During the insulin infusion, euglycemia was maintained by a variable infusion of 20% glucose solution. Plasma glucose was assayed every 10 minutes (Glucostat, Yellow Springs Instrument Co., Yellow Springs, Ohio). This glucose value was dissolved in normal saline with 40 meq/l KCl.

Euglycemic hyperinsulinemia was maintained for 2 hours. During the second hour, in steady-state hyperinsulinemia, three samples were withdrawn for subsequent measurement of plasma insulin concentration. A sample was obtained for plasma catecholamine assay at the end of the second hour. The quantity of exogenous glucose metabolized was calculated as the mean of the glucose infusion rate during the second hour of hyperinsulinemia. We made the assumption that during euglycemic hyperinsulinemia in the range of achieved plasma insulin, hepatic glucose output was completely suppressed.⁹,¹³ Glucose infusion rate then reflects total insulin-stimulated glucose metabolism during steady-state hyperinsulinemia. At the end of the study period, a urine sample was tested for glucosuria. The patient remained in the research center until he had consumed a meal and his blood glucose had returned to normal after withdrawal of the intravenous infusion.

Analytical Methods

Glucose was assayed by the glucose-oxidase method (YSI Glucose analyzer, Yellow Springs Instrument Co.). Insulin was assayed with standard radioimmunoassay (Amersham Corp., Arlington Heights, Ill.). Epinephrine and norepinephrine were assayed by radioenzymatic assay.

Calculations

Methods of statistical analysis of the data included analysis of variance, Student's t test to compare group mean values, multiple linear regression analysis, and Wilcoxon rank sum tests.

Results

Euglycemic hyperinsulinemic clamp studies in 17 lean black men provided technically complete data. The demographic data is presented in Table 1. The normotensive (n=8) and borderline hypertensive

<table>
<thead>
<tr>
<th>Parameter (mean±SD)</th>
<th>Normotensives (n=8)</th>
<th>Borderline hypertensives (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>24.0±1.3</td>
<td>24.0±1.3</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>70.9±10.0</td>
<td>81.1±8.5</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.76±0.07</td>
<td>1.82±0.11</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.0±2.6</td>
<td>23.8±1.5</td>
</tr>
<tr>
<td>Triceps skin fold (mm)</td>
<td>11.3±8.1</td>
<td>9.7±4.0</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>112±12</td>
<td>135±8</td>
</tr>
<tr>
<td>(range)</td>
<td>(102-130)</td>
<td>(126-145)</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>70±10</td>
<td>85±5</td>
</tr>
<tr>
<td>(range)</td>
<td>(56-80)</td>
<td>(79-94)</td>
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*p<0.05.  
fp<0.01.
(n=9) groups were similar in age. All subjects in this study had a BMI below 30 kg/m². Although the borderline hypertensive group was somewhat taller and heavier, the mean value of BMI (weight/height²) was similar between the groups. Triceps skin fold thickness was also similar in the two groups. Mean systolic and diastolic blood pressure were significantly greater in the borderline hypertensive group than the normotensive group. Table 2 provides data on fasting and insulin-stimulated metabolism. Both groups had similar fasting glucose concentrations.

In spite of the small sample size, the fasting insulin concentration in the borderline hypertensive group was significantly greater than in the normotensive group (p<0.01). The ratio of fasting insulin to fasting glucose was also significantly greater (p<0.01) in the borderline hypertensive group. These parameters indicate the presence of a relative fasting hyperinsulinemia in the borderline hypertensive group.

Figure 1 depicts the results of the euglycemic hyperinsulinemic clamp studies in the two groups. The mean glucose concentration during steady-state hyperinsulinemia was similar to fasting in both groups, and there was no difference between the two blood pressure groups. The mean “clamped” insulin concentrations were the same in both groups, approximately 70 microunits/ml greater than fasting. The mean value of the glucose infusion rate, or quantity of exogenous glucose metabolized during steady-state hyperinsulinemia, is significantly lower in the borderline hypertensive group when compared with the normotensive group (p<0.01). Therefore, compared with the normotensive group, the borderline hypertensive group exhibited resistance to the stimulus of steady-state hyperinsulinemia.

