Changes in Metabolic Syndrome Variables Since Childhood in Prehypertensive and Hypertensive Subjects
The Bogalusa Heart Study

Sathanur R. Srinivasan, Leann Myers, Gerald S. Berenson

Abstract—That essential hypertension is associated with metabolic syndrome is known. However, information is scant regarding the course of development of adverse levels of blood pressure and other risk variables of metabolic syndrome in youth at risk for developing hypertension. This aspect was studied, retrospectively, in a community-based cohort of normotensive ($n=2206$), prehypertensive ($n=721$), and hypertensive ($n=328$) subjects examined serially during childhood (4 to 11 years), adolescence (12 to 18 years), and adulthood (19 to 42 years). Prehypertensive subjects versus normotensive subjects had significantly higher body mass index and subscapular skinfold, systolic (SBP) and diastolic (DBP) blood pressures, and triglycerides beginning in childhood; higher glucose in adolescence; and higher low-density lipoprotein cholesterol, fasting insulin, and insulin resistance index in adulthood. Hypertensive subjects versus normotensive subjects had higher adiposity measures, SBP and DBP, glucose, and triglycerides beginning in childhood; higher insulin and insulin resistant index in childhood and adulthood; and lower high-density lipoprotein, cholesterol in adulthood.

Most of these variables progressed adversely at an increased rate in prehypertensive and hypertensive subjects. In a multivariate analysis, adverse changes in adiposity, SBP, and DBP were independently associated with prehypertensive status; and adverse changes in adiposity, SBP and DBP, insulin resistant index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides with hypertension status. As young adults, prehypertensive and hypertensive subjects showed significantly higher prevalence of obesity, hyperinsulinemia, hyperglycemia, and dyslipidemias. Thus, excess adiposity and blood pressure beginning in childhood and accelerated adverse longitudinal changes in risk variables of metabolic syndrome through young adulthood characterize the early natural history of hypertension. (Hypertension. 2006;48:33-39.)

Key Words: hypertension, essential ■ metabolism ■ insulin ■ lipids ■ metabolic syndrome ■ children ■ young adults ■ risk factors

Essential hypertension is an important risk factor for morbidity and mortality from coronary heart disease, stroke, and renal disease.1–3 Although clinical manifestations of hypertension do not generally emerge until middle age, the pathophysio logic precursors of adult hypertension are thought to originate very early in life, including the period of fetal development.4–6 Recognizing the importance of the evolution of high blood pressure levels from childhood to adulthood, as part of the early natural history of essential hypertension, the National High Blood Pressure Education Programs for adults7 and children8 provided guidelines for prevention and control of hypertension.

It is well recognized that hypertension, in general, does not occur in isolation but coexists in varying degrees with conditions of obesity, insulin resistance/hyperinsulinemia, and dyslipidemia, the interrelated metabolic disorders characteristic of metabolic syndrome.9–11 Further, prospective studies have shown that hypertension is preceded by a prehypertension stage characterized by abnormalities considered as potential metabolic precursors of hypertension.12–15 However, in this regard, the course of concurrent development of adverse levels of blood pressure and other risk variables of metabolic syndrome during the period of childhood, adolescence, and young adulthood in persons at risk still needs elucidation. This might be useful not only in assessing future risk but also in prevention and intervention algorithms.

As part of the Bogalusa Heart Study, a community-based investigation of the evolution of cardiovascular disease risk beginning in childhood,16 the present analysis examines the longitudinal trends in blood pressure and other risk variables of metabolic syndrome in a cohort of normotensive, prehypertensive, and hypertensive subjects as they grew from childhood into young adulthood.

Methods

Population
The Bogalusa Heart Study is being conducted in a semirural, biracial (65% white and 35% black) community of Bogalusa, LA. Between
Blood pressure measurements were obtained on the right arm of the subject in a relaxed, sitting position. Arm length and circumference were measured to ensure proper cuff size. SBP and DBP levels were recorded at the first, fourth, and fifth Korotkoff phases using a mercury sphygmomanometer. Blood pressure levels were reported as the mean of 6 replicate readings, taken by each of 2 randomly assigned and trained observers. For longitudinal analysis, fourth phase was used for diastolic pressure for both children and adults, because fourth phase is more reliably measured in childhood and more predictable of adult hypertension. To classify adults by hypertension status, fifth phase was used.

