Blood Pressure Increase With Impaired Glucose Tolerance in Young Adult American Blacks

Bonita Falkner, Katherine Sherif, Anne E. Sumner, Harvey Kushner

Abstract—Hypertension and non–insulin-dependent diabetes mellitus are more prevalent in blacks than whites. The convergence of these 2 disorders augments the expression and severity of cardiovascular disease. The purpose of this study was to determine whether alterations in glucose metabolism are related to an increase in blood pressure (BP). This study was conducted on 304 nondiabetic blacks (mean age=32 years). Measurements in all subjects included BP, anthropometric measures, oral glucose tolerance test, insulin clamp to measure insulin sensitivity, and plasma lipids. The sample was stratified according to plasma glucose on oral glucose tolerance test to normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetes mellitus (DM). A 2-way ANOVA was performed to determine differences between the metabolic groups. With the use of American Diabetic Association criteria, 20.4% of the samples were classified as IGT and 5.9% were diabetic. A significant increase in BP existed from NGT to IGT to DM, which was stronger in women than men (systolic blood pressure in women: NGT=122, IGT=127, and DM=140 mm Hg, \( P<0.001 \)) with a significant linear trend (\( P<0.001 \)). With the use of body mass index as a covariate, the group difference in BP remained significant (\( P=0.006 \)). Measures of insulin sensitivity demonstrated significant metabolic group differences (\( P<0.001 \)) with a linear trend (\( P<0.001 \)) of decreasing insulin sensitivity from NGT to DM. These results indicate that early alterations in glucose metabolism effects an upward shift in BP. The higher BP in IGT and DM may be due to vascular endothelial cell resistance to insulin action. (Hypertension. 1999;34:1086-1090.)

Key Words: insulin ■ glucose ■ diabetes mellitus ■ blood pressure ■ blacks ■ lipids

Hypertension and diabetes mellitus (DM) are both conditions that contribute to an increased risk and expression of cardiovascular disease. The risk for cardiovascular disease, as well as cardiovascular disease morbidity and mortality, are markedly augmented when hypertension and diabetes occur together. Both hypertension and non–insulin-dependent diabetes mellitus (NIDDM) occur at higher rates among black Americans, who also suffer a higher prevalence of cardiovascular disease.3

The insulin-resistance syndrome, which consists of high blood pressure (BP), obesity, glucose intolerance (or DM), and dyslipidemia, is strongly associated with cardiovascular disease.3 This metabolic syndrome of impaired insulin glucoregulatory action with hyperinsulinemia also occurs in blacks.4 It has been hypothesized that it is the hyperinsulinemia that emanates from impaired insulin action that contributes to vascular injury through lipid abnormalities and hypertension conferred by excess insulin.5,5 Alternatively, the elevated BP may be a more direct consequence of the tissue resistance to insulin action or insulin resistance.1 Impaired glucose tolerance (IGT) is a component of insulin resistance and is a high-risk status for the development of NIDDM.6 The purpose of this investigation was to determine whether IGT is associated with an increase in BP in young adult blacks.

Methods

Population

This study was conducted on 304 nondiabetic black men (\( n=108 \)) and women (\( n=196 \)). Each participant was drawn from a cohort that has been under study in investigations of BP and cardiovascular risk factors. All subjects in the cohort database were contacted and invited to participate; approximately 80% of these individuals continue to live in the Philadelphia area. Less than 10% of those contacted declined to participate for reasons of work schedules, illness, or lack of interest. On re-enrollment to this study, written informed consent was obtained from each participant on an institutionally approved protocol and consent form. Participants enrolled in this study included normotensives (BP <135 mm Hg systolic and <85 mm Hg diastolic) and borderline hypertensives (BP >135 and <150 mm Hg systolic or >85 and <90 mm Hg diastolic) on the basis of repeated measurements of BP. Subjects who were known diabetics were excluded from enrollment. The women in this study were studied during the follicular phase of the menstrual cycle.

