Plasma Renin Activity and Insulin Resistance in African American and White Children: The Bogalusa Heart Study

Wei Chen, Sathanur R. Srinivasan, and Gerald S. Berenson

Recent studies have suggested that the renin-angiotensin system is a feature of the insulin resistance syndrome. However, whether such a relationship occurs in childhood and in both African Americans and whites is not clear. We examined this issue in a sample of 264 African American and white children aged 7 to 16 years who participated in a cross-sectional survey of the Bogalusa Heart Study (n = 3524). Children were selected using a stratified random sampling procedure based on race-, age-, and sex-specific percentiles of diastolic blood pressure. Whites had higher plasma renin activity than African Americans (7.1 ± 3.6 ng/mL/h v 5.3 ± 3.5 ng/mL/h, P < .01). Renin activity correlated with blood pressure (BP) (r = 0.21, P < .05) and insulin resistance index defined by post-glucose 1-h insulin × 1-h glucose (r = 0.19, P < .05) only in white children. Other components of insulin resistance syndrome (percent body fat, systolic blood pressure, high-density lipoprotein cholesterol, and triglycerides) showed no relation to renin in both races using univariate analyses. The distribution of insulin resistance index and renin activity among children with elevated BP (above 90th percentile) showed that the percentage of children with both high insulin resistance index and renin values was significantly greater in whites than in African Americans (45.6% v 23.3%, P < .05). A multivariate factor analysis of risk variables of insulin resistance syndrome resulted in clusters of BP/adiposity (factor 1), lipids/adiposity (factor 2), and insulin resistance/renin/adiposity (factor 3) in white children, with adiposity linking the three factors. However, a different pattern emerged in African American children for factor 2 and factor 3, and renin was not part of the cluster in any of the three factors. These observations suggest that renin may be a component of insulin resistance syndrome detectable in early life only in whites. Am J Hypertens 2001;14:212–217 © 2001 American Journal of Hypertension, Ltd.

Key Words: Renin, insulin resistance syndrome, race, children, risk factor.

The role of the renin-angiotensin system in the pathogenesis of cardiovascular disease including hypertension is now well-recognized.1–6 Traditional cardiovascular risk variables including obesity, insulin resistance/hyperinsulinemia, hypertension, and dyslipidemia tend to coexist more often than expected by chance alone.7–9 The clustering phenomenon of these traditional risk variables is called syndrome X or insulin resistance metabolic syndrome.7,8,10 Recent studies have suggested that plasma renin activity, in both hypertensive and normotensive subjects, is associated with insulin resistance.6,11–14 Which is thought to be a primary defect underlying the multiple disorders of Syndrome X.7,8 Furthermore, increased clustering of risk variables of insulin resistance syndrome have been found in nonmodulating hypertension characterized by abnormal renin, aldosterone, and renal blood flow responses to angiotensin II.15,16 Whether plasma renin activity might constitute a part of the insulin resistance syndrome in early life is unknown.

Ethnic and racial variation in the associations among risk variables of insulin resistance syndrome has been demonstrated in previous studies.12,17–20 Increased clustering of obesity, hyperinsulinemia, hypertension, and dyslipidemia has been found in whites versus African Americans.17,20 Observations from the Bogalusa Heart Study showed African American–white divergence in the correlates of blood pressure (BP) including plasma renin activity in childhood.18,19 However, limited information is available on African American–white difference regarding the association between plasma renin activity and risk factors.
variables of insulin resistance syndrome, especially in children. This analysis examines the relation of plasma renin activity to insulin, percent body fat, BP, high density lipoprotein (HDL) cholesterol, and triglycerides in African American versus white school-aged children.