Laboratory Analyses

From 1973 to 1986, cholesterol and triglyceride levels were measured using chemical procedures on a Technicon Autoanalyzer II (Technicon Instrument) according to the Laboratory Manual of the Lipid Research Clinics Program. These variables were determined by enzymatic procedures on the Abbott VP instrument (Abbott Laboratories) between 1987 and 1996 and on the Hitachi 902 Automatic Analyzer (Roche Diagnostics) afterward. Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardization Program of the Centers for Disease Control and Prevention, which routinely monitors the precision and accuracy of cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol measurements since the beginning of this study. Measurements on the quality control samples assigned by the agency showed no consistent bias over time within or between surveys. Serum lipoprotein cholesterol were analyzed by using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures. Based on the National Cholesterol Education Program Adult Treatment Panel III guidelines, adult subjects were classified as dyslipidemic if they had high low-density lipoprotein (LDL) cholesterol (≥160 mg/dL), high triglycerides (≥200 mg/dL), or low HDL cholesterol (<40 mg/dL) or if they were on medication for dyslipidemia.

From 1976 to 1991, plasma glucose was measured by a glucose oxidase method using a Beckman glucose analyzer (Beckman Instruments). Since then, it has been measured enzymatically as part of a multichemistry (SM2A20) profile. Hyperglycemia was defined as fasting value ≥110 mg/dL. Plasma immunoreactive insulin levels were measured by a commercial radioimmunoassay kit (Phadebas, Pharmacia Diagnostics). Hyperinsulinemia was arbitrarily defined as fasting value >18 μU/mL, a value considered indicative of insulin resistance in normoglycemic subjects. In addition, an index of insulin resistance was calculated according to the homeostasis model assessment formula:

\[
\text{HOMA-IR} = \frac{\text{fasting glucose (mmol/L)}}{\text{fasting insulin (μU/mL)}}
\]

This model is considered useful to assess insulin resistance in epidemiological studies.

Statistical Analyses

All of the statistical analyses were performed with SAS version 9.1 software (SAS Institute). In the analyses, the race–sex groups were combined to increase statistical power and to simplify the presentation. Normalizing transformations were applied to some variables before analyses. Mean levels of risk variables in 4- to 11-, 12- to 18-, and ≥19-year age groups corresponding with the preadolescence, adolescence, and adulthood period were compared by their hypertension status in adulthood (normotensive versus prehypertensive and normotensive versus hypertensive). A single measurement per subject was used to calculate mean levels of risk variables within age groups. Mixed-models regression methods were used, with risk factor variable as the outcome measure; hypertension status as the predictor; and age, race, and sex as covariates. In this regard, the Aikake Information Criterion was used to choose between compound symmetric and autoregression covariance structure. Using data from the most recent screening, with 95.5% between 18 and 54 years of age, with a mean ±SD age of 11.6 ±3.9. The mean ±SD age was 27.0 ±6.5 at the most recent screening, with 95.5% between 18 and 42 years of age. Table 1 shows the distribution of the study cohort by the number of screenings and observations between childhood and adulthood. In all, 81% of subjects were screened ≥3 times and 54% 4 to 6 times.

Subjects from 6 cross-sectional studies of children who participated in at least 1 of the 7 cross-sectional screenings as young adults were eligible for the study. Of these, a total of 3255 subjects (64% white, 45% male) with no missing blood pressure data were included in the analyses. At the initial screening 98.8% were between 5 and 18 years of age, with a mean ±SD age of 11.6 ±3.9. The mean ±SD age was 27.0 ±6.5 at the most recent screening, with 95.5% between 18 and 42 years of age. Table 1 shows the distribution of the study cohort by the number of screenings and observations between childhood and adulthood. In all, 81% of subjects were screened ≥3 times and 54% 4 to 6 times.

Based on the blood pressure values at their last survey, adult subjects were classified as normotensive (n=2206), prehypertensive (n=721), and hypertensive (n=328) according to the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg, or use of antihypertensive medication; prehypertension as SBP between 120 and 139 mm Hg or DBP between 80 and 90 mm Hg; and normal blood pressure as both SBP and DBP <120 and 80 mm Hg, respectively. The institutional review board approved consent forms used for these surveys, and informed consent was obtained from study participants in adulthood and from parents or guardians in childhood.

