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Insulin Resistance and Hypertension in Non-obese Africans in Tanzania

Yasin M. Mgonda, Kaushik L. Ramaiya, Andrew B.M. Swai, Donald G. McLarty†, K. George M.M. Alberti

Abstract—Insulin sensitivity was assessed using a glucose-insulin infusion test in 15 newly diagnosed non-obese hypertensive black Tanzanians with normal glucose tolerance and in 15 normotensive control subjects matched for age, sex, and body mass index. The steady-state blood glucose and metabolic clearance rate of glucose (MCR) were used as measures of insulin sensitivity. The mean MCR (glucose) was significantly reduced (7.12±0.57 versus 9.50±0.69 μmol/kg per minute; \( P<.05 \)) and mean steady-state blood glucose was significantly elevated (5.0±0.3 versus 3.7±0.3 mmol/L; \( P<.01 \)) in subjects with hypertension compared with the normotensive group. For all subjects there was a significant inverse correlation between MCR (glucose) and systolic (\( P=.003 \)) and diastolic (\( P=.005 \)) blood pressure; and a positive correlation was found between fasting serum insulin levels and systolic (\( P=.005 \)) and diastolic (\( P=.004 \)) blood pressure. These observations were independent of body mass index and serum lipid levels. These data indicate a strong association between insulin mediated glucose uptake and blood pressure in this population of normal weight untreated urban Africans.

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Key Words: insulin resistance ■ Africans ■ blood pressure

A significant association has been demonstrated and confirmed between insulin resistance and essential hypertension, independent of glucose intolerance, and obesity.\(^1\)\(^-\)\(^11\) This finding forms part of the hypothesis that insulin resistance is central to the cluster of abnormalities (abnormal glucose tolerance, obesity, hypertension, and dyslipidemia) known as Syndrome X or the metabolic syndrome.\(^12\)\(^-\)\(^14\)

There is uncertainty as to whether the association between insulin resistance and hypertension applies to all populations. Epidemiological studies have cast doubt on the strength of this association in both Mauritians\(^15\) and Californians.\(^16\) Similarly, no correlation was reported between fasting serum insulin concentration and blood pressure measurements in normotensive black South Africans,\(^17\) although another recent report suggests that insulin resistance is an independent feature of essential hypertension in that group.\(^18\) No attention has been paid to this problem in other less-Westernized African settings. The main objective of this study therefore was to establish whether insulin resistance (insulin mediated glucose disposal) was associated with essential hypertension independent of obesity and glucose intolerance in African subjects in Dar es Salaam, Tanzania.

Methods

A total of 280 employees of Kilimanjaro Hotel, Ltd, the biggest tourist hotel in the city of Dar es Salaam, were screened for hypertension. Of those screened, 30 African subjects (15 patients and 15 control subjects) were enrolled for the study after obtaining informed consent from each subject. All subjects were from similar socioeconomic and occupational backgrounds, and all were physically active. They had a semi-Westernized diet, and the two groups were matched for age, sex, and body mass index. Hypertension was defined as blood pressure equal to or more than 160/95 mm Hg recorded on at least three occasions; body mass index was less than 30 kg/m\(^2\), and they had normal oral glucose tolerance based on 1985 WHO criteria.\(^19\) Exclusion criteria included subjects with clinical and biochemical evidence of cardiac, hepatic, renal, and endocrine disease, known as hypertension, history of excessive alcohol consumption, excessive smoking, and, for female subjects, the use of oral contraceptives. No subject was taking or had ever taken antihypertensive medication.

Physical Measures

Blood Pressure

Blood pressure was measured on three different occasions using a mercury sphygmomanometer. After measuring blood pressure on day 1, a second measurement was obtained about a week later, and a third measurement 1 to 3 days later. On each occasion at least 2 readings were taken and the mean value recorded. An appropriate adult cuff was applied 2 to 3 cm above the antecubital fossa of the right arm. Blood pressure was measured to the nearest 2 mm Hg, reading the calibration below the meniscus with the subject in the sitting position. Systolic and diastolic blood pressures were read at the 1st and 5th Korotkoff phases, respectively. The mean of the 3 blood pressure values obtained from the 3 visits was taken as the subject’s true blood pressure. Hypertension was defined as systolic and diastolic blood pressure equal to or more than 160 mm Hg and/or 90 mm Hg, respectively.

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Anthropometry
Weight was measured using a Seca bathroom weighing scale without shoes and in light clothing. Weight was recorded to the nearest 0.5 kg. Height was measured without shoes and/or cap and was recorded to the nearest centimeter. BMI is expressed as weight (kilograms) per height (meters) squared.

