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Association between Uric Acid and Cardiovascular Risk Variables in a Non-Hospitalized Population

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Abstract

Background: The association between uric acid (UA) and cardiovascular risk variables remains a controversial issue in epidemiological studies.

Objective: To evaluate the association between UA, blood pressure (BP), anthropometric indices and metabolic variables in a non-hospitalized population stratified by UA quintiles.

Methods: A cross-sectional observational study evaluated 756 individuals (369 males), mean aged 50.3 ± 16.12 years, divided in UA quintiles. BP, body mass index (BMI), abdominal circumference (AC), UA, glucose, insulin, HOMA-IR, total cholesterol (TC), LDL-c, HDL-c, triglycerides (TG) and creatinine (C) levels were obtained. The estimated glomerular filtration rate (eGFR) was calculated and arterial hypertension (AH) was considered when BP ≥ 140x90 mmHg, overweight/obesity (OW/O) was considered when BMI ≥ 25 kg/m² and metabolic syndrome (MS) was established according to the I Brazilian Guideline of MS.

Results: 1) there was no difference between the groups regarding the distribution by sex and age range; 2) the highest UA quintiles presented higher mean age ($p < 0.01$), BMI, AC ($p < 0.01$), SBP, DBP ($p < 0.001$), TC, LDL-c, TG ($p < 0.01$), C and eGFR ($p < 0.001$) and lower mean HDL-c ($p < 0.001$); 3) the group with the highest UA quintile showed higher prevalence of AH, OW/O and MS ($p < 0.001$); 4) higher percentages of the lowest quintiles of insulin ($p < 0.02$) and HOMA-IR ($p < 0.01$) were observed with the lowest quintiles of UA; 5) a logistic regression analysis showed that UA and the variables that compose MS were associated with the occurrence of MS ($p < 0.01$).

Conclusion: Higher quintiles of uric acid were associated with a worse cardiovascular risk profile and a worse kidney function profile in the non-hospitalized population sample studied. (Arq Bras Cardiol 2011;96(3):212-218)

Keywords: Cardiovascular diseases/epidemiology; uric acid; hypertension; risk factors; metabolic syndrome.

Introduction

Although the role of classic risk factors have been well-established in the context of cardiovascular disease (CVD), several emergent conditions, called risk marker, have not had their association definitely demonstrated. Studies are necessary to understand the actual role they have in this scenario and whether they can actually be of value in the early identification of individuals at risk of developing CVD. Among these studies, is the one on uric acid (UA), which has behaved as a cardiovascular risk factor in several cross-sectional studies[1-5]. However, the presence of several confounding variables, such as obesity, alcohol consumption, age, diabetes and use of diuretics have made it difficult, to date, to indisputably establish the role of UA as an independent risk factor for cardiovascular events.

The association between hyperuricemia and arterial hypertension has been under observation for more than a century[1], but whether hyperuricemia has a causal role in arterial hypertension (AH) or if it is only a marker of the physiopathological process is yet to be elucidated.

Recent experimental researches have established possible mechanisms through which hyperuricemia can cause hypertension. In animal models, UA caused a decrease in nitric oxide synthetase (NOS), afferent arteriole injury, increased renin production and renal tubule injury[6,7]. Moreover, a close association was demonstrated between hyperuricemia and metabolic syndrome in rats, due to a probable mechanism involving endothelial function inhibition[8]. It is known that insulin needs nitric oxide (NO) to stimulate glucose uptake and the NO availability is decreased when hyperuricemia occurs[9].

In this context, the inclusion of UA as variable for the stratification of cardiovascular risk seems interesting, as it is an easy-to-perform and low-cost test that can be useful in clinical

practice, especially in individuals with metabolic syndrome and arterial hypertension.

The present study aimed at evaluating the association between uric acid and cardiovascular risk factors in a non-hospitalized Brazilian population, covering a wide age range.