General Examination

Identical protocols were used by trained examiners across all of the surveys. Subjects were instructed to fast for 12 hours before screening, and compliance was determined by interview on the morning of examinations. Information on personal health and medication history were obtained by questionnaires. Anthropometric and blood pressure measurements were made in replicate, and mean values were used in all of the analyses.

Height and weight were measured 2 times and subcapular skinfold thickness 3 times. In the longitudinal analysis, body mass index (BMI) weight in kilograms divided by the square of height in meters) was used as a measure of overall adiposity and subcapular skinfold for truncal fatness. In addition, waist circumference was measured in triplicate since 1988 as an indicator of visceral fatness. Young adults were considered obese if their BMI was ≥30 or waist circumference was ≥100 cm.
equation method with age as predictor, adjusting for sex, race, and sex by race interactions, as necessary. Probability values were Bonferroni adjusted. Multivariate analyses (generalized estimation equation method) were used to determine which longitudinal changes in risk variables since childhood predicted adult hypertension status (normotensive versus prehypertensive and normotensive versus hypertensive). Risk variables were standardized based on age-, race-, and sex-specific means and SDs. The model included adjustment for age, race, sex, sex by race interactions, subscapular skinfold, HOMA-IR, LDL cholesterol, HDL cholesterol, triglycerides, SBP, and DBP. Nonsignificant terms ($P > 0.05$) were removed from the model by backward stepwise procedure.

### Results

Mean levels of blood pressure and other variables of metabolic syndrome in childhood (4 to 11 years), adolescence (12 to 18 years), and adulthood (19 to 42 years) are shown in Figures 1–4 by hypertension status in adulthood. A single measurement per subject was used in each age group. Comparisons were made after adjusting for age, race, and sex. Both prehypertensive and hypertensive groups versus the normotensive group displayed significantly higher levels of SBP, DBP, BMI, subscapular skinfold, and triglycerides from childhood through adulthood. The prehypertensive group versus the normotensive group had higher levels of glucose in adolescence and higher levels of LDL cholesterol, insulin, and HOMA-IR in adulthood. On the other hand, the hypertensive group versus normotensive group showed higher levels of glucose from childhood through adulthood, higher levels of insulin and HOMA-IR in childhood and adulthood, and lower levels of HDL cholesterol in adulthood.
Longitudinal rates of change in risk variable of metabolic syndrome are presented in Table 2 by adult hypertension status. Compared with the normotensive group, the rates of increase in BMI subscapular skinfold, SBP, DBP, LDL cholesterol, triglycerides, insulin, and HOMA-IR were significantly higher among the prehypertensive and hypertensive groups.

Independent associations between adverse longitudinal changes in risk variables since childhood and adult prehypertension and hypertension conditions were examined in a multivariate analysis, shown in Table 3. Adverse changes in subscapular skinfold, SBP, and DBP were independently associated with prehypertension status and adverse changes in subscapular skinfold, SBP, and DBP, HOMA-IR, LDL cholesterol, HDL cholesterol, and triglycerides with hypertension status.

The prevalence of cardiovascular risk factors related to metabolic syndrome in adulthood at the last survey is presented in Table 4 by hypertension status. Compared with the normotensive group, obesity in terms of excess generalized adiposity (BMI) or visceral adiposity (waist circumference), hyperinsulinemia indicative of insulin resistance, hyperglycemia, and high-risk levels of dyslipidemias were all significantly more prevalent among the prehypertensive (except HDL cholesterol) and hypertensive groups.

