Plasma Insulin Levels and Incidence of Hypertension in African Americans and Whites

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Background: Hyperinsulinemia may play an important role in the pathogenesis of hypertension in whites but the role of hyperinsulinemia in hypertension in African Americans is controversial.

Subjects and Methods: We studied the relationship between insulin levels and subsequent incidence of hypertension in 140 African Americans and 237 whites who were initially screened for possible participation in the Trials of Hypertension Prevention, phase I. Plasma insulin and serum glucose were measured at baseline and at a follow-up examination 7 years later. Blood pressure was measured by trained observers using a random-zero sphygmomanometer. Incident hypertension was defined as an average systolic pressure of 160 mm Hg or higher and/or diastolic pressure of 95 mm Hg or higher at a single visit and/or use of antihypertensive medication during follow-up.

Results: Over the 7 years of follow-up, the incidence of hypertension was 25.7% in the African Americans and 25.3% in the whites. Baseline plasma insulin and insulin-to-glucose ratio were associated with an increased risk of hypertension in both the African Americans and the whites. After adjustment for age, sex, race, body mass, heart rate, and alcohol consumption at baseline as well as intervention assignment in the Trials of Hypertension Prevention, phase I, a 1-SD (21 pmol/mmol) difference in baseline insulin-to-glucose ratio was associated with a 2.77 (95% confidence interval, 1.48-5.19) odds ratio of hypertension in the African Americans and a 1.69 (95% confidence interval, 1.08-2.64) odds ratio in the whites.

Conclusion: These results suggest that higher plasma insulin levels are associated with an increased risk of hypertension in both African Americans and whites.

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As early as 30 years ago, Welborn and colleagues1 observed elevated serum insulin levels in patients with hypertension. Since then, many studies have suggested that insulin resistance2-6 and the concomitant compensatory hyperinsulinemia7-13 may play an important role in the pathogenesis of hypertension. However, most of these investigations14-19 have been cross-sectional and have generated conflicting evidence in support of this hypothesis. It is well known that insulin resistance, hyperinsulinemia, obesity, hyperlipidemia, type 2 diabetes mellitus, and hypertension tend to cluster in patients. As such, the cross-sectional association between insulin resistance and hypertension may not reflect a causal relationship. The few prospective studies20-23 that have investigated the association between insulin and high blood pressure have yielded inconsistent results.

Another limitation of our current understanding of the relationship between blood pressure and insulin resistance is that most studies have been conducted in populations that were predominantly white. Several,24,25 but not all26-28 of the cross-sectional studies conducted in African American populations have failed to show a relationship between blood pressure and insulin levels or insulin resistance. On the basis of these studies, it has been proposed that the relationship between blood pressure and insulin resistance and, consequently, the mechanisms of insulin action on blood pressure may differ among ethnic groups.24

To address these questions, we performed a prospective study to investigate the relationship between plasma insulin levels and risk of hypertension in both African Americans and whites.

RESULTS

The 377 study participants (140 African Americans and 237 whites) were followed up for an average of 7.1 years (range,
SUBJECTS AND METHODS

STUDY PARTICIPANTS

The study population consisted of 463 screenees (171 African Americans and 292 whites) from the Baltimore, Md, clinical center of the Trials of Hypertension Prevention, phase 1 (TOHP-1). The Trials of Hypertension Prevention, phase 1 was a national, multicenter, randomized controlled trial designed to test the short-term feasibility and efficacy of 3 lifestyle (weight loss, sodium restriction, and stress management) and 4 nutritional supplement (calcium, magnesium, fish oil, and potassium) interventions aimed at lowering diastolic blood pressure in individuals whose blood pressure was initially in the high normal range (80-89 mm Hg diastolic). Most of the study participants were identified through a work-site screening program conducted between September 1987 and October 1988 at the Social Security Administration and the Health Care Financing Administration headquarters located in western Baltimore. Of the 463 screenees, 286 were enrolled in the TOHP-1 trial. At entry, the TOHP-1 trial participants had to be between 30 and 54 years of age, have a high normal blood pressure, and have had a blood pressure equal to or higher than 160 mm Hg systolic, 100 mm Hg diastolic, or use antihypertensive medications at the follow-up examination. A mean blood pressure of 160/95 mm Hg or higher, and/or (3) diastolic blood pressure of 95 mm Hg or higher at the follow-up examination. A mean blood pressure of 160/95 mm Hg or higher was used as the cutoff point for definition of hypertension in our study because the follow-up blood pressure measurements were obtained at a single visit. Furthermore, the presence of a systolic blood pressure lower than 160 mm Hg was used as an eligibility criterion for inclusion in TOHP-1.

