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SHORT COMMUNICATION

Uric acid: A new marker for metabolic syndrome? Results of a population-based study with adults

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Abstract *Background and aims:* Recently, studies have shown a positive association between serum uric acid (UA) and metabolic syndrome (MS). To evaluate the predictive capacity and the association of serum UA with pre-MS and MS, by sex, in adults.
Methods and results: Cross-sectional study with 932 adults, of both sexes, from Viçosa, Minas Gerais (MG), Brazil. Sociodemographic and behavioral data were obtained through a questionnaire and anthropometric, clinical, and biochemical evaluation. We used multinomial logistic regression and the area under receiver operating characteristic curve (AUC). The prevalence of pre-MS was 17.8% and of MS was 26.5%. The fitted models showed positive association of serum UA with pre-MS (OR = 1.62, 95% CI = 1.09–2.40) and MS (OR = 2.61, 95% CI = 1.99–3.42) among men. For women, similar results were found for MS (OR = 2.59, 95% CI = 1.81–3.73). The optimal cutoff points obtained by AUC for pre-MS and MS were 4.7 and 4.9 mg/dL among men and 3.1 and 3.4 mg/dL among women, respectively.
Conclusion: The results point to a positive association of UA with pre-MS and MS, with no significant differences between sexes. Therefore, UA can be used as an additional marker in the screening of these conditions.

Introduction

Uric acid (UA) is the final product of purine catabolism in humans, [1] under normal conditions, the main antioxidant in plasma. Although the increase in serum UA is a protective factor against oxidative stress [2], when your levels circulating go beyond the physiologic limit of solubility cause gout [3], and various cardiometabolic diseases [4–6].

Studies have pointed to a possible positive relationship between the MS components and the increase in serum UA [5,7], with several investigating the predictive role of serum UA in relation to MS [8–10] and increased total and cardiovascular mortality [11]. However, few assess the predictive role of UA with pre-MS.

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Thus, the present study aimed to evaluate the predictive capacity and the association of serum UA with pre-MS and MS, by sex, in adults.

Methods

Design and study population

A population-based study was conducted in the urban area of the city of Viçosa, MG, Brazil. The reference population consisted of adults (20–59 years old), of both sexes. The sample was calculated using the Open Epi® software, considering the following parameters: reference population of 43.431 individuals [12]; prevalence of outcome of 29.8% [13]; predicted sample error at 4%; study design effect at 1.6; percent loss estimated at 10%; control of confounding factors at 10%. The calculated final sample was 954 individuals.

The study was approved by the Human Research Ethics Committee (CAAE nº. 42073314.0.0000.5153). All participants have signed the Term of Free and Informed Consent. The detailed methodology of the research can be found in a previous publication [14].

Data collection

Sociodemographic and behavioral data were collected by a structured questionnaire. In addition, anthropometric and clinical parameters were measured and blood sample was collected. Waist circumference (WC) was measured at the midpoint between the last rib and the iliac crest. Blood samples were collected by venipuncture using the Vacutainer system (Becton Dikinson, UK), after 12-h of fasting. Fasting glucose was determined by the enzymatic glucose-oxidase method. Triglycerides, HDL-cholesterol, and UA were measured by the enzymatic colorimetric method. UA was obtained with commercial kits Bioclin (monoreagent uric acid K139). Blood pressure (BP) was measured in two moments using a properly calibrated digital pulse sphygmomanometer (Omron HEM 629) [15].

Variables

The MS was diagnosed according to Harmonizing Criteria of the Metabolic Syndrome, which considers the concomitant occurrence of at least three of the following alterations: increased waist circumference by sex and ethnicity (men $\geq$ 90 cm and women $\geq$80 cm for South Americans); hypertriglyceridemia ($\geq$150 mg/dL) or on treatment with lipid-lowering agents; reduced High Density Lipoprotein Cholesterol (HDL) ($<$40 mg/dL for men and $<$50 mg/dL for women) or on treatment with lipid-lowering drugs; high blood pressure (systolic $\geq$ 130 mmHg and/or diastolic $\geq$85 mmHg) or on antihypertensive treatment; high serum glucose ($\geq$100 mg/dL) or on treatment with antidiabetic agents. In turn, pre-MS was defined as the presence of two of these alterations [16].