Methods

The present was a cross-sectional study, of which sample was obtained from the database of a non-hospitalized population from the service of arterial hypertension of *Hospital Universitário Pedro Ernesto* of *Universidade do Estado do Rio de Janeiro* (UERJ). The sample was obtained among patients submitted to preoperative admission assessment of non-cardiac surgeries and clinical evaluation for regular physical activity. Individuals of both sexes, aged 20 years or older, whose demographic data, clinical history, physical examination data and laboratory assessment including uric acid, glucose, serum lipids and creatinine levels were available, were considered eligible for study enrollment.

The sample consisted of 756 individuals aged 20 years or older (mean of 50.3 years), of which 369 were males (48.8%). The patients were distributed by 20-year strata.

All individuals had their demographic data collected followed by a clinical assessment to collect medical history data; additionally, a physical examination was carried out, which consisted of BP levels, weight and height measurement for BMI calculation and abdominal circumference measurement. A blood sample was collected after a 12-hour fast for the laboratory assessment, which included: glucose, insulin, HOMA-IR[10], uric acid and creatinine levels. The glomerular filtration rate was also calculated through the Cockroft-Gault formula (140-age x weight/creatinine x 72 for men and for women, multiplied by the correction factor of 0.85), total cholesterol, HDL-c, triglycerides and LDL-c, through Friedewald's formula.

The measurement of insulin and HOMA-IR calculation was carried out in 498 patients, in whom insulin was measured and HOMA-IR was calculated according to the formula: fasting insulin x plasma fasting glucose/405. The diagnosis of MS was considered according to the criteria of the I Guideline for Metabolic Syndrome[11]. The diagnosis of arterial hypertension was considered according to the V Brazilian Guideline for Arterial Hypertension[12].

The sample was stratified by quintiles of uric acid according to sex and 5 groups were constituted, G1 to G5, according to the crescent order of UA quintiles. For the male sex (M), the values corresponding to the quintiles of UA were ≤ 4.5, > 4.5 and ≤ 5.2, > 5.2 and ≤ 5. 9, > 5.9 and ≤ 6.5, and >

6.5 mg/dl. For the female sex (F), the values were ≤ 3.26, > 3.26 and ≤ 3.9, > 3.9 and ≤ 4.5 and > 4.5 and ≤ 5.24 and > 5.24 mg/dl, respectively for the first, second, third, fourth and fifth quintiles of uric acid.

The data were analyzed using the statistical package "SPSS for Windows", release 8.0.0, Copyright SPSS Inc. 1989 - 1997.

The following statistical methods were employed, with the level of rejection of the nullity hypothesis set at 0.05 or 5.0% (p = 0.05):

- *Analysis of variance (F)* - used to compare the means of the variables that presented a normal distribution and homogeneity of variance at Bartley's test.

- *Tukey's Test* - used as complementary test for the analysis of variance, for comparison of means of the variables 2 x 2.

- *Chi-square Test (χ^2)* - used to compare the frequency distribution of categorical variables of independent samples.

- *Pearson's Correlation Test* - used to analyze the correlation between continuous variables.

This study was approved by the Ethics Committee of *Hospital Universitário Pedro Ernesto*, number 2322-CEP/HUPE, on December 10, 2008.

Results

The distribution of individuals was uniform by gender and age range analyzed (Table 1). The means of systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, triglycerides and creatinine significantly increased with the uric acid quintiles (Table 2). For HDL-c and for the eGFR, the opposite occurred: the higher means of these variables were observed together with the lowest quintiles of UA (Table 2). There was a prevalence of 48.3% of arterial hypertension, 33.6% of metabolic syndrome, 62.4% of overweight and obesity, 55.9% of hypercholesterolemia, 14.9% of altered fasting glycemia levels, 4.1% of diabetes, 24.9% of hypertriglyceridemia and 33.9% of low HDL levels in the total sample (Table 3).

The prevalences of arterial hypertension, overweight/obesity (Table 3) and metabolic syndrome (Figure 1) were significantly higher in the highest quintiles of uric acid (p < 0.0001).