Procedures

Enrollment assessment consisted of anthropometric measurements (height, weight, skinfold thickness, and circumference of arm, hips, thigh, and waist) and BP determination. Casual systolic (first phase) and diastolic (fifth phase) BP measurements were obtained by auscultation with a mercury column sphygmomanometer in the seated position after a 10-minute rest period. The average of 2 determinations was used as the BP (SBP, DBP, and...
MBP = DBP + (SBP - DBP)/3, in which SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure) at the time of the metabolic evaluation. With the use of the anthropometric measurements, body mass index (BMI), percent body fat, and fat-free mass were calculated.7 An oral glucose tolerance test (OGTT) was conducted at 8 AM after a 12-hour fast. A fasting blood sample for serum lipids and glucose was obtained, and then 75 g of glucose solution (Glucola, Ames Laboratories) was ingested. Blood samples were obtained at 30, 60, 90, and 120 minutes after ingestion of the glucose load and were assayed for glucose and insulin concentration. A serum sample was sent to the Lipid Research Laboratory where total cholesterol, HDL-C, and total triglycerides were analyzed with standard enzymatic methods and an automated analyzer (Hitachi 704). LDL was isolated according to the method of Bachorik et al.8 LDL cholesterol was calculated by the Friedewald equation.9 Apolipoprotein A-1 and apolipoprotein B were assayed turbidimetrically with commercial antibodies (Boehringer-Mannheim).

The euglycemic hyperinsulinemic clamp was used to measure insulin-stimulated glucose use.10,11 Each subject returned to the clinical research unit for the euglycemic clamp procedure at 8 AM after a 12-hour overnight fast. The euglycemic clamp procedure was conducted according to methods previously described.12,13 In brief, the subject rested for at least 20 minutes after placement of venous catheters for infusion and sample withdrawal. Before the onset of euglycemic hyperinsulinemia, 3 samples were withdrawn for determination of fasting plasma glucose and fasting insulin concentration. Hyperinsulinemia was established with a primed constant infusion of insulin with the method of Rizza et al14 to compute the priming dose and infusion rate of insulin. The target clamped-insulin concentration was 70 to 80 mU/m2 min.11 Glucose infusion was administered as 20% dextrose in water (Abbott). Insulin (Eli Lilly) was mixed with normal saline to a concentration of 1000 mU/mL. All solutions were delivered by syringe pumps (model 22, Harvard). Plasma glucose concentration was analyzed with the glucose oxidase technique (YSI Model 27, Glucostat). Plasma insulin concentration was determined with a solid phase radioimmunoassay (Coat-A-Count, Diagnostic Products Corp). The cross-reactivity with proinsulin in this assay is 40% at mid-curve (0 to 500). Plasma insulin concentrations in the study were well below mid-curve. Coefficient of variations for interassay and intra-assay variability for glucose, insulin, and the lipid assays were <5%.

### Data Analysis

We used the results of the OGTT on each subject to classify glucose metabolism status according to the criteria of the American Diabetes Association.6 With the use of these criteria, subjects were classified as normal glucose tolerance (NGT), IGT, or DM. Comparison of group means was performed with a 1-way ANOVA. The 3 glucose metabolism groups were compared within each gender separately, with a test for statistically significant linear trend in means. P values and linearity values <0.05 were considered statistically significant.

Note that the insulin levels were approximately log normally distributed; therefore, all analyses were performed with the observed values and the logarithmic transformed values for plasma insulin concentration. The P value presented in the results are for the measured insulin values not the logarithmic transformation of the insulin values. Insulin values measured during the OGTT were determined by the examination of the area under the curve of the 4 measurements by the trapezoidal rule to estimate the area. The results obtained by this method did not differ from the unweighted sum of the 4 insulin values. Bivariate correlation analyses with the Pearson correlation coefficient were also applied to all variables, which were examined in 3 sets (1 set for the entire study sample and 1 set for each gender). All cases included in this analysis had complete BP, anthropometric, and OGTT data.

### Results

Data were obtained on 304 young adult blacks: 108 men and 196 women. Emphasis was directed to enrolling women, and a larger sample of women than men was achieved. None of these subjects were known to have diabetes at the time of enrollment. Table 1 (left column) provides the mean age, BMI, and BP for the entire sample of men and women. The mean age was 32 years. The mean BMI was 27.8 for men and 31.9 for women. With the use of a BMI of >27.8,13 43.5% of the men were classified as obese; and with the use of a BMI of >27.2, 65.3% of the women were classified as obese. Table 1 also provides the age, BMI, and BP of subjects stratified according to glucose metabolism. Among men, 88

### Table 1. Body Size and BP in Metabolic Groups

<table>
<thead>
<tr>
<th></th>
<th>All Men (n=108)</th>
<th>NGT (n=88)</th>
<th>IGT + DM (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31.0±3.7</td>
<td>30.7±3.5</td>
<td>32.3±4.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>87.7±19.8</td>
<td>85.0±18.2</td>
<td>99.2±23.1</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI</td>
<td>27.8±6.0</td>
<td>26.7±5.5</td>
<td>32.3±6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central index</td>
<td>1.52±0.52</td>
<td>1.49±0.52</td>
<td>1.6±0.50</td>
<td>0.43</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>127±14</td>
<td>126±14</td>
<td>131±13</td>
<td>0.13</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>80±12</td>
<td>79±11</td>
<td>84±13</td>
<td>0.12</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>96±12</td>
<td>95±12</td>
<td>100±12</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Values are mean±SD. Central index indicates ratio of subscapular to triceps skinfold; P, level of significance between groups; and Linearity, linear trend across groups.