The main explanatory variable UA was used in its continuous form and expressed as mg/dL. The other variables used for adjustment purposes were: age (in years); schooling (in years of study); smoking (smoker, former smoker, and non-smoker); and physical activity level (physically active $\geq$ 150 min per week and physically inactive $<$150 min per week), which was assessed by the International Physical Activity Questionnaire (IPAQ), long version [17].

Data analysis

Statistical analyses were carried out using the STATA 13.1 software, taking into account the sampling design effect by using the svy set command. The analyses were weighted by sex, age, and schooling and the weights were determined by the ratio between the proportions of individuals according to IBGE data and in the sample.

The associations were tested using multinomial logistic regression, with crude and adjusted odds ratios (OR) and their respective 95% confidence intervals (95% CI) estimated. The contribution of each variable in the model was evaluated by the Wald test. The without MS was used as reference in all analyses.

The predictive capacity of UA for pre-MS and MS was evaluated by the area under the ROC curve, and an area $\leq$0.5 indicates that the model has no discrimination capacity. The ROC curves were also used to determine the optimal cutoff points, and those values with the highest sensitivity (SE) and specificity (SP) concomitant were selected.

The analyses were stratified according to sex and the group of individuals without MS was considered as reference in all analyses. The level of significance was 5%.

Results

In this study, the sample consisted of 932 participants, 50.8% male, 31% aged 20–29 years, 46.6% completed 12 or more years of study, 65.8% non-smokers, and 72.5% physically inactive. The mean serum UA level was 4.11 mg/dL ($\pm$0.22 mg/dL) and the prevalence of pre-MS and MS was 17.8% (95% CI: 14.11–22.43) and 26.5% (95% CI: 16.77–39.21), respectively. UA means were significantly higher among men (5.42 $\pm$ 0.10 mg/dL) and women (4.16 $\pm$ 0.17 mg/dL) with MS than those without MS (4.43 $\pm$ 0.07 mg/dL and 3.09 $\pm$ 0.045 mg/dL, respectively). The mean UA was also significantly higher in women with pre-MS (3.35 $\pm$ 0.10 mg/dL), but not in men (4.86 $\pm$ 0.18 mg/dL), than in those without MS.

In Fig. 1, it can be seen that the UA means were significantly higher among men and women with MS when compared to those without MS.

Table 1 shows the crude and adjusted OR for the association between serum UA levels and pre-MS and MS according to sex. In the male-adjusted model, the increase of 1 mg/dL in serum UA was associated with 62% increase in pre-MS chance and 161% increase in MS chance among those with higher UA values (OR = 2.59; CI: 1.81–3.73), and the association with pre-MS had borderline statistical significance (p = 0.052).

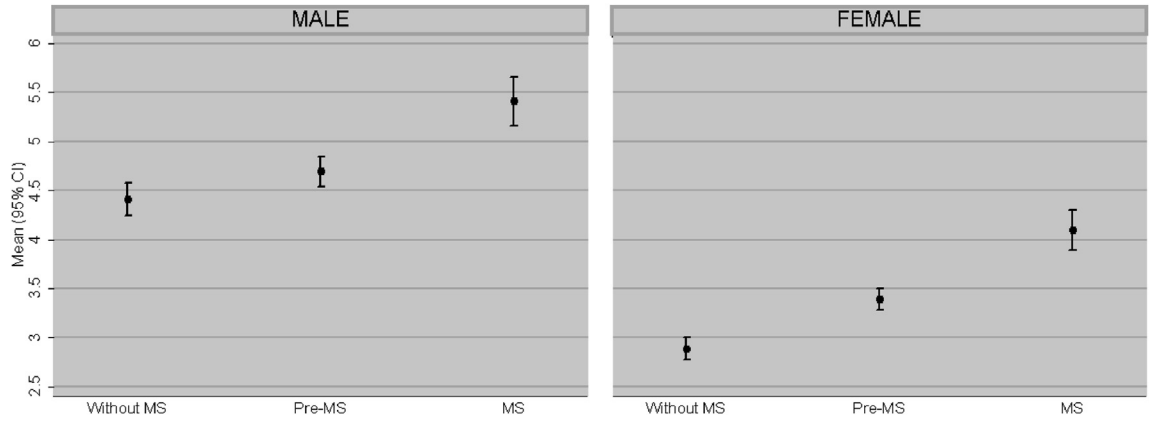

Figure 1 Uric acid averages (UA) according to the presence of metabolic syndrome (MS), according to sex. Viçosa, MG, Brazil 2012–2014.