Regarding insulin and HOMA-IR, there was a higher predominance of the highest quintiles of insulin and HOMA-IR in the upper quintiles of uric acid with χ^2 = 35.761 and p = 0.003 for HOMA-IR and χ^2 = 31.393 and p = 0.012 for insulin (Figures 2 and 3).

Table 1 - **Distribution of the population by sex and age ranges**

Age range	Male	Female	Total	χ^2	p Value
20 to 39 years	107 (30.3%)	107 (27.7%)	214 (29.0%)	2.698	0.260
40 to 59 years	139 (39.4%)	140 (36.3%)	279 (37.8%)		
≥ 60 years	107 (30.3%)	139 (36.0%)	246 (33.3%)		
Total n (%)	353 (100%)	386 (100%)	739 (100%)		

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Table 2 - Means of blood pressure, anthropometric, metabolic and kidney function variables by UA quintiles

Variables	G1	G2	G3	G4	G5	F	p	Comparison 2 by 2
SBP (mmHg)	130.80 ± 21.10	133.41 ± 20.60	133.52 ± 21.79	138.23 ± 20.48	144.29 ± 23.91	9.17	<0.0001	1<4; 1<5; 2<5; 3<5
DBP (mmHg)	82.32 ± 11.80	82.81 ± 12.00	85.29 ± 13.30	84.76 ± 11.60	89.15 ± 13.40	7.09	<0.0001	1<5; 2<5; 3<5
BMI (kg/m²)	25.54 ± 4.80	26.66 ± 4.60	26.94 ± 4.00	27.16 ± 4.10	27.89 ± 4.40	5.60	<0.0001	1<3; 1<4; 1<5;
AC (cm)	95.77 ± 13.70	98.47 ± 12.52	98.95 ± 9.99	99.45 ± 10.45	101.26 ± 11.05	4.34	0.002	1=2=3=4<5
Cholesterol (mg/dl)	201.8 ± 47.00	213.2 ± 56.60	209.6 ± 46.90	212.40 ± 45.40	229.8 ± 51.10	6.37	<0.0001	1<5; 2<5; 3<5; 4<5
Triglycerides (mg/dl)	99.61 ± 57.80	113.45 ± 62.30	121.96 ± 82.7	126.99 ± 63.0	141.64 ± 85.90	7.22	<0.0001	1<3; 1<4; 1<5; 2<5
HDL-c (mg/dl)	54.52 ± 14.60	51.76 ± 14.00	49.06 ± 14.40	48.48 ± 12.10	50.23 ± 14.50	4.10	0.003	1<3; 1<3; 1<4
LDL-c (mg/dl)	130.19 ± 43.63	137.35 ± 46.40	138.11 ± 41.07	139.12 ± 43.12	152.00 ± 47.59	4.44	0.002	1<5; 2<5
Creatinine (mg/dl)	0.79 ± 0.18	0.80 ± 0.20	0.83 ± 0.25	0.87 ± 0.20	0.92 ± 0.28	8.13	<0.0001	1<4; 1<5;2<5
GFR (ml/min)	112.16 ± 43.70	108.77 ± 39.40	103.25 ± 28.70	102.46 ± 33.50	94.62 ± 31.90	5.07	<0.0001	
Glucose (mg/dl)	92.00 ± 29.02	88.31 ± 17.66	90.40 ± 20.30	91.87 ± 21.71	92.82 ± 18.50	1.01	0.39	
Homa-IR	2.65 ± 5. 59	2.21 ± 2.02	2.29 ± 3.54	2.60 ± 2.91	2.67 ± 2.95	0.37	0.82	
Insulin	12.11 ± 30.08	10.29 ± 7.74	10.66 ± 19.36	10.78 ± 6.33	11.33 ± 16.83	0.17	0.95	

SBP - systolic blood pressure; DBP - diastolic blood pressure; BMI - body mass index; AC - abdominal circumference; GFR - glomerular filtration rate ; mmHg - millimeters of mercury; mg/dl - milligrams per deciliter; ml/min - milliliters per minute