Methods
Study Subjects
As part of the Bogalusa Heart Study, 3542 children (63% white, 37% African American) ages 5 to 14 years residing in the community of Bogalusa, Louisiana, were examined during 1973 to 1974, representing 93% of all eligible individuals. A sample (n = 368) of children was selected in 1975 to 1976 based on diastolic (fourth phase) BP as described previously for a study on parameters selected in 1975 to 1976 based on diastolic (fourth phase) triceps and subscapular skinfolds (STSS) and was subsequently used to derive total percent body fat (PBF). The STSS-to-D<sub>b</sub> conversion was based on race- and sex-specific regression equations derived from the pooled body density and skinfold data from several samples of white and African American children measured in different laboratories. The D<sub>b</sub>-to-PBF conversion was based on the following equations:

\[
PBF_{males} = [(5.68 - 0.041 \times \text{age})/D_b - (5.31 - 0.045 \times \text{age})] \times 100,
\]

\[
PBF_{females} = [(5.69 - 0.038 \times \text{age})/D_b - (5.31 - 0.041 \times \text{age})] \times 100.
\]

Laboratory Analyses
Cholesterol and triglycerides were measured by the use of chemical procedures with a Technicon AutoAnalyzer II (Technicon Instrument Corp, Tarrytown, NY) according to the Laboratory Manual of the Lipid Research Clinics Program. HDL cholesterol was measured by a heparin-calcium precipitation procedure. The laboratory was monitored for precision and accuracy of lipid measurements by the surveillance program of Centers for Disease Control and Prevention, Atlanta, GA.

In the analysis of risk variable clustering, factor analysis was performed using principal component analysis with varimax rotation to condense intercorrelated risk variables to a few hypothetical underlying "factors." The R-mode factor analyses, methods for studying the relationships among variables, were done adjusting for sex and age in African Americans and whites. The default cutoff point of the eigenvalue is set to 1.0 in SAS FACTOR procedure. Only variables with loadings (absolute

Statistical Methods
All data analyses were performed using Statistical Analytical Software (SAS). To improve the normality of distributions, triglycerides and insulin resistance index were log-transformed for significance tests, correlation, and factor analyses. All statistical analyses were done separately for whites and African Americans. Analysis of covariance was used to test the significance of differences in mean levels of study variables adjusting for age in each race–sex group. The relationship between renin activity and other cardiovascular risk variables was examined using partial Pearson correlation adjusting for age and sex.

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Table 1. Selected characteristics of study sample by race and sex

<table>
<thead>
<tr>
<th></th>
<th>Whites</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>N</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>11.9 ± 2.7</td>
<td>11.8 ± 2.4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>18.9 ± 3.8</td>
<td>18.0 ± 3.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>43.7 ± 16.6</td>
<td>40.3 ± 12.8</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>17.8 ± 7.3b,y</td>
<td>22.3 ± 5.1b</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>105.4 ± 12.4</td>
<td>103.9 ± 11.6</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>61.5 ± 9.3</td>
<td>60.7 ± 10.1</td>
</tr>
<tr>
<td>Fasting insulin (µU/mL)</td>
<td>31.1 ± 13.7y</td>
<td>28.7 ± 15.7y</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>93.8 ± 11.1</td>
<td>97.4 ± 11.6y</td>
</tr>
<tr>
<td>Insulin resistance index†</td>
<td>60.4 ± 57.1b</td>
<td>92.9 ± 74.2b</td>
</tr>
<tr>
<td>Plasma Renin Activity (ng/mL/h)</td>
<td>7.2 ± 3.5</td>
<td>7.0 ± 3.7y</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>58.5 ± 15.9ab,y</td>
<td>51.9 ± 16.5n,y</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>68.2 ± 29.4x</td>
<td>72.5 ± 38.8x</td>
</tr>
</tbody>
</table>

* 14 children with missing values for renin activity are not included.
† 1-h insulin (µU/mL) × 1-h glucose (mg/dL)/100.
Sex difference (adjusted for age); a: P < .05; b: P < .01.
Race difference (adjusted for age); x: P < .05; y: P < .01.

Values (mean ± SD) greater than or equal to 0.3 were considered in interpretation in the present study.

