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Does serum uric acid predict incident metabolic syndrome in a population with high prevalence of obesity?

Liberato Aldo Ferrara[1], **Hong Wang**[2], **Jason G Umans**[2,3], **Nora Franceschini**[4], **Stacey Jolly**[5], **Elisa T. Lee**[6], **Jeunliang Yeh**[6], **Richard B. Devereux**[7], **Barbara V. Howard**[2,3], and **Giovanni de Simone**[7,8]

[1]Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

[2]MedStar Health Research Institute, Washington, D.C

[3]Georgetown-Howard Universities Center for Clinical and Translational Science, Washington, D.C

[4]University of North Carolina at Chapel Hill, Chapel Hill, NC

[5]General Internal Medicine, Cleveland Clinic Medicine Institute

[6]Center for American Indian Health Research, University of Oklahoma, Oklahoma City, OK

[7]Department of Medicine, Weill Cornell Medical College, New York, N.Y

[8]Department of Translational Medical Sciences, Federico II University, Naples, Italy

Abstract

Objective—To evaluate whether uric acid (UA) predicts 4-yr incidence of metabolic syndrome (MetS) in non-diabetic participants of the Strong Heart Study (SHS) cohort.

Design and Methods—In this population-based prospective study we analyzed 1499 American Indians (890 women), without diabetes or MetS, controlled during the 4th SHS exam and reexamined 4 years later during the 5th SHS exam. Participants were divided into sex-specific tertiles of UA and the first two tertiles (group N) were compared with the third tertile (group H).

Results—Body mass index (BMI =28.3±7 vs. 31.1±7 kg/m^2), fat-free mass (FFM = 52.0±14 vs. 54.9±11 kg), waist-to-hip ratio, HOMA-IR (3.66 vs. 4.26), BP and indices of inflammation were significantly higher in group H than in group N (all p<0.001). Incident MetS at the time of the 5th exam was more frequent in group H than group N (35 vs. 28%, OR 1.44 (95% CI=1.10-1.91; p< 0.01). This association was still significant (OR= 1.13, p=0.04) independently of family relatedness, sex, history of hypertension, HOMA-IR, central adiposity and renal function, but disappeared when fat-free mass was included in the model.

Address for correspondence: L. Aldo Ferrara, MD Department of Clinical Medicine and Surgery, Federico II University Hospital Via S. Pansini 5 80131 Naples (Italy) Phone and Fax: +390817462303 ferrara@unina.it.

COMPETING INTEREST:
The authors have no competing interests.

Conclusions—In the SHS, UA levels are associated to parameters of insulin resistance and to indices of inflammation. UA levels, however, do not predict incident MetS independently of the initial obesity-related increased FFM.

Keywords

Uric Acid; Metabolic Syndrome; Obesity; Fat Free Mass; Strong Heart Study

INTRODUCTION

Serum levels of serum uric acid (UA) are closely related to protein metabolism and to renal function. Among variables that influence UA levels, sex, lean body mass and serum creatinine have been found strongly related (1). UA has an endothelial pro-inflammatory effect and is linked to individual components of the metabolic syndrome (MetS), such as arterial hypertension, insulin resistance and increased triglycerides (2-3).

The role of UA as a risk factor for arteriosclerosis and its relations with cardiovascular (CV) risk factors has been also extensively investigated in the past. A prospective study in a large population with a strong prevalence of male patients showed that high UA was associated with 60% higher risk of development of MetS in the following 6 years (4). In a large Chinese population sample, UA was related to MetS components, particularly in women (5). UA also predicted development of MetS in adolescents over a follow-up of 2.7 years (6), an effect that was independent of waist circumference, blood pressure and HDL-cholesterol. However, whether body composition influences these associations has never been tested.

Because UA is a potent antioxidant, it is uncertain whether high circulating UA exacerbates CV burden, or alternatively could offset other factors increasing oxidative stress (7). Thus, establishing the temporal relation between high levels of UA and development of MetS might help clarify the relation between UA and CV risk.