Table 3 - Prevalence of cardiovascular risk factors in the total sample and by quintiles of uric acid

Prevalences	Total	G1	G2	G3	G4	G5	χ^2	p
OW/O n (%)	466 (62.3)	68 (44.4)	95 (60.9)	99 (64.7)	92 (66.7)	112 (75.7)	33.67	<0.0001
SAH n (%)	365 (48.4)	58 (37.9)	67 (42.9)	68 (44.2)	73 (51.8)	99 (66.0)	28.95	<0.0001
Diabetes n (%)	31 (4.1)	8 (5.3)	6 (3.8)	4 (2.6)	6 (4.3)	7 (4.7)	15.92	0.44
Glucose intolerance n (%)	142 (18.9)	27 (17.8)	20 (12.8)	31 (20.4)	23 (16.3)	41 (27.5)	11.92	0.018
High cholesterol n (%)	420 (55.8)	72 (47.1)	79 50.6)	84 (54.5)	80 (56.7)	105 (70.5)	19.57	0.001
Triglycerides Alto n (%)	186 (24.9)	22 (14.4)	37 (23.9)	40 (26.5)	38 (27.0)	49 (33.1)	15.01	0.05
Low HDL-c n (%)	240 (34.0)	37 (26.8)	51 (34.5)	49 (34.0)	47 (36.2)	56 (38.4)	4.69	0.32
High LDL-c n (%)	376 (53.5)	61 (44.2)	71 (48)	74 (52.1)	74 (56.9)	96 (66.2)	16.745	0.002

OW/O - overweight and obesity; SAH - systemic arterial hypertension; n (%) - number and percentage.
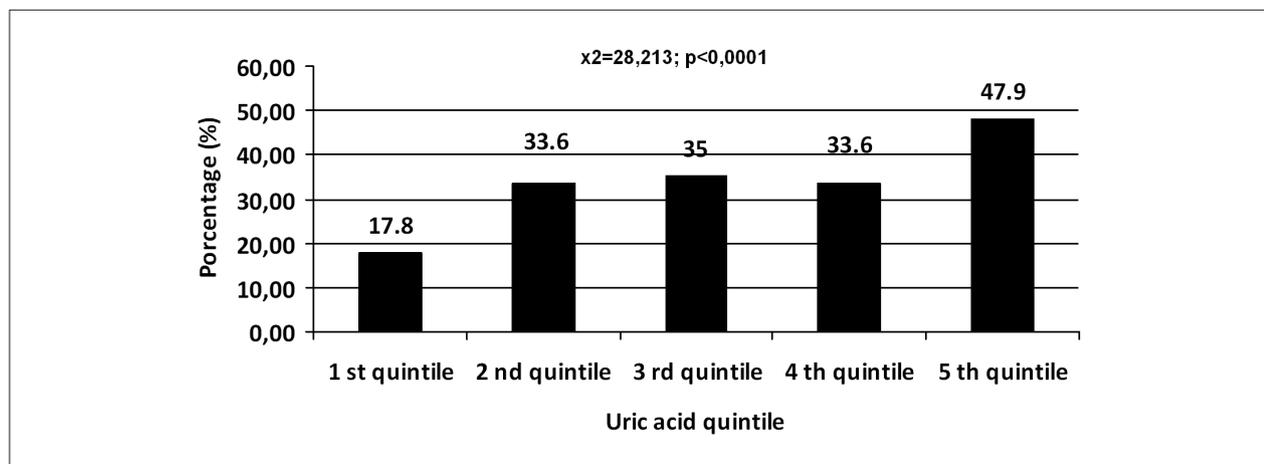

