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Low sensitivity for the metabolic syndrome to detect uric acid elevations in females and non-Hispanic-black male adolescents: An analysis of NHANES 1999–2006

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ABSTRACT

Background: Uric acid is tightly linked to the metabolic syndrome (MetS) and among adults higher uric acid levels are associated with future risk for diabetes, cardiovascular disease, hypertension and renal disease.
Objective: Evaluate the sensitivity of MetS to identify adolescents with elevated uric acid levels on a race/ethnicity and gender-specific basis.
Methods: We evaluated 3296 male and female adolescents 12–19 y participating in the National Health and Nutrition Evaluation Survey 1999–06, comprised of 67.6% non-Hispanic whites, 15.1% non-Hispanic blacks, and 17.3% Hispanics. We used a definition of MetS modified for use in adolescents and evaluated the sensitivity of a diagnosis of MetS to identify individuals with uric acid elevations (approximately the 95th percentile of uric acid by gender among normal-weight adolescents).
Results: When used as a screening test to identify individuals with uric acid elevations MetS performed more poorly among females (18.0%) than among males (37.0%) ($p < 0.001$). Among males, MetS exhibited a lower sensitivity among non-Hispanic blacks (17.8%) compared to Hispanics (45.9%) ($p < 0.01$) and non-Hispanic whites (37.4%) ($p < 0.05$). There were no race/ethnicity differences in detecting elevated uric acid levels among females (non-Hispanic-white 15.5%, non-Hispanic-black 19.4%, Hispanic 26.5%, $p > 0.05$).
Conclusion: Current criteria to diagnose MetS exhibit racial/ethnic and gender differences in the ability to identify adolescents with elevated uric acid levels, performing poorly among non-Hispanic-black males and among females. Given emerging data regarding the ability of uric acid elevations for predicting future disease, these data may have implications regarding the use of MetS as a marker of risk among all gender and racial/ethnic groups.

1. Introduction

Uric acid is a product of purine breakdown that is linked to oxidative stress [1] and has emerged in adults as an independent risk factor for future cardiovascular disease (CVD) [2,3], type 2 diabetes mellitus (T2DM) [4,5], hypertension [6] and renal failure [7]. Among adolescents, levels of uric acid are associated with an increase in carotid artery media thickness [8] and future hypertension [9]. These associations have raised the prospect of using uric acid as a marker of future disease risk [10].

Uric acid is also tightly linked to the metabolic syndrome (MetS) [11,12], a cluster of cardiovascular risk factors including elevated waist circumference (WC), increased blood pressure (BP), high triglycerides, low HDL-cholesterol and fasting hyperglycemia. Currently utilized criteria for diagnosing MetS such as those from the Adult Treatment Panel III (ATP-III) are based on specific cut-off values for these individual components [13]. MetS is strongly associated with insulin resistance and is a predictor of future T2DM in adolescents [14] and of future cardiovascular disease in adults [15]. Indeed, some have advocated that a diagnosis of MetS be a trigger for increased intervention among obese adolescents [16], who are at increasing risk for future CVD [17].

However, MetS exhibits racial/ethnic discrepancies that may decrease its effectiveness in predicting long-term risk for disease among all ethnicities [18–20]. Non-Hispanic-black adolescents exhibit a lower prevalence of MetS despite having a higher degree of insulin resistance [21,22] and higher rates of T2DM [23,24] and death from CVD [25]. This suggests that among

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non-Hispanic-black adolescents MetS may be under-diagnosed [26]. Additionally, females have an overall lower prevalence of MetS than males [19] but appear to have a tighter link between high uric acid and CVD [12].

Given the long-term associations of elevated uric acid and future disease, the association of uric acid with MetS, and racial/ethnic and gender discrepancies in MetS, our goal was to evaluate the ability of a classification of MetS to identify individuals with elevated uric acid levels on a race/ethnicity- and gender-specific basis. We applied a commonly used set of pediatric MetS criteria (the ATP-III criteria adapted for use in adolescence [11,22,27]) to adolescent data from the National Health and Nutrition Examination Survey (NHANES), with the hypothesis that MetS would perform more poorly at detecting elevated uric acid levels among non-Hispanic black adolescents than among non-Hispanic whites and Hispanics. In such a way we aimed to further detail racial/ethnic differences in currently used MetS criteria in assessing long-term risk.

2. Methods

Data were obtained from NHANES (1999–2006), a complex, multistage probability sample of the US population. These annual cross-sectional surveys are conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control (CDC), with randomly selected subjects undergoing anthropometric and blood pressure measurements, answering questionnaires and undergoing phlebotomy (http://www.cdc.gov/nchs/nhanes.htm). The NCHS ethics review board reviewed and approved the survey and participants gave informed consent prior to participation. WC, blood pressure (BP), and laboratory measures of triglycerides, HDL-C, and glucose were obtained using standardized protocols and calibrated equipment [11]. All blood samples used for analyses were obtained following a fast ≥8 h prior to the blood draw. Serum uric acid was measured by a colorimetric method in which uric acid is oxidized by uricase to form allantoin and H_2O_2. For NHANES 1999–2002 this method was used by Hitachi model 704 analyzer, Roche Diagnostics and from 2003 to 2006 this was measured by Beckman Synchron LX20, Beckman Coulter, Inc.