Waist circumference was taken as the maximum abdominal girth and recorded to the nearest centimeter. Hip circumference was taken as the maximum circumference at the level of the greater trochanter and also recorded to the nearest centimeter. The waist/hip ratio was calculated by dividing the waist circumference by the hip circumference in centimeters. Body fat percentage was determined using bioelectric impedance measurement.²⁰

Biochemical Measures
Oral Glucose Tolerance Test
All subjects underwent a 75-g oral glucose tolerance test. After an overnight fast (10 to 14 hours) subjects reported to the study center by 8:00 AM. After a short rest, fasting blood samples were collected from the antecubital vein and immediately placed in fluoride oxalate and analyzed immediately by the glucose oxidase method using a Yellow Springs analyzer (Yellow Spring). Other aliquots were kept in an ice-cold container and, within 4 hours of collection, were centrifuged and kept frozen at −40°C until the serum samples were transported to Newcastle on Tyne, UK, for determination of serum cholesterol, triglyceride, and insulin levels. Glucose, 75 g, dissolved in 300 mL of water was consumed in about 5 minutes. Blood samples for determination of blood glucose and serum insulin were collected at 15, 30, 60, and 120 minutes. For quality control of glucose measurements, aliquots were stored and frozen for analysis by a hexokinase fluorimetric method using a Cobas Bio centrifugal analyzer (Roche Products, Ltd.) in Newcastle on Tyne.

Insulin Sensitivity Test
Insulin sensitivity was assessed in both patients and control subjects. The modified Harano technique (glucose-insulin infusion technique) was used.²¹ Subjects reported at the study center on the morning of the overnight fast (10 to 14 hours) subjects reported to the study center by 8:00 AM. After an short rest, fasting blood samples were collected from the antecubital vein and immediately placed in fluoride oxalate and analyzed immediately by the glucose oxidase method using a Yellow Springs analyzer (Yellow Spring). Other aliquots were kept in an ice-cold container and, within 4 hours of collection, were centrifuged and kept frozen at −40°C until the serum samples were transported to Newcastle on Tyne, UK, for determination of serum cholesterol, triglyceride, and insulin levels. Glucose, 75 g, dissolved in 300 mL of water was consumed in about 5 minutes. Blood samples for determination of blood glucose and serum insulin were collected at 15, 30, 60, and 120 minutes. For quality control of glucose measurements, aliquots were stored and frozen for analysis by a hexokinase fluorimetric method using a Cobas Bio centrifugal analyzer (Roche Products, Ltd.) in Newcastle on Tyne.

Selected Abbreviations and Acronyms
BMI = body mass index
GIR = glucose infusion rate
HOMA = homeostatic model assessment
1/G = insulin to glucose ratio
MCR = metabolic clearance rate of glucose
SSBG = steady-state blood glucose
SSPI = steady-state plasma insulin
SPSS = Statistical Package for Social Sciences
WHO = World Health Organization

Results
The hypertensive and normotensive groups were matched for age, sex, and body mass index (Table 1). Percentage body fat, although higher in the hypertensive group compared with the normotensive group (25.5% versus 18.2%; P=.08) did not reach statistical significance. The waist/hip ratios of the two groups were also similar, indicating proportionately similar central fat distribution despite the tendency to a different total body fat content. The mean systolic and diastolic blood pressure measurements were obviously significantly greater in the hypertensive group than the normotensive group.

Blood glucose and serum insulin responses to a 75-g oral glucose load in the two groups are shown in Table 2. All subjects had normal glucose tolerance. The blood glucose responses of the two groups were comparable except for the slightly but significantly higher fasting levels in the hypertensive group (P=.04). Basal insulin levels tended to be higher in hypertensive subjects, whereas other values were not significantly different.

Table 3 shows the other metabolic measurements in the two groups. The mean serum total cholesterol levels were significantly elevated in the hypertensive group (4.8 mmol/L versus 3.9 mmol/L; P<.05), although the triglyceride levels did not differ between the two groups.

The mean MCR was significantly reduced in the hypertensive subjects, whereas the mean SSPI levels achieved during the glucose-insulin infusion were equivalent. The mean SSBG was significantly elevated in the hypertensive minutes was calculated by dividing GIR by SSBG concentration. Basal insulin sensitivity (HOMA) was calculated using the following equation: Insulin Resistance (IR) = Blood Glucose × Serum Insulin (mmol/L · pmol/L)/22.5, as modified from Matthews et al.²² Serum triglycerides and cholesterol were measured by lipase/glycerol kinase and cholesterol oxidase methods, respectively, on a Cobas Bio fast centrifugal analyzer (Roche Products, Ltd.) using a commercial kit (Boehringer Mannheim). Insulin²³ and C-peptide²⁴ were measured by radioimmunoassay with interassay coefficients of variation of 6.8% and 4.4%, respectively.

Statistical Analysis
Analyses were performed using the SPSS.²⁵ Methods included one-way ANOVA, Student’s t test to compare group mean values, multiple linear regression analysis, and correlations assessed by univariate analysis using Spearman’s rank correlation coefficient (r). Results are presented as mean±SE.