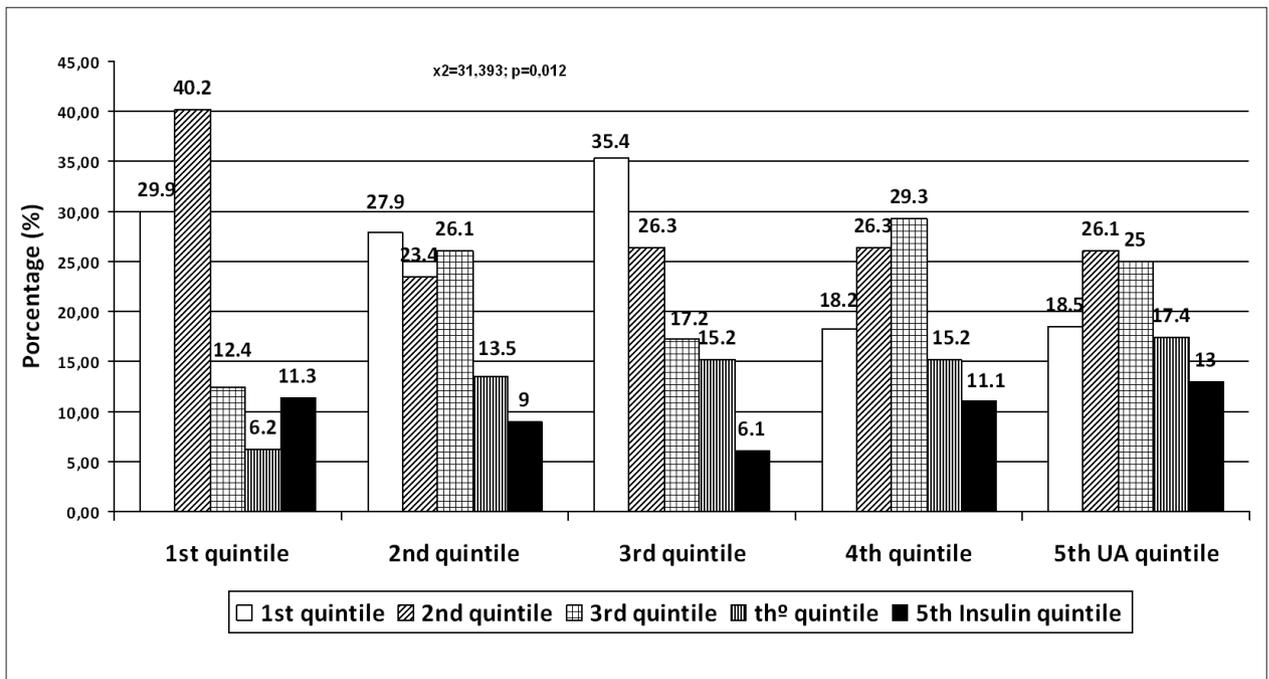*Figure 1 - Prevalence of metabolic syndrome according to uric acid quintile.*