The catecholamine data are also presented in Table 2. Mean values of epinephrine and norepinephrine were compared between the normotensive and borderline hypertensive groups, both fasting and during the clamp procedure. The standard deviation was noted to be large in the normotensive group. However, using both t tests and Wilcoxon rank sum tests, there were no statistically significant differences between the groups. After 120 minutes of hyperinsulinemia, there was no change in plasma epinephrine or norepinephrine in either group. Based on these plasma catecholamine levels, there was no evidence that the procedure had induced a stress effect, nor was there evidence that euglycemic hyperinsulinemia induced a rise in catecholamine levels.

The data demonstrated differences between the borderline hypertensive and normotensive groups in both the fasting state and during the stimulus of euglycemic hyperinsulinemia. A regression analysis of fasting plasma insulin with the glucose infusion rate was performed for the entire subject population. This analysis demonstrated a significant inverse correlation of fasting plasma insulin with glucose infusion rate (r=-0.60, p<0.01), indicating that insulin resistance reflected by a low glucose infusion rate corresponded with higher fasting plasma insulin concentration.
centation. The variables of glucose infusion rate and blood pressure and body weight were also analyzed for the entire population. A stepwise multiple linear regression of glucose infusion rate on weight, height, systolic blood pressure, diastolic blood pressure, and BMI was performed. The glucose infusion rate was significantly correlated with systolic blood pressure (r=0.61, p<0.01). After systolic blood pressure was entered into the equation, no other variable contributed significantly to the equation. Therefore, the relation of insulin resistance and blood pressure is intact across the entire spectrum of systolic blood pressures represented in these young black men.

Because body weight was greater in the hypertensive group (p<0.05), further analysis was performed to clarify the relation of body size, blood pressure, and insulin resistance. A regression analysis of body weight versus glucose infusion rate showed no significant correlation. BMI was no different between the two groups. Also, triceps skin fold thickness was not significantly different (Table 1). The greater weight in the hypertensive group appeared to be due to their greater height rather than greater adipose mass. To assess further the body composition in our subjects, preexisting anthropometric data on these subjects were evaluated. Based on measurements that had been obtained at age 20–22 years, the percent muscle mass was calculated according to the method of Heymsfield et al.14 At that age, the mean percent muscle mass was 38.6±5.2% in the normotensive and 41.7±4.4% in the borderline hypertensive group, which was not different. Percent body fat was also determined,15 resulting in a mean of 13.0±1.8% for the normotensive and a mean of 15.5±2.5% for the borderline hypertensive group, which was also not different. The normal value of percent adipose weight for nonobese males age 20–29 years is 17.9±6.1.15 Differences between the two groups in adipose distribution or central obesity could not be detected in this sample size. No subject had any pronounced change in height or weight in the interval between those anthropometric measurements and participation in the clamp study. Therefore, there is no difference in percent body mass as muscle or adipose tissue in our normotensive and marginal hypertensive groups to account for the measured differences in glucose infusion rate.

Discussion

The data in this study on young blacks demonstrate a significant relation of higher blood pressure with insulin resistance, as determined during euglycemic hyperinsulinemia. Similar to the findings of Ferrannini et al,9 who demonstrated insulin resistance in adults with clearly established hypertension, we identified evidence of insulin resistance in younger black subjects with only borderline hypertension.

Fasting insulin concentration is another parameter that has been correlated with hypertension.16–18 In the present study, the subjects were young, glucose tolerant, and nonobese. Even in this small sample size, the group with higher blood pressure also had higher fasting insulin concentration. Additionally, insulin resistance, as demonstrated by the clamp technique, occurred at BMI levels below 30 kg/m² and was correlated with elevated blood pressure. Therefore, the data in the present study suggest that insulin resistance may be an antecedent of essential hypertension.

