Impact of Childhood Metabolic Syndrome Components on the Risk of Elevated Uric Acid in Adulthood: The Bogalusa Heart Study

PAUL MUNTNER, PHD; SATHANUR SRINIVASAN, PHD; ANDY MENKE, MPH; DHARMENDRAKUMAR A. PATEL, MD; WEI CHEN, MD; GERALD BERENSON, MD

ABSTRACT: *Background*: Cross-sectional studies indicate metabolic syndrome is a risk factor for elevated serum uric acid. However, longitudinal data on this association are limited. *Methods*: Bogalusa Heart Study participants (n = 517) were examined as children, aged 5 to 17 years, and as adults 13 to 21 years later. Childhood metabolic syndrome components included the highest quartile (specific for year of age, race, sex, and study year) of body mass index, insulin resistance, blood pressure, and triglycerides and lowest quartile of HDL cholesterol. Metabolic syndrome was defined as the presence of 3 or more of these components and elevated serum uric acid, in adulthood, as values at or above the 90th percentile (specific for race and sex). *Results*: For males, after multivariate adjustment, the odds ratios (95% confidence interval) of elevated serum uric acid associated with high blood pressure, low HDL-cholesterol, high triglycerides, insulin resistance, and high body mass index were 2.61 (1.13, 6.03), 1.47 (0.57, 3.80), 1.30 (0.55, 3.08), 2.87 (1.23, 6.71), and 3.25 (1.36, 7.74), respectively. The analogous odds ratios for females were 2.12 (0.99, 4.54), 0.38 (0.14, 1.04), 1.16 (0.54, 2.46), 1.78 (0.83, 3.79), and 3.55 (1.73, 7.31), respectively. Males and females with the metabolic syndrome in childhood were 2.60 (1.08, 6.27) and 3.01 (1.34, 6.75) times more likely to have elevated serum uric acid as adults, respectively. *Conclusions*: Metabolic syndrome and high body mass index in childhood were predictors of elevated uric acid in adulthood.
KEY INDEXING TERMS: Metabolic syndrome; Uric acid; Gout; Childhood. **[Am J Med Sci 2008;335(5):332–337.]**

Metabolic syndrome is highly prevalent among children and adolescents in the United States.[1–3] Data from the Third National Health and Nutritional Examination Survey indicate 63% of adolescents age 12 to 19 years in the United States have at least one component of the metabolic syndrome (high blood pressure, elevated triglycerides, low HDL-cholesterol, elevated serum glucose, or abdominal obesity).[1] Additionally, the metabolic syndrome, defined by the presence of 3 or more of these components, was present in 9% of children and adolescents. Data from the Bogalusa Heart Study have demonstrated an association between the metabolic syndrome in childhood and subclinical atherosclerosis and arterial stiffness in adulthood.[4,5]

In adults, metabolic syndrome is associated with an increased risk of cardiovascular and renal disease.[6,7] Furthermore, several cross-sectional studies indicate metabolic syndrome, insulin resistance and overweight are risk factors for elevated serum uric acid and gout.[8–13] Although longitudinal data indicate overweight is associated with elevated serum uric acid and gout, such data for insulin resistance and metabolic syndrome are sparse.[14,15]

The goal of the current study was to determine the association between metabolic syndrome and its individual components in childhood and elevated serum uric acid in adulthood. To accomplish this goal, we analyzed longitudinal data including up to 21 years of follow-up from the Bogalusa Heart Study.

Materials and Methods

Study Population

The Bogalusa Heart Study consists of multiple cross-sectional examinations of children aged 5 to 17 years residing in the biracial (65% white, 35% black) community of Bogalusa, Louisiana and young adults who participated as children.[16] The current

Department of Epidemiology (PM, SS, AM, DAP, WC, GB), Tulane University, New Orleans, Louisiana; Department of Medicine (PM, GB), and Center for Cardiovascular Health (SS, DAP, WC, GB), New Orleans, Louisiana.

Submitted May 29, 2007; accepted in revised form July 18, 2007.

The Bogalusa Heart Study has been supported by National Institute of Child Health and Human Development grant HD-047247, National Heart, Lung, Blood Institute grant HL-38844, and National Institute on Aging grant AG-16592.

Correspondence: Paul Muntner, PhD, Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, 1430 Tulane Avenue SL18, New Orleans, LA (E-mail: pmuntner@tulane.edu).

study cohort includes those who participated in at least 1 examination as a child in 1981–1982, 1984–1985, or 1987–1988 (ie, baseline visit), and returned for a follow-up examination as an adult between 2000 and 2002 (ie, follow-up visit). Accordingly, 517 participants (67% white, 42% males) with a mean follow-up period of 17 years (range: 13 to 21 years) were selected for the current study.

General Examination

As described elsewhere, all examinations used the same protocols and procedures.[17] Participants were instructed to fast for 12 to 14 hours before the examination and compliance was ascertained by interview. Height and weight were measured twice to the nearest 0.1 cm and 0.1 kg, respectively. The average height and weight were used to calculate body mass index as weight in kilograms divided by height in meters squared. Systolic and diastolic (4th Korotkoff phase for children and 5th Korotkoff phase for adults) blood pressure levels were measured in 3 replicates each by 2 randomly assigned trained observers on the right arm of participants in a relaxed sitting position. Average values of the 6 measurements were used for analyses. Questionnaire data relevant to the current analysis included cigarette smoking and alcohol consumption in adulthood. Cigarette smoking was defined as smoking at least 1 cigarette a week and alcohol consumption was categorized into 3 levels (less than 1 drink per day, 1 to less than 3 drinks per day, and 3 or more drinks per day).

