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Relationship between Uric Acid and Metabolic Syndrome among Users of a Primary Care Clinic in Mexico

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Abstract

Introduction: Metabolic syndrome and hyperuricemia are important risk factors for cardiovascular disease.

Objective: To assess the association between uric acid and metabolic syndrome.

Methods: A cross-sectional analytic study enrolled 203 volunteers, aged ≥ 20 years, who presented to a primary care clinic that provides care for a state university staff and their families. Hyperuricemia was defined as a blood uric acid level of ≥ 7.0 mg/dL in men and ≥ 6.0 mg/dL in women. Metabolic syndrome was defined according to the National Cholesterol Education Program, Adult *Treatment P*anel III (ATPIII) criteria. The association between these variables was assessed using Pearson´s correlation and multivariate regression.

Results: The mean age was 52 ± 13.5 years. Sixty percent of the subjects were female. The prevalence of metabolic syndrome in subjects with and without hyperuricemia was 49% and 33%, respectively. There was a statistically significant association between the uric acid level and metabolic syndrome in the gender-adjusted multivariate analysis (odds ratio=1.5, 95% confidence intervals=1.2 to 1.9). We identified hyperglycemia as a predictor for hyperuricemia (odds ratio=e 3.0, 95% confidence interval=1.4 to 6.3).

Conclusion: The results showed that high concentrations of uric acid are associated with metabolic syndrome and suggest that the presence of fasting hyperglycemia is strongly associated with hyperuricemia in women.

Keywords: Hyperuricemia; Metabolic syndrome; Primary care

Introduction

Metabolic syndrome (MS) and hyperuricemia (HU) are important risk factors for cardiovascular disease (CVD), which is a well-recognized cause of mortality [1,2].

MS affects approximately one-quarter of the population older than 40 years of age [3,4]. Different epidemiologic and clinical trials have shown an association between hyperuricemia and MS [5-7].

Some authors suggest that hyperuricemia should be considered a marker for MS given the noted independent positive association between these variables and the association of uric acid (UA) levels with the incidence of MS [4-7].

Despite the last national health survey in Mexico realized in 2012, [8] showed a high prevalence of overweight and obesity (70.5%), hypercholesterolemia (35.5%), hypertriglyceridemia (29.9%), arterial hypertension (31.5%) and diabetes mellitus type 2 (9.2%), which are conditions that have contributed to epidemiological data related to metabolic syndrome [8-11]. However, the literature is limited regarding this association in Mexico; therefore, this study aimed to evaluate the association between UA levels and MS in patients from a primary care clinic that provides care for a state university staff and their families.

Material and Methods

Study design and population studied: A cross-sectional study was conducted in a primary care clinic, located in Xalapa, Veracruz (Mexico), that provides care for a state university staff and their families.

Volunteers aged 20 years and older, who were not pregnant and did not have kidney disease were selected between July 1, 2012, and March 31, 2013, to participate in the study. The absence of kidney disease and pregnancy was verified using medical records. All consecutive attendants to the clinic were invited to participate.

Sample

To calculate our sample size, we used the previously reported MS prevalence of 66.2% and 37% in patients with and without hyperuricemia, respectively [12].We estimated the need for at least 36 subjects with and without hyperuricemia to calculate at ratio differences.

Measurements

A questionnaire was used to collect the demographic characteristics and lifestyle data concerning the participants. We conducted the STEP wise 17-item questionnaire [13] to obtain information regarding alcohol and tobacco consumption. Waist circumference was measured using an anthropometric tape that was placed midway between the lower costal margin and the iliac crest. Well-trained nurses measured the systolic blood pressure (SBP) and diastolic blood pressure (DBP) two times in the left arm of the participants according to a standardized protocol. The average of the two readings was calculated to determine the reported blood pressure for each participant.

Biochemical determinations

Blood was drawn from each subject during fasting for measurement of the HDL cholesterol, triglycerides, plasma glucose and uric acid concentrations. These variables were measured using standard enzymatic automated methods. The uric acid level was assayed using the colorimetric uricase-peroxidase system.

Definition of metabolic syndrome

MS was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [14,15] criteria as follows: blood pressure ≥ 130/85 mmHg; triglycerides ≥ 150 mg/dL; HDL cholesterol <40 mg/dL in men and <50 mg/dL in women; fasting blood glucose ≥100 mg/dL. The following criteria were recommended by the Latin American Diabetes Association (ALAD) [16] for the determination of abdominal obesity: waist circumference ≥ 94 cm in men and ≥ 88 cm in women.

Assessment of uric acid concentration: Hyperuricemia was defined as ≥ 7.0 mg/dL in men and ≥ 6.0 mg/dL in women, which is consistent with prior epidemiologic studies examining hyperuricemia and cardiovascular outcomes [6].

Ethical issues

The study was authorized by the Technical Council of the "Instituto de Salud Pública" (Public Health Institute) of the University of Veracruz. All participants provided written consent to participate in the study. This research is a post-graduate thesis and the Technical Council of the Institute of Public Health guaranteed the ethical aspect with the file 095/2013 and Project number 37495201250.

Statistical analysis

The Kolmogorov-Smirnov test was used to analyze the distribution of continuous variables. The means and standard deviations for the variables with normal or medium distribution and minimum and maximum values were expressed when this distribution was not found.