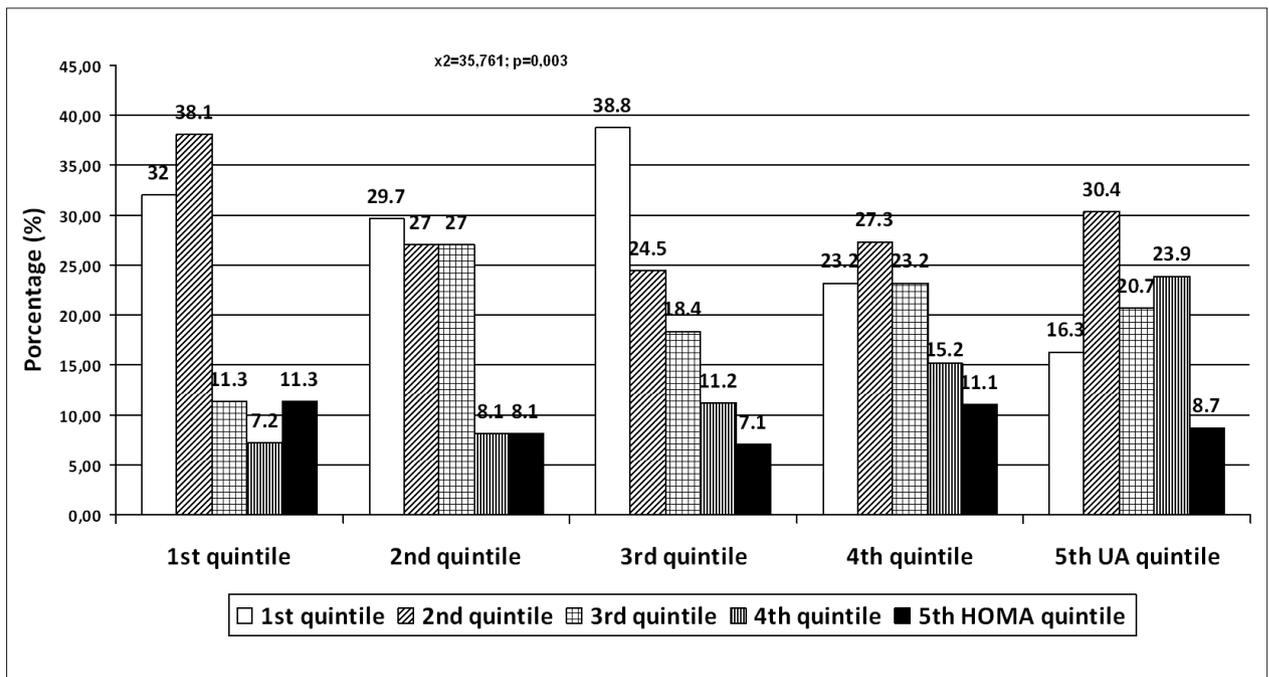*Figure 2 - Insulin quintile according to uric acid (UA) quintile.*

Figure 3 - HOMA-IR Quintile according to uric acid (UA) quintile.

Discussion

This study brought contributions to the better understanding of the behavior of uric acid in relation to the clinical, metabolic and renal function variables associated with a higher cardiovascular risk, especially as it included a significant number of non-hospitalized individuals from the Brazilian population, whose data were scarcely available up to the present moment. Several studies have demonstrated that UA is an independent risk variable for cardiovascular risk factors[2-5, 13-25].

The population studied in the present study is a convenience sample, with no sample size calculation, and thus, cannot reflect the characteristics of the general population. On the other hand, the fact that it has a

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representative size and its non-hospital origin might have attenuated the possible selection bias.

Regarding the mean age of the individuals in this series (50.3 years), there are no significant differences in relation to most studies on the subject[3,18], except for the studies carried out in children and adolescents, such as the one by Bogalusa[14] or the trial carried out by Forman et al[26], in which mean age was 61 years.

Regarding the presence of risk factors, an increased prevalence of systemic arterial hypertension was observed in the present study (48.3%), in contrast with the expected rate of 31.0% for the Brazilian southeast region. A possible explanation for this fact might be the age range of these individuals, as elderly patients (> 80 years) were included in the study, as well as the fact that 30.0% of the study population was older than 60 years, an age range at which the prevalence of arterial hypertension is known to be higher.

MS was observed in 34.5% of these individuals, higher than the prevalences described in several studies[24,27]. It is noteworthy the fact that there are no national data on the subject for the purpose of comparison[28]. However, several studies have shown prevalences of MS that vary from 8.0% to 70.7%, depending on the age range. It is possible that the rates observed in the present study are due not only to the oldest age range to which these individuals belong, but also because this population presented more than 60.0% of obesity prevalence.

Regarding diabetes, a similar prevalence was found to that observed in our country, which is 4.0%[2], in large series, such as the Framingham study's[2], which showed a prevalence of 2.7% of diabetes in the studied population.

From the hemodynamic point of view, it can be observed that there were higher means of BP at the highest quintiles of UA, which corresponds to the results found by Conen et al[29].