Discussion

The present community-based study shows that, among the risk variables of metabolic syndrome examined adiposity, SBP, DBP, and triglycerides were consistently higher from...
TABLE 2. Longitudinal Rates of Change in Risk Variables of Metabolic Syndrome Since Childhood in the Study Cohort by Adult Hypertension Status: The Bogalusa Heart Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Prehypertensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m² per y</td>
<td>0.42</td>
<td>0.55*</td>
<td>0.56*</td>
</tr>
<tr>
<td>Subscapular skinfold, mm/y</td>
<td>0.68</td>
<td>0.81*</td>
<td>0.92*</td>
</tr>
<tr>
<td>Systolic BP, mm Hg/y</td>
<td>0.36</td>
<td>0.87*</td>
<td>0.96*</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg/y</td>
<td>0.50</td>
<td>0.84*</td>
<td>0.92*</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>1.42</td>
<td>1.93*</td>
<td>1.80*</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>-0.52</td>
<td>-0.59</td>
<td>-0.49</td>
</tr>
<tr>
<td>Triglycerides, mg/dL per y</td>
<td>2.08</td>
<td>3.32*</td>
<td>4.52*</td>
</tr>
<tr>
<td>Insulin, μU/mL per y</td>
<td>0.05</td>
<td>0.16†</td>
<td>0.16§</td>
</tr>
<tr>
<td>Glucose, mg/dL per y</td>
<td>-0.74</td>
<td>-0.83</td>
<td>-0.54</td>
</tr>
<tr>
<td>HOMA–IR, y</td>
<td>-0.02</td>
<td>0.01†</td>
<td>0.01§</td>
</tr>
</tbody>
</table>

Values are regression slope with respect to age in years adjusted for race and sex, and the race by sex interaction, as applicable. Different from normotensive: *P<0.0001; †P<0.01; ‡P<0.001; §P<0.05. ‖Fasting subjects only.

Adulthood, and associated independently with conditions of prehypertension and hypertension in adulthood are consistent with the concept of the tracking (persistence) of risk factor variables over time. Persistence of elevated blood pressure over time has been demonstrated in both pediatric and adult populations.24–27 In addition, this study supports the previous data showing earlier blood pressure elevations ultimately progressing to clinical hypertension.24–28 The importance of the observed childhood blood pressure elevations progressing to hypertension in young adulthood is underscored by the fact that adverse anatomic cardiovascular changes characteristic of hypertension already occur in children with elevated blood pressure.8,29–33

Previous studies have shown obesity as an independent risk factor for hypertension.13,34–36 Furthermore, an earlier report from this community found higher blood pressure and adiposity in childhood as independent predictors of adult hypertension in whites as well as in blacks.25 The present study extends those previous findings in terms of association between metabolic syndrome variables and early natural history of essential hypertension. In this study, both prehypertensive and hypertensive subjects displayed excess adiposity since childhood. Of note, adverse changes in adiposity, other than blood pressure, was the only other independent correlate of prehypertension status, a condition antecedent to clinical hypertension. On the other hand, adverse changes in other variables of metabolic syndrome, such as insulin resistance measure (HOMA-IR), and lipid variables were also independently associated with hypertension status. It should be noted that in a related previous study regarding the role of adiposity versus insulin in the development of metabolic syndrome, we have demonstrated the temporal nature of the association between obesity and hyperinsulinemia/insulin resistance be-

TABLE 3. Adverse Longitudinal Changes in Risk Variables Since Childhood as Independent Correlates of Adult Prehypertension and Hypertension Status: The Bogalusa Heart Study

<table>
<thead>
<tr>
<th>Normotensive vs Independent Variable</th>
<th>β*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehypertensive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subscapular skinfold</td>
<td>0.0029†</td>
<td>0.0016–0.0041</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.01†</td>
<td>0.009–0.011</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.0012‡</td>
<td>0.0004–0.0016</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subscapular skinfold</td>
<td>0.0473†</td>
<td>0.0232–0.0714</td>
</tr>
<tr>
<td>Syst. BP</td>
<td>0.109†</td>
<td>0.086–0.1319</td>
</tr>
<tr>
<td>Diast. BP</td>
<td>0.023§</td>
<td>0.005–0.041</td>
</tr>
<tr>
<td>HOMA–IR</td>
<td>0.015§</td>
<td>0.0025–0.0276</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.0239§</td>
<td>0.0028–0.0449</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.021†</td>
<td>0.005–0.0371</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.0149§</td>
<td>0.0012–0.0285</td>
</tr>
</tbody>
</table>

*Generalized estimation equation method regression coefficient adjusted for age, race, sex, and race by sex interactions, as applicable. Model includes subscapular skinfold, HOMA-IR, LDL cholesterol, HDL cholesterol, triglycerides, syst. BP and diast. BP.