In consideration of the association of UA with the several above mentioned potential confounders, all able to independently increase the risk of MetS and the development of arteriosclerosis, aim of the present study was to evaluate the independent role of UA.ito influence the development of MetS, devolving special interest to body dimensions not only in terms of size, i.e. body mass index (BMI) but also to body composition [fatty mass (FA) and free-fat mass (FFM)]. Accordingly, we analysed the cohort of the Strong Heart Study (SHS), a population-based study with high prevalence of overweight/obesity to assess whether UA predicts development of MetS , independently of a number of known potential confounders and body composition, which is altered in the context of obesity.

METHODS

Study Population

The Strong Heart Study (SHS) is a population-based study to evaluate CV risk factors and disease in 4,549 American Indians, aged 45-74 ys. from 13 communities in Arizona, southwestern Oklahoma and North/South Dakota, which has been extensively described (8-9). Population of the present study (n= 3555) was recruited among subjects seen at the 4th

SHS examination, conducted in 2001-2003, which enrolled members of large multi-generation families (Strong Heart Family Study [SHFS]) that also included adolescents (8). For the purpose of the present study we analyzed participants meeting the following inclusion criteria:

- **a.** Absence of prevalent CV disease (heart failure, coronary artery disease [history of myocardial infarction, previous angioplasty or by-pass], stroke, valve replacement or significant valvular disease [aortic or mitral stenosis and/or more than mild regurgitation]
- **b.** Absence of diabetes mellitus;
- **c.** Triglyceride levels <750 mg/dL
- **d.** Absence of prevalent MetS, based on the ATP III criteria.

Laboratory evaluations

Clinical examinations and collection of blood samples after a 12-hour fast were performed in the morning by the study staff.

Diabetes mellitus was diagnosed if fasting blood glucose (FBG) was ≥126 mg/dL or if patients were taking oral hypoglycaemic drugs or insulin (10). Hypertension was defined as blood pressure >140/90 mmHg or use of antihypertensive treatment (11). Hypercholesterolemia was defined by total cholesterol >200 mg/dL or use of lipid lowering treatment (12). Similarly, hypertriglyceridemia was defied as fasting triglyceride >200 mg/dL or triglyceride-lowering therapy. Obesity was defined as BMI >30 kg/m^2 (13). Waist circumference was used as a measure of central fat distribution. MetS was defined according to the modified ATP-3 criteria (14). Homeostatic model assessment index was used to estimate insulin resistance (HOMA-IR) (15).

A random urine sample was obtained to measure creatinine and albumin content. Urinary albumin/creatinine ratio (UACR) was calculated and proteinuria was diagnosed as UACR >30 μg/mg. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD equation (16). C-reactive protein and fibrinogen were measured by standard methods.

Fat-free mass and adipose body mass were estimated by using an RJL bioelectric impedance meter (model B14101; RJL Equipment Co). To estimate fat-free mass (FFM, in kg), we used sex-specific equations based on total body water, using bioelectric resistance, which had been previously validated in the American Indian populations (17).

Statistical analysis

Data were analyzed using SPSS 17.0 (SPSS, Chicago, IL). Data are expressed as mean±SD, except for variables that were skewed (C-Reactive Protein, urinary albumin/creatinine, fasting insulin and HOMA-IR),). The non-normal distributed variables were logarithmically transformed for parametric statistics and were expressed as median and interquartile range. According to sex-specific cut-offs for tertiles of serum uric acid, participants were divided into group N (lowest and middle tertiles), and group H (highest tertile).