As for the prevalence of arterial hypertension by quintiles of UA, it was clearly demonstrated that there was a significant association between these variables. This has been the result found in several publications, as it can be verified since 1994 with The Olivetti Heart Study[23], where UA was associated with cardiovascular risk factors such as arterial hypertension or, in the study carried out by Perlstein et al[4] in 2,062 individuals, over a 21-year period, where arterial hypertension was also associated with higher quintiles of UA. Similarly the series by Mellen et al[3], during a nine-year follow-up period, showed that arterial hypertension was more prevalent in patients with higher levels of UA, in a sample of 9,104 bi-ethnic individuals of both sexes.

The biological explanation for this fact is supported by studies carried out with animal models with rats, which showed the development of arterial hypertension after the induction of hyperuricemia, caused by a probable decrease in nitric oxide in the renal macula densa and by direct stimulation of the renin-angiotensin system, with both mechanisms causing vasoconstriction and therefore, blood pressure increase[6,7].

However, on the other hand, there is the possibility that the increase in UA might be present in clinical conditions known to be pro-inflammatory, such as systemic arterial hypertension and MS, due to its antioxidant action, and therefore, represents only a biochemical defense mechanism[30-32] against atherosclerosis progression. Thus, it would not be an independent risk factor for these syndromes, but just part of the clinical picture.

Regarding the metabolic variables, the prevalences of cholesterol, triglycerides and glucose intolerance were significantly higher in the higher quintiles of UA. The association with cholesterol and triglycerides was also found in the population studied by the Normative Aging Study. As for HDL-c, this study demonstrated an inverse association with the quintiles of UA and the same was verified in the 425 patients studied by Zocalli et al[27].

At the analysis of distribution of insulin and HOMA-IR quintiles, in relation to the quintiles of UA, the present study showed a significant association between higher quintiles of UA and higher quintiles of both insulin and HOMA-IR, a finding that is consistent with the ones observed by Formam et al[26]. Regarding HOMA-IR, Ishizaka et al[24] demonstrated higher prevalences of this variable by quintiles of UA. As for the presence of diabetes, the present study showed that the prevalence of this pathology was significantly higher in the groups with higher levels of UA, a result consistent with large longitudinal studies, such as the Framingham study[2] or the cohort of 9,104 individuals from the ARIC study[3]. These findings suggest that hyperuricemia is associated with insulin resistance, a condition underlying metabolic syndrome.

Regarding the MS, there was also a higher prevalence in the groups presenting higher levels of UA, and similarly, the literature demonstrates such association, as it can be observed in the study by Kawada et al[25], where 981 Japanese workers were assessed and which showed an association between MS and hyperuricemia.

The Ishizaka[24] also demonstrated a significant association between MS and UA levels, in a cross-sectional study of 8,144 individuals of both sexes, stratified by quartiles of UA. The highest prevalence of MS with increasing levels of UA was also demonstrated by a study carried out by Choi and Ford[16, 17] using data from NHANES. In some other studies, such as the one by Coutinho et al[33] and Desai et al[15], it can be observed that US was associated with components that constitute MS, and the higher the number of components of the syndrome, the higher the association.

Recently, in a study carried out in Brazil by Franco et al[34], in hypertensive patients from Cuiaba, demonstrated a higher prevalence of MS in patients with hyperuricemia[34].

Among the limitations of the present study is the fact this is not a population-based sample. However, the number of individuals studied is quite significant and corresponds to a real scenario of assessment of cardiovascular risk factors in a non-hospital population. Data such as use of medications, alcohol consumption and presence of menopause were not available and are factors that can interfere, at least partially, with the observed results. Additionally, the present was a cross-sectional study, allowing only the analysis of the association of variables, without temporal inferences.

Conclusions and perspectives

The present study indicates the possibility that the uric acid is associated with cardiovascular risk variables and metabolic syndrome and that it can be useful in the individual cardiovascular risk assessment.

The existence of a physiopathological rational basis to explain the association between the uric acid and cardiovascular risk factor, together with the fact that uric acid is easy to measure and the existence of the appropriate therapy to treat it, reinforce the need for new researches to better understand its participation in the cardiovascular disease scenario.

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