Glucose was administered as 20% dextrose in water (Abbott).
were classified with NGT, 17 were classified with IGT, and 3 were classified with DM. Because only 3 men were classified with DM, the IGT and DM were analyzed as 1 group (IGT + DM). According to the American Diabetes Association criteria, 6 5.9% of this cohort met OGTT diagnostic criteria for DM. In addition, 20.4% of the cohort met the diagnostic criteria for IGT. In this sample of young adult blacks, 26.3% have either IGT or DM.

As shown in Table 1, both weight and BMI increase as metabolic status shifts from NGT to IGT to DM in both men and women. Except for body weight in women, which was marginally significant, the other group differences in weight and BMI were statistically significant and there was a statistically significant linear trend. Note that the mean BMI among the women with NGT was 31.0, a level indicating a marginally significant, the other group differences in weight and BMI were statistically significant and there was a marginally significant linear trend. Among the men and women, there were statistically significant metabolic group differences and a significant linear trend. However, the DM group of men and women demonstrated higher total cholesterol, triglyceride, and apolipoprotein B mean values, resulting in statistically significant group differences and a significant linear trend. Thus, substantially altered plasma lipid levels were not detected until diabetic criteria in glucose metabolism were met in this sample of young adult blacks. With BMI as a covariate in the ANOVA, there continued to be statistically significant differences for total cholesterol \((P<0.02)\) and triglycerides \((P=0.03)\).

We have previously demonstrated a significant relationship of insulin resistance with BP in young blacks. 12,4 Correlation analyses of the measure of insulin sensitivity from the insulin clamp procedure and BP demonstrated the same relationships in this study. The figure demonstrates the statistically significant correlation of the computed mean BP with the insulin

**TABLE 2.** Insulin-Sensitivity Measures in Metabolic Groups

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Men (n=106)</td>
<td>All Women (n=196)</td>
</tr>
<tr>
<td></td>
<td>NGT (n=88)</td>
<td>NGT (n=136)</td>
</tr>
<tr>
<td></td>
<td>IGT (n=17)</td>
<td>IGT (n=45)</td>
</tr>
<tr>
<td></td>
<td>DM (n=3)</td>
<td>DM (n=15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M+</td>
<td>6.2±2.9</td>
<td>5.0±2.7</td>
</tr>
<tr>
<td>M’+</td>
<td>7.9±3.5</td>
<td>7.6±3.7</td>
</tr>
<tr>
<td>M’’</td>
<td>8.6±3.5</td>
<td>6.9±5.4</td>
</tr>
<tr>
<td>Insulin0, pmol/L</td>
<td>86±93</td>
<td>100±72</td>
</tr>
<tr>
<td>Insulin0, pmol/L</td>
<td>1966±1366</td>
<td>2346±1435</td>
</tr>
</tbody>
</table>

Values are mean±SD. ApoA indicates apolipoprotein A1; ApoB, apolipoprotein B. \(P\) and Linearity are the same as in Table 1.
sensitivity index for the entire cohort \( r = -0.33, P < 0.001 \). The correlation coefficient is statistically significant for men separately \( r = -0.33, P < 0.001 \) and for women separately \( r = -0.34, P < 0.001 \). Despite the marginal difference in mean plasma lipid concentration among the 3 metabolic groups, the correlation analyses demonstrated statistically significant correlations of BP with plasma lipids. These correlation coefficients are presented in Table 4. These analyses demonstrate a consistently strong relationship of BP with insulin resistance, and also correlations of BP with lipid alterations in blacks at a young age.

**Discussion**

The results of this study demonstrate a linear upward trend in BP that is not entirely due to obesity, with a shift from normal glucose metabolism to impaired glucose metabolism and DM by OGTT criteria in young adult blacks. This trend corresponds to a highly significant inverse correlation of BP with insulin sensitivity. Although there are statistically significant correlations of BP with plasma lipids, significant dyslipidemia is expressed only in subjects that meet the OGTT criteria for diabetes.