A follow-up evaluation was conducted between November 1994 and September 1995. Of the 463 TOHP-1 screenees, 377 (81.4%) took part in the follow-up study. One of the 86 nonrespondents had died, 3 were seriously ill, and the remaining 82 refused to participate. In general, the nonrespondents and respondents had similar baseline characteristics, including race, sex, socioeconomic status (education and employment), health habits (cigarette smoking, alcohol consumption, and physical activity), body weight, heart rate, and blood pressure. However, the non-respondents were, on average, 1.5 years younger than the respondents (P = .02).

DATA COLLECTION

Baseline observations were obtained at 3 screening visits. Demographic characteristics, medical history, and data on health habits were collected at the initial screening visit. Nine blood pressure measurements, 3 at each of the 3 screening visits, were obtained using the Hawksley random-zero sphygmomanometer. Blood pressure was measured after the individual had been seated quietly for 5 minutes. The screenees were instructed not to eat or smoke for at least 30 minutes prior to their blood pressure measurement. The first and fifth Korotkoff sounds were recorded as systolic and diastolic pressure, respectively. Body height and weight were measured at the first screening visit and body mass index was calculated as an indicator of obesity. Nonfasting blood specimens were collected at the third screening visit and stored at −20°C until assayed.

At the follow-up visit, medical history, especially personal history of hypertension and use of antihypertensive medications, was evaluated by questionnaire. Alcohol consumption and other health habits were also reassessed. Three blood pressure measurements were obtained using the same methods as those employed at the baseline visits. Body weight, height, and waist and hip circumference were also measured at the follow-up visit. Waist-to-hip ratio was computed as an index of fat distribution. A 12-hour fasting blood sample was collected and stored at −70°C until assayed. All the study data were collected carefully by specially trained, experienced observers using standardized methods, with stringent application of quality control procedures aimed at improving the accuracy and precision of the study findings. All data collectors were required to pass an initial series of certification examinations as well as periodic re-certification evaluations.

Plasma insulin was measured in duplicate by radioimmunoassay using the double antibody method described by Soeldner and Slone. The lower limit of detection of the assay was 15 pmol/L and the intra-assay coefficient of variation was 11.5%. Both the baseline and follow-up specimens were assayed during December 1995. Baseline plasma specimens were only available for 245 participants. However, the baseline characteristics were similar among study participants whose baseline insulin was or was not measured. Serum glucose concentration was measured by the glucose oxidase method (Beckman Instruments Inc, Fullerton, Calif).

Hypertension during follow-up was defined as: (1) diagnosis of hypertension by a physician during the follow-up period resulting in the initiation of antihypertensive therapy, as assessed by questionnaire, and/or (2) systolic blood pressure of 160 mm Hg or higher, and/or (3) diastolic blood pressure of 95 mm Hg or higher at the follow-up examination. A mean blood pressure of 160/95 mm Hg or higher was used as the cutoff point for definition of hypertension in our study because the follow-up blood pressure measurements were obtained at a single visit. Furthermore, the presence of a systolic blood pressure lower than 160 mm Hg was used as an eligibility criterion for inclusion in TOHP-1.