Results

Table 1 shows the levels (mean ± SD) of risk variables by race and sex. Sex differences were significant for percent body fat (females > males), insulin resistance index (females > males), and HDL cholesterol (males > females). Significant race difference in percent body fat was observed only for males (whites > African Americans), and in fasting glucose only for females (whites > African Americans). Levels of fasting insulin, renin activity, and triglycerides in white children were significantly higher than in African American children, and African American children showed higher HDL cholesterol than white children. No significant race difference was observed for blood pressure and insulin resistance index.

Fig. 1 shows partial Pearson correlation coefficients, adjusted for sex and age, between renin activity and other risk variables by race. Renin activity was significantly correlated with DBP ($r = 0.21, P < .05$) and insulin resistance index ($r = 0.19, P < .05$), but not with other variables in white children. Renin activity was not related to any of the variables in African American children.

Three factors were generated for African American and white children that fitted the criterion of an eigenvalue greater than 1.0. The factor loading patterns of risk factors related to syndrome X are presented by race in Table 2. Factor 1 consisted of percent body fat, SBP and DBP, and the loading coefficients were very similar in African American and white children. However, the loading patterns of factors 2 and 3 were different between white and African American children. Percent body fat, HDL cholesterol, and triglycerides loaded on factor 2 in whites, but percent body fat was not a component of factor 2 in African Americans. Percent body fat, insulin resistance index, and renin were included in factor 3 in white children, whereas renin was not included in any of the three factors in African American children. It should be noted that percent body fat loaded on all the three factors in white children. These three factors explained 70.8% and 60.7% of the total variance of the seven risk variables in white and African American children, respectively.

The relation of insulin resistance index to renin activity was examined in white and African American children with high BP (DBP >90th percentiles specific for age and sex in the total sample distribution), and the results are shown in Fig. 2. White children with high BP showed a significantly higher proportion of individuals having increased levels (above the median) of both insulin resis-
tance index and renin activity (21 of 46 = 45.6%) than African American children with high BP (7 of 30 = 23.3%).

Discussion

The present community-based study demonstrates marked African American–white difference in the association of plasma renin activity with blood pressure and insulin resistance as defined by the product of 1-h post-glucose insulin and glucose responses in early life. Recent studies in adults have shown a positive relation between renin activity and insulin resistance in both hypertensive and normotensive subjects.6,11–14 Whereas in this study such association was found in white children, but not in African American children. To our knowledge, no comparable data showing a lack of relationship in African Americans in this regard are available in either children or adults. The complexity of mechanisms contributing to hypertension may overshadow this relationship in African Americans.

In the current study, African American children showed lower renin activity in both the entire sample and the high blood pressure strata. It is well-known that African American adults with hypertension have low renin levels.19,31 Furthermore, insulin–blood pressure association in childhood also differ between African Americans and whites, with the former showing no association and the latter a positive trend. A similar racial difference has been reported previously in adults.17 As discussed below, the lack of associations of renin with BP and insulin in African Americans may partially account for the inconsistencies in the insulin–BP relationship reported earlier in African Americans and whites.17,32–35

The renin-angiotensin system has been generally recognized to play a central role in the regulation of BP by providing a homeostatic control mechanism for sodium

Table 2. Factor loading of risk variables of insulin resistance syndrome by race

<table>
<thead>
<tr>
<th></th>
<th>White (n = 132)</th>
<th></th>
<th>African Americans (n = 132)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Factor 1</td>
<td>Factor 2</td>
<td>Factor 3</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>0.36</td>
<td>-0.41</td>
<td>0.60</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.88</td>
<td>-0.16</td>
<td>0.15</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.91</td>
<td>-0.00</td>
<td>0.13</td>
</tr>
<tr>
<td>Insulin resistance index*</td>
<td>-0.00</td>
<td>-0.06</td>
<td>0.92</td>
</tr>
<tr>
<td>Renin activity</td>
<td>0.20</td>
<td>0.18</td>
<td>0.36</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.02</td>
<td>0.90</td>
<td>0.07</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.16</td>
<td>-0.85</td>
<td>0.09</td>
</tr>
<tr>
<td>Variance explained (%)</td>
<td>25.6</td>
<td>25.3</td>
<td>19.9</td>
</tr>
<tr>
<td>Cumulative variance (%)</td>
<td>25.6</td>
<td>50.9</td>
<td>70.8</td>
</tr>
</tbody>
</table>

BP = blood pressure.