Previous investigations have implicated the hyperinsulinemia of insulin resistance as the mechanism that mediates BP elevation through the action of insulin on increasing sympathetic nervous system activity \(^{14}\) or on increasing renal sodium reabsorption. \(^{15}\) Investigations by Anderson et al. \(^{16,17}\) examined the effect of euglycemic hyperinsulinemia during a clamp procedure in both normotensive and hypertensive subjects. Although they demonstrated a significant increase in muscle sympathetic activity in response to the hyperinsulinemia, there was a decrease in BP in both normotensive and hypertensive subjects. There was also a decrease in peripheral vascular resistance, which indicated a vasodilator rather than a pressor effect of insulin. A previous investigation on BP sensitivity to sodium in this black American cohort did detect a significant relationship of plasma insulin with sodium sensitivity, but this relationship was strongly associated with obesity. \(^{18}\) On the other hand, the experimental works of Hall et al. \(^{19,20}\) detected no pressor effect of hyperinsulinemia in dogs. Thus, although an increase in sodium retention may contribute to an increase in BP in black Americans, this may not be the only explanation for the excess in hypertension or cardiovascular disease experienced by this minority group.

In humans with normal glucose tolerant, insulin has a vasodilator effect, resulting in an increase in blood flow and a decrease in vascular resistance. \(^{21}\) Studies by Baron et al. \(^{21}\) have shown that in insulin resistance associated with obesity and in insulin resistance associated with NIDDM, \(^{22}\) there is a blunted vasodilator response to insulin as well as an attenuated effect of insulin in decreasing vascular resistance. These investigators suggested that there may be a hemodynamic basis for the insulin resistance observed in patients with hypertension.

The above findings of a reduced vasodilator response to insulin in the insulin-resistant conditions of obesity and NIDDM are supported by the observations of Heise et al. \(^{23}\) in patients with hypertension and insulin resistance. Compared with normotensive subjects, obese insulin-resistant subjects show a significant attenuation in the increase in leg blood flow during insulin infusion. These investigators also demonstrated a small BP-lowering effect of exogenous insulin in the hypertensive insulin-resistant patients. Together these data support the concept of vascular resistance to the vasodilator action of insulin in insulin-resistant conditions.

Endothelium-dependent vasodilation is abnormal in patients with Type 1 (insulin dependent) DM \(^{24}\) and in patients with NIDDM. \(^{25}\) The endothelial dysfunction may be secondary to underlying mechanisms that result in reduced bioavailability of nitric oxide. \(^{25}\) Concurrent studies of endothelial-mediated vasodilation were not conducted in the present study. However, the upward trend in BP associated with impaired glucose metabolism and insulin resistance suggests that this relationship in this young adult black cohort may be related to vascular or endothelial resistance to insulin’s vasodilator action.

There may be some limitations to this study, such as the lower number of men than women enrolled and the sample selection. Participants in this study have also participated in

**TABLE 4. Correlation Coefficients of Mean Blood Pressure With Plasma Lipids**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( r )</td>
<td>( P )</td>
<td>( r )</td>
<td>( P )</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.25</td>
<td>0.01</td>
<td>0.15</td>
<td>0.04</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.02</td>
<td>0.98</td>
<td>-0.02</td>
<td>0.80</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.19</td>
<td>0.06</td>
<td>0.10</td>
<td>0.19</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.33</td>
<td>0.001</td>
<td>0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoA</td>
<td>0.08</td>
<td>0.40</td>
<td>-0.10</td>
<td>0.16</td>
</tr>
<tr>
<td>ApoB</td>
<td>0.29</td>
<td>0.003</td>
<td>0.29</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ApoA indicates apolipoprotein A1; ApoB, apolipoprotein B.
previous studies in our laboratory. Although on one hand this sample provides a prospective view on cardiovascular risk, their continuing participation could render the sample less generalizable. Other potential confounding factors that were not controlled include diet, fitness level, smoking, and night-shift work.

It has been estimated that ≈50% of diabetic subjects already have some form of significant cardiovascular disease by the time their diabetes is first diagnosed.26 In this young black cohort, metabolic alterations predictive of NIDDM along with lipid and BP risk factors are detectable in 26% of the cohort by 32 years of age. However, the HDL-C levels appeared to be conserved in this young black American sample. It is possible that pathways to vascular injury are underway before clinical expression of DM or sustained hypertension.

Acknowledgements
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References
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