Indicator variables were included in all multivariate analyses for the three field centers, Arizona, South/North Dakota and Oklahoma). The impact of relatedness was considered by standard kinship coefficients (0.25 for parent-offspring, 0.25 for full siblings, 0.125 for half siblings and 0 for no consanguinity), used as covariates, as previously reported. Descriptive statistics were obtained, using one-factor ANOVA or chi-square distribution for categories (with Monte Carlo method for computation of exact 2-tailed p value, when appropriate). Binary logistic regression analysis was also used to evaluate the effect of initial uric acid on incident MetS, controlling for by confounders identified in exploratory analyses, using a hierarchical model building with the main covariates (age, sex, field center, systolic and diastolic BP, prevalence of clear-cut arterial hypertension and level of uric acid) forced into the regression, followed by backward stepwise addition of HOMA-IR, fasting glucose and waist-to-hip ratio, and, eventually, forcing fat-free mass into the model. Collinearity test for variable used in the multivariable analysis was performed using linear modelling of the outcome variables with calculation of the variance inflation factor (VIF) of the independent predictors. A VIF < 2 was considered optimal to warranty stability, though a VIF might be tolerated up to the value of 4. The null hypothesis was rejected at 2-tailed α <0.05.

RESULTS

Among 3555 individuals examined in the 4th SHS exam, prevalent metabolic syndrome (MetS) or diabetes were found in 1729 individuals (1094 women or 63%) who were, therefore, excluded from the analysis. Of the remaining 1836 participants, 1499 (890 women) returned 4 years later at the time of the 5th SHS exam and were included in the present analysis.

Sex-specific cut-points for tertiles of UA were: lowest tertile, UA< 5.4 mg/dL; middle tertile, UA=5.4-6.3 mg/dL; highest tertile, UA> 6.4 mg/dL for men; lowest tertile, UA< 3.7 mg/dL; middle tertile, UA=3.7-4.7 mg/dL; highest tertile, UA> 4.7 mg/dL for women.. On the basis of their UA, 985 individuals were included into Group N (lowest and middle tertile) and 514 into Group H (highest tertile).

Initial obesity was present in 578 individuals:313 (31.8%) in Group N and 265 (51.7 %) in Group H (OR 2.29, 95%CI 1.84-2.83, p< 0.001); hypertension was present in 154 individuals: 89 (9.0%) in Group N and 65 (12.7%) in Group H (OR 2.59, 95%CI 1.47-2.06, p< 0.01).

Table 1 displays demographic and metabolic characteristics of two groups. Participants in Group B exhibited higher BMI paralleling higher FFM, central adipose mass, higher blood pressure, glucose, HOMA-IR, total and LDL-cholesterol, triglycerides, inflammatory markers (CRP and PAI-1), and serum creatinine, whereas eGFR was lower (all p<0.005).

UA was significantly correlated with demographic and anthropometric variables as well as with glucose and lipid profiles, inflammation and renal function (table 2). The greatest correlation was found with FFM, with a coefficient of determination of more than 30% (table 2).

Incident MetS at the 5th phase was observed in 454 individuals (272 or 28% in Group N and 182 or 35% in Group H). Participants with elevated serum UA, therefore, had a significantly increased risk of presenting with the phenotype of MetS at the follow-up control, 4 years later (OR 1.44; 95% CI 1.14-1.81, p<0.01).

Multivariable logistic regression analysis, adjusting for age, sex, BP values, history of hypertension and degree of relatedness, confirmed that incident MetS was associated with higher baseline UA (OR= 1.24/mg×dL^{-1}, 95% CI=1.11-1.39, p< 0.0001). The association remained statistically significant, albeit slightly reduced, when adding HOMA-IR, central adiposity and GFR to covariates (OR= 1.14, 95% CI=1.02-1.26; p= 0.02), but it became non-significant when fat-free mass was included in the model (Table 3). Since we found slight, though statistically acceptable, degree of multicollinearity between sex (VIF=2.24) and lean body mass (VIF=2.62), we also included in the equation the interaction sex × FFM but the final model did not change.

DISCUSSION

While this study, performed in a non-diabetic population-based cohort with high prevalence of obesity but without MetS indicates that UA levels are associated to increased risk of subsequent development of MetS, it also demonstrated that the effect is concealed when body composition, and namely the amount of FFM, is considered among the potential confounders, contradicting the studies that have suggested a causal effect (19).