Laboratory Analyses

From 1981 to 1986, cholesterol and triglyceride levels were measured using chemical procedures on a Technicon Autoanalyzer II (Technicon Instruments, Tarrytown, NY). These variables were determined by enzymatic procedures on the Abbott VP instrument (Abbott Laboratories, Chicago, IL) between 1987 and 1996 and on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN) after 1996. Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardization Program of the Centers for Disease Control and Prevention, which has routinely monitored the precision and accuracy of cholesterol and triglyceride measurements since 1973. Serum lipoprotein cholesterols were analyzed by using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures.

From 1981 to 1991, plasma glucose was measured by a glucose oxidase method using a Beckman Glucose Analyzer (Beckman Instruments, Palo Alto, CA). Since then, it has been measured enzymatically as part of a multichemistry (SMA20) profile. Plasma immunoreactive insulin levels were measured by a commercial radioimmunoassay kit (Phadebas, Pharmacia Diagnostics, Piscataway, NJ). An index of insulin resistance was calculated according to the homeostasis model assessment formula: HOMA-IR = fasting insulin (μU/mL) $\times$ fasting glucose (mmol/L)/22.5.

Serum uric acid levels were determined as part of SMA20 profile by uricase method. Urinary albumin excretion was assessed at the follow-up visit in 2000–2002 using a morning spot urine sample. An enzyme-linked immunosorbent assay procedure using an albuwell kit (Exocell, Philadelphia, PA) was used to quantify urinary albumin concentration. Urinary creatinine excretion was measured using the commercially available Jaffe reaction kit (Sigmachemicals, St. Louis, MO). Microalbuminuria was defined as a urinary albumin-to-creatinine ratio greater than 3 mg/mmol.

Definition of Metabolic Syndrome

Five metabolic syndrome components were considered in the current analyses. These included high blood pressure, high triglycerides, high homeostasis model assessment of insulin resistance, high body mass index, and low HDL cholesterol. Because the acceptable cut-points for the metabolic syndrome components are not established for children, high and low levels were defined as above the age-, race-, sex-, and study year-specific 75th and 25th percentiles, respectively. These cut-points were derived from the overall children population from the 1981–1982 (n = 2832), 1984–1985 (n = 2149), and 1987–1988 (n = 2582) surveys. For Bogalusa Heart Study participants with multiple examinations in childhood, components of the metabolic syndrome were determined to be present if levels exceeded the 75th percentile (less than 25th percentile for HDL-cholesterol) for $\geq$50% of the study visits and elevated levels (low levels for HDL-cholesterol) were present at the last childhood visit. Metabolic syndrome was defined as coexistence of 3 or more of these components.

Definition of Elevated Serum Uric Acid

Elevated serum uric acid in adults was defined as values equal to or greater than the 90th percentile of the race–sex specific distribution for the 1203 participants examined in 2000–2002. Specifically, elevated serum uric acid was defined as $\geq$7.8 mg/dL for white males, $\geq$8.0 mg/dL for black males, $\geq$5.8 mg/dL for white females and $\geq$5.8 mg/dL for black females. These cut-points were applied to the 517 adult study participants in 2000–2002 who had visits in childhood (ie, between 1981 and 1988) and were included in the current study.

Statistical Analyses

All data management and analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC). Mean levels of each metabolic syndrome component were calculated at baseline, using the most contemporary study visit, and follow-up for each race and sex group, separately. Additionally, the prevalence of cigarette smoking, alcohol consumption, and microalbuminuria at follow-up was calculated. Levels were compared between males and females and blacks and whites using t tests. Next, mean serum uric acid levels and the prevalence of elevated serum uric acid were calculated for participants with and without the metabolic syndrome and each of its 5 components, separately, in childhood. The statistical significance of differences in means and prevalences were determined using t tests and χ^2 tests, respectively. The odds ratio of elevated serum uric acid associated with metabolic syndrome and each of its components, separately, in childhood was determined after multivariate adjustment for race and follow-up age, cigarette smoking, alcohol consumption, and microalbuminuria. Analyses were repeated for whites and blacks, separately, with similar results (data not shown).

Results

On average, children and adolescents were 15.0 years of age (range: 7.4–18.0 years) at baseline and adults were 32.3 years (range: 23.8–38.1 years) of age at follow-up. Among males at baseline, HDL-cholesterol was higher among black children and adolescents (Table 1). Also at baseline, triglycerides were higher for white, compared with black, males and females. Differences were noted between males and females for systolic and diastolic blood pressure among both whites and blacks and for HDL-cholesterol for whites. At follow-up, the mean serum uric acid was 6.30 mg/dL and 6.69 mg/dL in white and black males (P = 0.108) and 4.54 mg/dL and 4.47 mg/dL in white and black females (P = 0.615).

Mean serum uric acid levels in adulthood were similar for males and females with, compared with their counterparts without, high blood pressure, low HDL-cholesterol, and high triglycerides in childhood (Table 2). However, the mean uric acid level was higher for females with insulin resistance and both males and females with high body mass index. Also, a substantially higher prevalence of elevated serum uric acid in adulthood were present for males and