Loadings with absolute values ≥0.30 are in bold type.

* 1-h insulin (µU/mL) × 1-h glucose (mg/dL)/100.

FIG. 2. Relationship between plasma renin activity and insulin resistance index in the high blood pressure stratum in African American and white children: The Bogalusa Heart Study. High blood pressure was defined by diastolic blood pressure above 90th percentiles specific for age and sex in the distribution of the total population. Mean values (medians) for children of all strata combined are presented by dotted lines. White children showed a significantly (P < .05) higher proportion of high insulin resistance–high renin (21 of 46 = 45.6%) than African American children (7 of 30 = 23.3%).
balance, intravascular volume, and vascular tone and structure. Moreover, hyperinsulinemia/insulin resistance has been implicated in sodium and fluid retention, enhanced sympathetic nervous system activity, and stimulation of renin-angiotensin axis. It is of interest that renin-angiotensin system is thought to be associated with hyperinsulinemia/insulin resistance and related disorders of carbohydrate–lipid metabolism only among those with normal- to high-renin activity. This is consistent with the current observations showing an African American–white difference in clustering patterns of risk variables of insulin resistance syndrome and renin activity. Furthermore, in view of interrelationships between dietary salt, salt sensitivity, the renin-angiotensin system, and insulin sensitivity, lower renin activity, and higher salt sensitivity among African Americans versus whites may be another potential factor contributing to the observed racial difference. Our study has limitation in that the lack of information on salt intake in the study subjects precludes the examination of confounding effect of sodium intake on the observed African American–white differential in the relation of plasma renin activity to features of insulin resistance syndrome. However, the 24-h urinary sodium excretion data, a surrogate for sodium intake, in this sample showed neither race difference nor relationship to plasma renin activity in African American and white children.

Both obesity and insulin resistance are considered to play a major role in the multiple disorders of syndrome X. In this study, the clustering characteristics by factor analysis showed clusters of BP/adiposity (factor 1), lipids/adiposity (factor 2), and insulin resistance/renin/adiposity (factor 3) in white children, with adiposity linking the three factors. Whereas adiposity and renin, respectively, did not form part of factors 2 and 3 in African American children. Earlier studies including our own showed an African American–white difference in the clustering of risk variables of insulin resistance syndrome, with whites showing stronger clustering than African Americans. In our earlier studies, results of factor analysis based on 4522 individuals from the same population showed that the two factors were linked by the shared correlations with obesity and hyperinsulinemia in children (ages 5 to 11 years), with white children showing higher loadings than African American children. However, the shared correlations with obesity and hyperinsulinemia in adolescents (ages 12 to 17 years) were noted only for whites, but not for African Americans.

The observed African American–white difference in the involvement of renin activity as part of the syndrome X in early life may reflect the difference in morbidity and mortality of coronary heart disease between the two racial groups. It has been reported that concomitant conditions of hyperinsulinemia/insulin resistance, dyslipidemia, and a family history of myocardial infarction are generally absent in low-renin hypertensive subjects, a situation analogous to that seen in African American populations. This has been attributed to the differential effect of renin status on the risk of coronary heart disease found in earlier studies.

In summary, plasma renin activity is found to be a part of the features of insulin resistance syndrome in white children, but not in African American children. Although the mechanisms linking renin-angiotensin system and syndrome X is not clear, the presence of this association in whites versus African Americans early in life suggests an increased burden of cardiac risk in whites with syndrome X and high renin levels. Recent findings of the Heart Outcomes Prevention Evaluation Study showing the beneficial effects of angiotensin converting enzyme inhibitors, which blocks the activation of the renin-angiotensin-aldosterone system, on cardiovascular events and incidence of onset of type 2 diabetes in patients with vascular disease further underscore the pathogenic importance of this metabolic syndrome.

Acknowledgments

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References

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