Growth during childhood and adolescence correlates with an increase in blood pressure.19 Additionally, many studies in adult populations have verified a correlation of weight and blood pressure.20 Although there was a significant difference in weight between our normotensive and marginal hypertensive groups, the two groups were not different with respect to percent adipose and percent muscle mass. Although insulin resistance has been strongly correlated with obesity,21,22 greater adipose mass does not explain the relative insulin resistance of these black research subjects with borderline hypertension.

An investigation by Yki-Jarvinen and Koivisto23 used the euglycemic hyperinsulinemic clamp technique to study muscle tissue sensitivity to insulin. These investigators studied a group of lean male athletes, in whom greater weight was not related to increased adipose tissue but rather to increased muscle mass. They demonstrated in lean male athletes that total glucose metabolism was directly related to the percent muscle mass. The heavier athletes had greater insulin sensitivity than the lighter weight athletes, possibly due to the presence of greater muscle mass, which is very sensitive to insulin. However, our heavier borderline hypertensive subjects, who were also taller, were more insulin resistant than their lighter weight counterparts, despite no difference in percent adipose mass, percent muscle mass, or BMI. This observation raises the possibility that in these borderline hypertensive individuals, the insulin resistance may be associated with greater somatic growth.

The data obtained from the insulin clamp studies further validated the difference in insulin concentration present during fasting in our two blood pressure groups. Mean fasting insulin level in the borderline hypertensive group was 15.46±5.17 microunits/ml which, although within a normal clinical range, is significantly higher than the mean fasting insulin level for the normotensive group (8.56±4.31 microunits/ml). When fasting insulin concentration is compared with fasting glucose concentration by calculating the fasting insulin-to-fasting glucose ratio, the difference between the groups is accentuated. Hence, for a given level of glycemia, the borderline hypertensive group maintains greater insulinemia than does the normotensive group. Reaven24 has proposed that glucose tolerance can be normalized despite severe insulin resistance in individuals having pancreatic β-cell capacity to increase insulin secretion. Thus, the hyperinsulinemia is established to overcome the peripheral insulin resistance and normalize glycemia. This hypothesis is further supported.
by Zavaroni et al, who examined 247 lean subjects with normal glucose tolerance. Subjects with a fasting insulin concentration greater than 2 SDs above the population mean had an augmented insulin response during oral glucose tolerance testing. This group also had significantly higher blood pressure.

The demonstration of insulin resistance in a young high-risk population exhibiting mild blood pressure elevation suggests a causal relation. There is evidence that small increments in plasma insulin levels enhance renal tubular sodium reabsorption. Rocchini et al studied obese adolescents with hyperinsulinemia. These investigators demonstrated that blood pressure sensitivity to dietary sodium load was reduced when plasma insulin concentration was lower after a weight reduction program. Because of reports of greater blood pressure sensitivity to sodium and delayed renal sodium excretion in blacks, this is a plausible mechanism to explain the association of insulin resistance and essential hypertension and is an area that warrants further study in black populations.

There is also some evidence that insulin resistance in essential hypertension may be related to augmented sympathetic nervous system activity. Rowe et al demonstrated a significant increase in plasma norepinephrine levels in response to euglycemic hyperinsulinemia, which suggests that elevated plasma insulin may itself increase sympathetic nervous system activity in the absence of changes in blood glucose. In our population, there was no difference in plasma catecholamine levels in the basal state. There was also no increase in catecholamine levels in either group in response to the hyperinsulinemia. In these young individuals, plasma catecholamine levels alone may not be sufficiently sensitive to detect this mechanism.

This study examined the relation of insulin resistance to blood pressure in nonobese healthy young black men. Despite a small sample size, there exists a significant inverse correlation of blood pressure with both fasting insulin and also with the metabolism of exogenous glucose during euglycemic hyperinsulinemia. The results of this study suggest that a defect in insulin-stimulated glucose metabolism may be an antecedent to hypertension in blacks. Thus, in our lean black hypertensive group, insulin resistance may be the result of a primary defect that leads to hyperinsulinism, increased somatic growth, and ultimately, hypertension.

References


KEY WORDS: blood pressure, essential hypertension, ethnic groups, insulin resistance, glucose, body composition
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