STATISTICAL ANALYSIS

Analysis of covariance was used to examine the significance of differences in characteristics at baseline and during follow-up between the African American and white participants, adjusted for sex. Univariate and multivariate logistic regression analyses were used to explore the relationship of baseline insulin and glucose levels to the subsequent risk of hypertension. Univariate and multivariate linear regression analyses were also used to examine the relationship of insulin and insulin-to-glucose ratio at baseline to changes in blood pressure level during follow-up. Insulin-to-glucose ratio was calculated as a predictor variable to reduce the variation inherent in use of nonfasting insulin levels. In the linear regression analyses, we assumed that the study participants who were receiving antihypertensive medications at the follow-up examination had a blood pressure equal to or higher than 160 mm Hg systolic and 95 mm Hg diastolic. Odds ratios (ORs) or regression coefficients associated with a 1-SD difference in insulin or glucose, based on the total sample, were reported for the overall cohort and separately for African Americans and whites. Assumptions for the statistical models were tested in exploratory data analysis. No significant interaction was detected between race, sex, and insulin or insulin-to-glucose ratio on the risk of hypertension. All analyses were performed using SAS software.
The characteristics of the study participants by race are presented in Table 1. Because the proportion of male participants was significantly lower in African Americans than in whites, all analyses were adjusted for sex. Mean age, alcohol consumption, heart rate, body mass index, systolic and diastolic blood pressure, and plasma insulin and glucose at baseline were similar in the African American and white participants. Over the 7 years of follow-up, changes in systolic and diastolic blood pressure were not significantly different between the African Americans and the whites. However, the increase in body mass index during follow-up was significantly greater in the African Americans compared with the whites (for both, \( P < .05 \)). At the follow-up examination, mean levels (SD) of fasting plasma insulin, measured in picomolar per liter, were similar in African Americans, 92.7 (74.5) and whites, 82.7 (50.0). Mean (SD) insulin-to-glucose ratios were also similar in African Americans, 16.4 (7.6) and whites, 51.1 (7.5).

### INSULIN LEVELS AND RISK OF HYPERTENSION

Over the 7-year follow-up, baseline plasma insulin levels and insulin-to-glucose ratios were positively related to the odds of hypertension in the entire cohort and in the African Americans and the whites separately (Table 2). A significant dose-response relationship was observed for the association between tertiles of baseline insulin-to-glucose ratio and hypertension (Figure). A similar dose-response relationship was also observed for the association between insulin levels and hypertension. In the overall cohort, a 1-SD higher level of insulin at the baseline examination (107 pmol/L) was associated with an 82% increase in the odds of hypertension during follow-up, after adjustment for age, sex, race, body mass index, heart rate, and alcohol consumption at baseline, as well as intervention assignment in TOHP-1 (sodium reduction or weight loss vs all others). Likewise, a baseline insulin-to-glucose ratio that was 1 SD higher (21 pmol/mmol) was associated with a 95% increase in the odds of hypertension after adjustment for the same covariates. In a race-stratified analysis, baseline plasma insulin levels were positively associated with the odds of hypertension in both the African Americans and whites. This relationship persisted in the African Americans but not in the whites after adjustment for the previously mentioned covariates. In both the African Americans and the whites, baseline insulin-to-glucose ratios were associ-
increased odds of hypertension, independent of all the other covariates measured.

**INSULIN LEVELS AND CHANGES IN BLOOD PRESSURE**

The relationship of baseline insulin levels and insulin-to-glucose ratios to changes in blood pressure during follow-up is presented in Table 3. In the total sample, baseline insulin levels and insulin-to-glucose ratios were positively and significantly associated with increases in both systolic and diastolic blood pressure during follow-up. These relationships remained significant after adjustment for age, sex, race, heart rate, and alcohol consumption at the baseline evaluation; change in body mass index during follow-up; and intervention assignment in the Trials of Hypertension Prevention, phase 1 (sodium reduction or weight loss vs all others).

Race-stratified analyses also showed consistent relationships between both baseline insulin levels and insulin-to-glucose ratios and the corresponding changes in blood pressure during follow-up. After adjustment for the previously mentioned covariates, baseline insulin levels and insulin-to-glucose ratios remained positively and significantly associated with an increase in systolic blood pressure in both the African Americans and the whites. For diastolic blood pressure, only the association with baseline insulin-to-glucose ratios in whites reached the customary level of statistical significance (P<.05).