In a study in Korea including ~2400 individuals, high levels of UA (>6.5 mg/dL in men and >5.1 mg/dL in women) were associated with a more than two-fold probability of MetS (20) independently of sex. This study was observational and cross-sectional and no adjustment was made for prevalent diabetes mellitus and body composition.

In a prospective study in a large population, including mainly men, high UA levels (>6.5 mg/dL in men and >4.6 mg/dL in women) were related to a higher 5.5 yr. incidence of MetS in comparison with individuals in the lowest tertile (OR=1.6 for men and 2.0 for women) (4), but, again, no attempt was made to adjust for concomitant diabetes mellitus and body composition. In Japan hyperuricemia was identified as a predictor of MetS independently of parameters of lipid and glucose metabolisms (19;-21) as well as in a study performed in the Mongolian population (22), but body composition was never taken into account. In another study (6), serum UA was even associated with development of MetS in children and adolescents (age range: 10-15 yrs) and also predicted components of MetS, such as future waist circumference, systolic blood pressure, triglyceride and HDL-cholesterol, but no relation was reported with body composition. In a recent cohort study on about 70000 participants, serum levels of uric acid were found associated with increased risk of hypertension and ischaemic heart diseases; mendelian randomization analysis, however, did not confirm such a causal role whilst highlighted the effects of body mass index on uric acid level and suggested a role for elevated body mass index or obesity in the development of uric acid related conditions (23)

Considered all together, these study were perfectly consistent with our results if FFM was not included in the multivariable analysis. But, doing that one would exclude the most potent correlate of UA and MetS.

The relationship between FFM and UA, found in our study, has been cross-sectionally reported previously (1) and is of particular interest in the context of the SHS cohort, because of the high prevalence of obesity (24). The association between UA and central adiposity is likely mediated by the well known increase in FFM that occurs in obesity and appears consistent with the evidence of the association of markers of inflammation to both UA and central obesity, though the design of the study does not allow to infer cause-effect relationships. Our results suggest that UA might participate to the biological phenomena characterizing development of MetS, but that this might be unrestrained by the obesity-associated alteration of body composition, similar to other abnormalities related to obesity. Rather, we might speculate that UA might be responsible for generating a vicious circle.

The pro-oxidative action of UA may, in fact, accelerate adipose tissue formation (25) and contribute to insulin resistance through UA-induced decrease of nitric oxide that reduces glucose uptake in the skeletal muscle. The effect of UA on insulin resistance may explain its association with hepatic steatosis (26), a common condition in central obesity. Insulin resistance augments hepatic free fatty acid uptake by inducing peripheral lipolysis, and the consequent hyperinsulinemia accelerates hepatic fatty acid synthesis and decreases hepatic production of apolipoprotein B-100, which is required for triglycerides release (27). In addition, UA induces inflammatory oxidative changes in adipocytes, potentially facilitating the development of other characteristics of metabolic syndrome [28]. In contrast, some observations in the literature indicate that at certain levels UA is such a powerful antioxidant, likewise ascorbate, as to reduce the oxo-heme oxidant formed by peroxide reaction with hemoglobin, protects erythrocyte ghosts against lipid peroxidation, and protects erythrocytes from peroxidative damage leading to lysis (29). Moreover, it has been also suggested that UA is responsible for the increase in plasma antioxidant activity in healthy individuals after apple juice consumption through an increase in plasma polyphenols (30).

In conclusion, the results of the present study suggest that in a population with high prevalence of obesity but without diabetes, serum UA is associated with the development of MetS, but that this association is influenced by other MetS components and is not independent of the obesity-related increase in FFM. How much the FFM-related increase in UA contributes to development, persistence and aggravation of MetS should be better explored.