Table 1 Multinomial logistic regression models for the association of serum uric acid levels with pre-syndrome and metabolic syndrome, according to sex. Viçosa, MG, Brazil, 2012–2014.

	without MS OR	*p*	pre-MS OR (CI 95%)	*p*	MS OR (CI 95%)	*p*
Men						
Model 1[a]	1.0		1.44 (0.99–2.09)	0.050	2.12 (1.77–2.53)	<0.001
Model 2[b]	1.0		1.62 (1.09–2.40)	0.020	2.61 (1.99–3.42)	<0.001
Women						
Model 1[a]	1.0		1.43 (1.09–1.88)	0.015	3.23 (2.39–4.36)	<0.001
Model 2[b]	1.0		1.33 (0.99–1.77)	0.052	2.59 (1.81–3.73)	<0.001

CI: confidence interval; OR: odds ratio; MS: metabolic syndrome.
Without MS as reference category. Pre-MS (presence of two alterations).
[a] Crude model.
[b] Adjusted model for age, education, smoking and physical activity.

Table 2 Areas under the ROC curves (AUC), cutoff points, sensitivity and specificity of serum uric acid levels in relation to pre-MS and MS, according to sex. Viçosa, MG, Brazil 2012–2014.

	AUC	(CI 95%)	Cutoff poits	Sensitivity	Specificity
Men					
UA Pre-MS	0.62	(0.54–0.69)	4.7	61.64	61.60
UA MS	0.70	(0.64–0.76)	4.9	62.92	62.50
Women					
UA Pre-MS	0.59	(0.53–0.66)	3.1	61.45	52.22
UA MS	0.74	(0.68–0.79)	3.4	69.44	64.91

UA Pre-MS – serum uric acid in Pre-MS; UA MS: serum uric acid in metabolic syndrome; AUC – areas under the ROC curves. CI: confidence interval.

The optimal UA cutoff points defined from the AUC analysis are presented in Table 2. Cutoff points of pre-MS were 4.7 and 3.1 mg/dL for men and women, respectively. Cutoff point of MS was 4.9 mg/dL for males and 3.4 mg/dL for females.

Discussion

The results of the present study show a strong association between serum UA levels and occurrence of pre-MS and MS, without significant differences by sex. It is also worth noting that high UA levels were found among pre-MS individuals, indicating that this group should also be the target of preventive measures.

Others epidemiological studies also found higher serum UA levels among MS individuals [4,5,8,9]. Ciarla et al. [5] showed levels increased gradually with the number of MS components. Silva et al. [6] found a positive association between serum UA concentrations and MS and also demonstrated its association with pre-MS, corroborating with our findings. In addition, other studies have found associations between UA concentrations and the individual components of MS, showing that the higher the number of MS components, the higher the serum UA levels are found [2,5–7,9,18]. Ciarla et al. [19] found associations between UA levels and several cardiometabolic parameters both in individuals with≥ 5 mg/dl and < 5 mg/dl de UA, suggested that lower level are already able to exert negative influence on the individual cardiovascular risk profile. In the study by Virdis et al. [11] they also found this association. The levels of UA increase the risk of total mortality and cardiovascular mortality are significantly lower than those used in the definition of hyperuricemia in clinical practice. These findings corroborate our results since our cutoff points were <5 mg/dl of UA.

Some studies have suggested that, because UA is an effective antioxidant, its increase may be compensatory due to the oxidative stress associated with MS [20]. However, it has also been proposed that increased UA levels may be a cardiometabolic risk factor, since they may aggravate insulin resistance and other processes associated such as hypertension, obesity, and endothelial dysfunction, increasing cardiovascular risk [7].

The cutoff points for SM were slightly lower than those reported for similar age groups (5.3 and 4.0 mg/dL for men and women, respectively). However, the results of the AUC in our study were slightly higher than those of that study (0.652 men and 0.665 women) [8].

In conclusion, the results of this study revealed that serum UA levels were strongly associated with pre-MS and MS, with no significant differences between sexes. We can suggest, therefore, the use of UA as an additional marker for MS screening in clinical and public health practice, especially because of its easiness of measuring and low cost.

We propose that further research should be undertaken, especially of longitudinal design, to elucidate the directionality of the relations between UA and cardiometabolic abnormalities.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the topic addressed.

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