†P<0.0001; †P<0.01; ‡P<0.05.
ginning in childhood\textsuperscript{37} and between childhood obesity and the incidence of metabolic syndrome in young adulthood.\textsuperscript{38} independent of baseline insulin levels. Taken together, these findings strongly suggest that excess adiposity, rather than hyperinsulinemia/insulin resistance, may play a primary role in the early natural history of essential hypertension. As a limitation, the current study did not compare the serial changes of underlying features of metabolic syndrome since childhood by race, although black excess in the prevalence of hypertension is well known. The inadequate sample size of the black versus white cohort by hypertension status precluded such longitudinal analysis.

The current observational study, although longitudinal in nature, cannot address the issue of causality but only suggest putative mechanisms for the observed relationships. Obesity, per se, could raise blood pressure by adversely altering intravascular volume, cardiac output, cardiac systolic and diastolic function, renal-pressure natriuresis, and renal medullary compression.\textsuperscript{39–40} As a highly active endocrine organ, adipose tissue also plays an important role in the regulation of metabolic and hemodynamic processes through mechanisms that include activation of the sympathetic nervous system and adipose renin–angiotensin–aldosterone system along with suppression of natriuretic peptides activity.\textsuperscript{41–48} Hyperinsulinemia/insulin resistance, another underlying feature of metabolic syndrome,\textsuperscript{9–11} is also considered to play a role in the pathogenesis of hypertension.\textsuperscript{9–11,49,50} Because obesity and hyperinsulinemia/insulin resistance often coexist\textsuperscript{9–11} and insulin resistance and sympathetic activation can reciprocate both ways,\textsuperscript{50,51} the association between hyperinsulinemia/insulin resistance and hypertension may reflect concurrent mechanisms related to the effects of excess adiposity on blood pressure and insulin.\textsuperscript{52}

It is also apparent from the present study that, as young adults, the prehypertensive and hypertensive subjects already displayed increased prevalence of cardiovascular risk factors related to metabolic syndrome, such as measures of generalized and visceral obesity, adverse glucose homeostasis, and dyslipidemia. Of note, the adverse trends in mean levels of risk variables of metabolic syndrome in childhood, adolescence, and adulthood, as well as the prevalence of corresponding high-risk conditions of metabolic syndrome, were highest among the hypertensive group, followed by the prehypertensive group. This is consistent with previous studies in adult populations showing clustering of metabolic abnormalities associated with the development of hypertension.\textsuperscript{12–15} The current data, by showing the highest adverse trends in risk variables of metabolic syndrome among the hypertensive group, suggest that metabolic sequelae of obesity might have been well established much earlier in the hypertensive group versus the prehypertensive group.

Perspectives

The pathophysiological precursors of hypertension are thought to already begin in childhood. Furthermore, hypertension often occurs in conjunction with obesity and insulin resistance/hyperinsulinemia, considered to be antecedent abnormalities of metabolic syndrome. In a community-based longitudinal cohort, we found that adult prehypertensive and hypertensive versus normotensive subjects displayed excess adiposity and blood pressure, rather than insulin resistance/hyperinsulinemia, beginning in childhood, and accelerated adverse longitudinal changes in risk variables of metabolic syndrome from childhood through young adulthood. Although the precise mechanisms linking the antecedent abnormalities of metabolic syndrome and hypertension are uncertain at present, the current findings support a primary role for excess adiposity in the early natural history of hypertension. Of note, these results, when viewed in the context of the upward secular trends in adiposity and blood pressure in American youth,\textsuperscript{53–55} underscore the importance of control of excess adiposity early in life in the general population.

Acknowledgments

The Bogalusa Heart Study is a joint effort of many investigators and staff whose contributions are gratefully acknowledged. We especially thank the Bogalusa School System, teachers, parents, and, most importantly, the participants as children and young adults.

Sources of Funding

The study is supported by National Institutes of Health grants AG-16592 from the National Institute on Aging; HL-38844 from the National Heart, Blood, and Lung Institute; and HD-43820 from the National Institute of Child Health and Human Development.

Disclosures

None.

References


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Hypertension. 2006;48:33-39; originally published online June 12, 2006;
doi: 10.1161/01.HYP.0000226410.11198.f4

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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