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Highlights

1. The present study confirms the results of previous cross-sectional observations that have stressed the close association between uric acid and main components of metabolic syndrome, particularly in large population samples in the far East Asia.
2. Other observations have also suggested a prospective role of uric acid in the development of metabolic syndrome. No-one of them, however, included in the prospective analysis parameters of body composition
3. This study proved that role of uric acid in the development of metabolic syndrome is significantly reduced when parameters of central adiposity (waist-to-hip ratio) are included in the analysis and is completely concealed when fat-free mass is taken in account.
4. Uric acid does not appear to influence development of metabolic syndrome independently of lean mass, which has been always found closely correlated to it.

Table 1

Characteristics of Participants in the Lower Two Thirds and Upper Third of Serum Uric Acid Level

	Group N (n= 985)	Group H (n= 514)
Age (yrs)	32.7±14	32.7±15
Sex (M/F) (n)	403/582	206/308
BMI (kg/m^2)	28.3±7	31.1±7**
Fat-Free Mass (kg)	52.0±11	54.9±11**
Waist/Hip ratio	0.87±0.07	0.89±0.08**
SBP (mmHg)	115.7±12	117.8±14*
DBP (mmHg)	72.9±10	74.8±10**
HR (b/min)	65.0±10	65.8±11
Fasting Blood Glucose (mg/dL)	89.9±8	91.4±9*
Fasting insulinemia (mU/L)	9.5 (6.4- 14.3)	10.9 (7.5-17.5)**
HOMA-IR	3.66 (2.43-5.60)	4.26 (2.83-6.67)**
Cholesterol (mg/dL)	171.4±33	177.4±34**
HDL Cholesterol (mg/dL)	55.4±14	54.2±14
LDL Cholesterol (mg/dL)	94.0±28	98.3±28*
Triglycerides (mg/dL)	111.1±49	124.0±62**
Uric Acid (mg/dL)	4.3±1	6.1±1.1**
Creatinine (mg/dL)	0.80±0.16	0.85±0.19**
C-Reactive Protein (log)	1.43 (0.89-5.56)	3.28 (1.17-7.21)**
Fibrinogen (mg/dL)	365.0±80	370.9±86
PAI-1 (ng/mL)	42.2±31	58.6±47**
Creatinine (mg/dL)	0.80±0.16	0.85±0.19**
GFR (mg/mL/1.73m^2)	106.3±24	98.5±21**
Urinary albumin/creatinine (mg/g)	6.40 (4.1-12-1)	5.76 (3.96-11.40)

GFR: Glomerular Filtration Rate.

Significances:

* p< 0.005

** p< 0.001

Table 2

Correlations between Serum Uric Acid and Demographic, Anthropometric and Biochemical Parameters

	r	p
Body Mass Index	0.11	< 0.001
Fat-Free Mass	0.55	< 0.001
Waist-to-Hip ratio	0.26	< 0.001
Systolic Blood Pressure	0.24	< 0.001
Diastolic Blood Pressure	0.21	< 0.001
Fasting Blood Glucose	0.16	< 0.001
Serum Insulin	0.064	0.01
Total Cholesterol	0.16	< 0.001
Triglycerides	0.18	< 0.001
Low Density Liproprotein-cholesterol	0.19	< 0.001
High Density Liproprotein-cholesterol	−0.14	< 0.001
Plasminogen Activator Inhibitor-1	0.17	< 0.001
Serum Creatinine	0.53	< 0.001
Glomerular Filtration Rate	−0.124	< 0.001

Table 3

Association of incident metabolic syndrome with age, sex, blood pressure, uric acid, body composition and insulin sensitivity.

	OR	95% CI	p
Age (×5 yrs)	1.00	0.99-1.01	0.91
Sex	4.11	1.66-6.35	0.001
Systolic BP (×5 mmHg)	1.01	0.998-1.027	0.08
Diastolic BP (×5 mmHg)	1.01	0.995-1.027	016
Uric Acid (mg/dL)	1.11	0.99-1.25	0.07
Central fat distribution	1.64	1.34-2.01	0.001
HOMA-R	1.02	0.99-1.05	0.11
FFM	1.04	1.02-1.06	0.001

BP=blood pressure.