TABLE 1. Clinical Characteristics of Hypertensive and Normotensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (n=15)</th>
<th>Normotensive (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>11/4</td>
<td>11/4</td>
</tr>
<tr>
<td>Age, y</td>
<td>385 (1.7)</td>
<td>386 (1.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.6 (0.9)</td>
<td>24.4 (0.9)</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.89 (0.02)</td>
<td>0.89 (0.01)</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>25.5 (2.8)</td>
<td>18.1 (2.7)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>178 (6)</td>
<td>131 (3)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>111 (2)</td>
<td>83 (5)</td>
</tr>
</tbody>
</table>

§P<.001.
group compared with the normotensive subjects. The mean fasting C-peptide levels were similar in both groups, although the mean 150 minutes and 180 minutes levels were significantly higher in the hypertensive group, reflecting the higher glucose levels. The mean fasting serum insulin to fasting blood glucose ratio in the hypertensive group, although higher, did not reach statistical significance. However, basal insulin resistance assessed by the HOMA method was twice as high in hypertensives as in controls (12.84[3.78] versus 5.76[1.08] mmol/L \cdot pmol/L; \textit{P} = .052).

Table 4 shows Spearman’s rank correlation coefficients (\(\rho\)) of MCR and fasting serum insulin concentration with various variables. There were significant correlations of MCR and fasting insulin only with systolic and diastolic blood pressure. Stepwise multiple linear regression of fasting serum insulin and MCR glucose on systolic and diastolic blood pressure, body mass index, waist/hip ratio, percentage body fat, serum cholesterol, and serum triglyceride was performed. In both the regression models, after diastolic blood pressure (\(r = .52, \textit{P} = .01\), and \(r = .40, \textit{P} = .04\)) was entered into the equation, no other variable contributed significantly.

**Discussion**

The results of the present study demonstrate that the hypertensive black African subjects show higher SSBG and lower mean MCR of glucose than normotensive subjects, indicating lower insulin sensitivity in the hypertensive group. Previous studies have shown that in the glucose-insulin infusion test, after 150 minutes, steady-state levels of glucose and insulin are achieved. During the steady-state phase, the net glucose and insulin disposal is zero. The mean blood glucose concentration in the steady-state phase therefore reflects the net sensitivity of tissues to insulin stimulated glucose disposal. The MCR of glucose is another index for measuring tissue insulin sensitivity and allows for differences in glucose levels.

The diminished tissue sensitivity to insulin stimulated glucose disposal found in the present study is in keeping with the results obtained in young black American males with borderline hypertension¹⁰ and in black South African male and female subjects with essential hypertension.¹⁸ In the hypertensive group, the metabolic clearance rate of glucose was reduced by 35% compared with that of normotensive subjects.
Fasting insulin concentration has also been correlated with hypertension, although there have been reports of no association or weak association in normotensive black African subjects. In the present study, the hypertensive group tended to have higher fasting serum insulin levels compared with normotensive subjects, although the association was not significant. Similarly, the fasting I/G, although higher in the hypertensive subjects than the normotensive subjects, was not statistically significant. However, calculation of basal insulin sensitivity by the HOMA method reached borderline significance. It should be remembered that these measures are of the basal state, whereas the glucose-insulin infusion test, and the euglycemic clamp used by others are measurements of the stimulated state so that identical results would not necessarily be expected.

Also of interest are the HOMA results in relation to other published values. The control subjects were significantly more insulin sensitive than populations we have studied in the UK and Mauritius. This finding is possibly due to the greater physical activity and lower percentage body fat in many populations.

There was a significant positive correlation of fasting levels of serum insulin and a negative correlation of metabolic clearance rate with systolic and diastolic blood pressure independent of waist/hip ratio, body mass index, percent body fat, serum cholesterol, and serum triglycerides. In the present study, where the subjects were non-obese (mean BMI < 25 kg/m²), adiposity does not explain the relative insulin resistance, although insulin resistance has been strongly correlated with degree of adiposity. A caveat should be added, however, in that body fat as measured by impedance tended to be higher in hypertensive subjects, although this increase was not significant. Studies in blacks in United States and in South Africa have also reported significant correlation between fasting serum insulin levels and blood pressure levels independent of indices of obesity in nonobese hypertensive subjects, whereas a recent study in urbanized hypertensive Zimbabweans also showed raised fasting insulin levels.

Our study, like other similar studies in black populations in United States and South Africa raises further the possibility of a causal relation between hypertension and insulin resistance. The degree of cause and effect relationship needs further investigation to detect interethnic variations in this and in the full-blown metabolic syndrome.

Few data are available on insulin sensitivity in un complicated black hypertension subjects in Africa. The subjects in this study had received no antihypertensive drugs, were normal body weight, and physically active. Similarly they had normal triglyceride levels, although cholesterol levels were slightly higher than in control subjects. Thus the hypertensive subjects lacked the other component parts of the metabolic syndrome. The results show unequivocally that insulin sensitivity was decreased although by a relatively small proportion compared with, for example, the input of diabetes or severe obesity. Thus a black stock, likely to be genetically homogeneous, shows similar features to those found in Europids.

**Acknowledgment**

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**References**