**CROSS-SECTIONAL ANALYSIS**

In a cross-sectional analysis based on observations at the follow-up examination, the relationship of insulin levels and insulin-to-glucose ratios to prevalence of hypertension was similar to that observed in the prospective analysis. A 1-SD higher level of plasma insulin (60 pmol/L) was associated with a 59% (95% confidence interval [CI] for OR, 1.11-1.86) higher odds of hypertension. These estimates were independent of age, sex, race, body mass index, waist/hip ratio, heart rate, and alcohol consumption at the follow-up examination. In race-stratified analysis, a 1-SD higher level of plasma insulin (60 pmol/L) was associated with a 68% (95% CI for OR, 0.94-3.01) and 58% (95% CI for OR, 1.06-2.37) increase in the odds of hypertension in African Americans and whites, respectively. Likewise, a 1-SD higher level of insulin-to-glucose ratio (7.5 pmol/mmol) was associated with a 37% (95% CI for OR, 0.91-2.07) and 53% (95% CI for OR, 1.09-2.15) higher odds of hypertension in African Americans and whites, respectively.

At the follow-up examination, plasma insulin levels were positively and significantly associated with systolic blood pressure in participants who were not taking antihypertensive medications. This was true both for the total sample (β = 2.48; P<.01) as well as for the African Americans (β = 2.06; P<.05) and whites (β = 3.05; P<.05) separately in race-stratified analyses after adjustment for

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**Table 3. Relationship of a 1-SD Higher Level of Insulin and Insulin-to-Glucose Ratio at Baseline to Subsequent Change in Blood Pressure Over 7 Years of Follow-up in 92 African Americans and 153 Whites**

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<th>Unadjusted</th>
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<th>Adjusted†</th>
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<td></td>
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<td>Diastolic Pressure</td>
<td>Systolic Pressure</td>
<td>Diastolic Pressure</td>
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<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
<td>β</td>
<td>95% CI</td>
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<tr>
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<tr>
<td>Insulin, 107 pmol/L</td>
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<td>1.92-5.98‡</td>
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<td>1.63-5.78‡</td>
<td>1.42</td>
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<td>ratio, 21 pmol/mmol</td>
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<tr>
<td>African Americans</td>
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<tr>
<td>Insulin, 107 pmol/L</td>
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<td>1.02-7.37§</td>
<td>1.07</td>
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<td>Whites</td>
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* CI indicates confidence interval.
† Multivariate linear regression model adjusted for age, sex, race, heart rate, and alcohol consumption at baseline, change in body mass index over follow-up, as well as intervention assignment in the Trials of Hypertension Prevention, phase 1 (sodium reduction or weight loss vs all others).
‡ P<.001.
§ P<.01.
|| P<.05.
This study is, to our knowledge, one of the first prospective investigations to have identified a significant positive relationship between baseline insulin levels and subsequent risk of hypertension in African Americans. Most previous reports linking insulin resistance to hypertension have been from studies that were conducted in samples where the participants were predominantly white. The few cross-sectional studies in which the insulin-blood pressure relationship has been examined in African Americans have produced contradictory results. Saad et al\(^{24}\) observed racial differences in the relationship of insulin resistance to blood pressure. They used the euglycemic-hyperinsulinemia clamp technique to study insulin resistance and blood pressure in 116 Pima Indians, 33 whites, and 42 African Americans. Fasting insulin levels, and the rate of glucose disposal during low-dose and high-dose insulin infusions were significantly associated with blood pressure in whites, even after adjustment for age, sex, body weight, and percentage of body fat, but this was not the case in African Americans.\(^{24}\) In another study,\(^{25}\) insulin resistance was not associated with blood pressure in 37 female and 53 male African Americans with type 2 diabetes mellitus. In the Bogalusa Heart Study,\(^{26}\) fasting insulin was associated with blood pressure in white but not in African American children.\(^{26}\) However, 2 recent studies\(^{27,28}\) found that young African American men with borderline hypertension demonstrated an increased insulin resistance compared with their counterparts who were normotensive. In a third study,\(^{29}\) insulin resistance was positively associated with blood pressure in normotensive African Americans.