2.1. MetS classification

MetS was defined by a commonly used pediatric/adolescent adaptation of the Adult Treatment Panel III (ATP III) criteria [11,13,22,27]. Participants had to meet ≥3 of the following 5 criteria: concentration of triglycerides ≥ 110 mg/dL, HDL-C ≤ 40 mg/dL, WC ≥90th percentile for age/sex (or ATP III limit of 102 cm for males and 88 cm for females, whichever was lower) [13,28], glucose concentration ≥100 mg/dL, and systolic or diastolic BP ≥90th percentile (age, height, and sex-specific) [29]. Similarly, hypertension was defined as systolic or diastolic BP ≥90th percentile for age, height, and sex. Elevated uric acid levels were defined as approximately the 95th percentile of uric acid levels among lean adolescents (BMI <85th percentile) on a gender-specific basis. As in prior studies [22] lean individuals were chosen to determine these cut-offs because of the strong association between uric acid and adiposity [11].

Data from non-Hispanic-white, non-Hispanic-black, or Hispanic (Mexican-American/other Hispanic) adolescents 12–19 y.o. were analyzed. Children <12 y were excluded since fasting values for triglycerides and glucose were only obtained in participants ≥12 y.o. Subjects were excluded if they were pregnant or taking antihyperlipidemic or anti-diabetic medications, as these are all likely to alter lipid and insulin levels in a manner that may not reflect baseline MetS–uric acid correlations. Individuals taking antihypertensive medication were classified as having hypertension.

2.2. Statistical analysis

Statistical significance was defined as a p-value < 0.05. Statistical analysis was performed using SAS (version 9.2, Cary, NC) and SUDAAN (version 10; Research Triangle Institute, Research Triangle Park, NC), which accounts for the survey design when estimating standard errors to obtain population-based estimates. We combined all data sets from the 3 two-year cycles (1999–2006) for statistical analyses to increase total sample size. Prevalence rates of MetS were calculated by gender, race/ethnicity, and compared via chi-square tests. Mean uric acid levels were compared among groups using either unpaired t-tests or analysis of variance (ANOVA). The homeostasis model of insulin resistance (HOMA) was calculated as described previously [22].

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of MetS to identify elevated uric acid (approximately the 95th percentile of uric acid levels among lean adolescents, as described above) was computed by gender and race/ethnicity. All analyses incorporated the sampling weights included in NHANES.

3. Results

3.1. Sample characteristics

The sample consisted of 3296 non-Hispanic-white, non-Hispanic-black and Hispanic adolescents age 12–19 y.o. with data for all variables tested. Numbers of subjects with and without and values for individual MetS components by race/ethnicity are shown for male and female subjects in Tables 1 and 2, respectively. The numbers of subjects with MetS are the total number in the sample and have not been adjusted to reflect oversampling of minorities in NHANES. Regarding use of anti-hypertensive medications, 12 subjects total were on anti-hypertensive medications, and of these 3 had MetS, including 1 subject on each of the following classes: beta-blocker, angiotensin-converting-enzyme inhibitor and diuretic. Non-Hispanic-black males had the lowest rate of MetS of all the groups (Table 1). Among males non-Hispanic blacks with and without MetS had lower levels of triglycerides than non-Hispanic whites (Table 1) while among females non-Hispanic blacks only had the lowest levels of triglycerides among those without MetS (Table 2). Among males, non-Hispanic blacks with and without MetS had higher systolic BP than non-Hispanic whites and Hispanics (Table 1), while among females non-Hispanic blacks only had the highest systolic BP among those without MetS (Table 2).

Table 3 shows MetS-related characteristics by gender, race/ethnicity and MetS status. Among males with MetS, non-Hispanic blacks with had the highest BMI of the three groups and also had the highest levels of insulin of the three groups. Among females non-Hispanic blacks with and without MetS had the highest levels of BMI and insulin of the three groups. Among males with MetS there were no differences in levels of uric acid between racial/ethnic groups, while among males without MetS non-Hispanic-white males had the highest levels of uric acid. Among females with and without MetS non-Hispanic whites had the highest level of uric acid of the three groups.

3.2. Sensitivity of MetS for detecting high uric acid

A classification of MetS exhibited a lower sensitivity among females (18.0%, CI 12.1–29.1) than males (37.0%, CI 29.1–45.8) at identifying individuals with elevated uric acid levels (approximately the 95th percentile among lean individuals, 7.0 mg/dL for males and 5.5 mg/dL for females) ($p < 0.05$). There was no gender-specific difference in specificity of MetS to