Few prospective studies\(^{20-23,36,37}\) have investigated the relationship of insulin and glucose levels to risk of hypertension. Skarfors and coworkers\(^{20}\) followed up a group of middle-aged Swedish men (n = 2322) for 10 years. Both fasting insulin levels and insulin levels taken 60 minutes after an intravenous glucose tolerance test were associated with blood pressure in whites, even after adjustment for age, sex, body mass index, heart rate, waist-to-hip ratio, and alcohol consumption.

COMMENT

In our investigation, nonfasting insulin levels at baseline were significantly associated with the odds of developing hypertension and changes in blood pressure over a 7-year period of follow-up, independent of several important risk factors for hypertension. Compared with insulin levels alone, insulin-to-glucose ratios were an even stronger predictor of the risk of subsequent hypertension. This may be because the insulin-to-glucose ratio reduced the variation in serum insulin levels due to the nonfasting status at the baseline visit.

Several possible mechanisms have been proposed to explain the association between insulin resistance and hypertension. In addition to effects on glucose metabolism, insulin has sympathetic nervous system and renal actions that are hypothesized to raise blood pressure. The compensatory hyperinsulinemia that occurs with insulin resistance increases sodium reabsorption and sympathetic nervous system activity, which combine to elevate blood pressure. A direct effect of insulin on the kidney is indicated by the observation that infusion of insulin into the renal artery results in a 50% decrease in sodium excretion, without any change in sodium excretion by the contralateral organ.\(^{38}\) Most investigators\(^{30}\) agree that insulin increases sodium reabsorption in the distal tubule in men. Moreover, insulin resistance is associated with high sodium-lithium countertransport, which correlates closely with the reabsorptive capacity of the distal tubule.\(^{30}\) Recently, it has also been suggested that insulin resistance and compensatory hyperinsulinemia increase plasma renin activity and plasma aldosterone levels in normotensives and mild hypertensives.\(^{41,42}\)

There are several potential limitations to the findings in our study. First, the study participants were predominantly recruited by means of a work-site screening program. As such, they are not a representative sample of the community. It is unlikely, however, that this selection would have biased the assessment of the relationship between insulin and blood pressure. The selection process may have affected the incidence of hypertension but the selection fractions were equally applied to those with high and low insulin levels. Thus, the relative odds of hypertension associated with insulin levels and insulin-to-glucose ratios that were noted in our study are likely to be generalizable. A second potential concern is that our baseline blood specimens were not obtained under fasting conditions. However, the resulting variation in time from breakfast to venipuncture should have increased random measurement error in the assessment of baseline insulin and glucose levels and as a consequence should have led to a reduction in the strength of the observed association, ie, should have biased the OR toward one. Another potential limitation of our study was the fact that the assays of baseline insulin were performed 7 years after the participants’ blood sample had been collected. Again, however, this is unlikely to have had a major impact on our results. In 1 study,\(^{43}\) no change in insulin levels was detected in repeated assays of 34 samples, stored at −20°C over an 8-year period. Moreover, any decline in insulin levels over time would probably have been proportionately similar for all the plasma specimens and would thus have little effect on the relationship between insulin levels and risk of hypertension.
In conclusion, the results of our study suggest that high circulating levels of plasma insulin are associated with an increased risk of hypertension in both African Americans and whites. Elevated insulin levels may precede clinical hypertension and be important in its cause. Because insulin resistance and hyperinsulinemia have been linked to hypertension, obesity, hyperlipidemia, diabetes, and coronary heart disease, preventive measures that reduce insulin resistance may be of central importance both for primary prevention of hypertension and for reduction of the overall risk of cardiovascular disease in both African Americans and whites.

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