Categorical variables were analyzed using the chi-square test or Fisher's exact test accordingly. Continuous variables without normal distribution were analyzed using the Mann-Whitney U test. The correlation between UA and MS and its components was assessed using Spearman´s Rho correlation coefficient. A logistic regression analysis was conducted to assess the relationship between hyperuricemia and MS. Models were developed where MS was the dependent variable, and the level of uric acid, age, and gender were the covariates.

Variables	With hyperuricemia (n=69)	Without hyperuricemia (n=134)	p
Both Sex, n (%)			
Men	47 (68.1)	31 (23,1)	<0.001
Women	22 (31.9)	103 (76.9)	<0.001
Smoker, n (%)	10 (40)	15 (60)	0.5
Alcohol intake, n (%)	38 (38)	62 (62)	0.24
Comorbidities, n (%)	17(26.1)	48 (73.9)	0.09
Characteristics			
Age (years)	57 (85, 20)	54 (82,20)	0.45
WC (cm)	89 (126,71)	86 (128,65)	0.006
SBP (mmHg)	120 (160,100)	120 (150, 90)	0.35
DBP (mmHg)	80 (110,70)	80 (110,60)	0.35
Glucose (mg/dL)	94 (160,74)	88 (163, 68)	<0.001
HDLChol (mg/dL), mean ± SD	42 ± 10.5	46 ± 9.9	0.004
Triglycerides (mg/dL)	185 (413, 54)	147 (779,48)	<0.001
Men			
Age (years)	55 (85, 20)	57 (76, 20)	0.75
WC (cm)	92 (117, 71)	92 (113, 78)	0.98
SBP (mmHg)	120 (160, 100)	120 (150, 100)	0.78
DBP (mmHg)	80 (110,70)	80 (100, 70)	0.99
Glucose (mg/dL)	94 (160,74)	90 (136, 78)	0.27
HDLChol (mg/dL)a, mean ± SD	39.8 ± 9.8	42.2 ± 8.9	0.28
Triglycerides (mg/dL)	187 (413,54)	151 (302,48)	0.04
Women			
Age (years)	58 (84, 22)	53 (82, 21)	0.18
WC (cm)	87 (126, 76)	84 (128, 65)	0.2
SBP (mmHg)	120 (150, 100)	120 (150, 90)	0.99
DBP (mmHg)	80 (100, 70)	80 (110, 60)	0.86
Glucose (mg/dL)	95 (126, 78)	87 (163, 68)	0.01
HDLChol (mg/dL), mean ± SD	45.7 ± 10.7	47.3 ± 9.9	0.5
Triglycerides (mg/dL)	178 (364,62)	145 (779,49)	0.08

Table 1: Comparison of age and biochemical characteristics among patients with or without hyperuricemia.
unless otherwise stated the values are expressed as median, máximum and minimum value: median (max, min). WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, a HDLCol: HDL cholesterol (media, SD: Standard Deviation. Mann-Whitney U-

Test was used for comparing independent groups. Chi square was used for comparing proportions.

A second set of models included the presence of hyperuricemia as the dependent variable and abdominal obesity, hypertension, hyperglycemia, hypocholesterolemia-cholesterol, hypertriglyceridemia, age and gender as covariates, $p \leq 0.05$ was considered to be statistically significant. A total of 313 subjects were enrolled to participate in the study. Of these, 110 (35%) subjects were excluded because they lacked laboratory analysis results.

Results

A final sample of 203 participants were included in the analysis. Of these, 61.6% were women. The prevalence of hyperuricemia was 34%, and the prevalence of MS was 38.4%. A total of 12.3% of the participants were smokers (consuming an average of 5 ± 9 cigarettes daily), and the prevalence of smoking was higher in men. Twenty percent of the participants reported drinking alcohol on a weekly basis.

Subjects with hyperuricemia had a greater waist circumference, higher levels of glucose and triglycerides, and lower levels of HDL cholesterol (Table 1) than subjects with normal uric levels. Additionally, the proportion of men in the group with hyperuricemia was almost 3 times higher than the proportion of men without hyperuricemia, which is in agreement with other reports [17].When the results were stratified by gender, median levels of triglycerides were significantly higher in men than in women, and the levels were higher in the group with hyperuricemia (p=0.04). The median fasting glucose level was higher in women with hyperuricemia (p=0.01). All of the other variables were not significantly different between genders. No gender association was found with smoking and alcohol intake.

There was a significant correlation between MS and waist circumference, diastolic blood pressure, fasting glucose, HDL (negative correlation), triglycerides and number of criteria for the total sample (Table 2). Women showed a significant correlation with the same variables, except for diastolic blood pressure. Men showed a significant correlation only with triglycerides and the number of criteria for MS.

Variables	General		Men		Women	
	Rho	p	Rho	p	Rho	p
Age (years)	0.09	0.22	-0.007	0.95	0.16	0.08
Waist Circumference	0.33	<0.001	0.05	0.69	0.32	<0.001
Systolic Blood Pressure	0.1	0.15	0.09	0.45	0.07	0.42
Diastolic Blood Pressure	0.19	0.007	0.14	0.21	0.16	0.08
Fasting glucose	0.26	<0.001	0.17	0.15	0.25	0.005
HDL cholesterol	-0.29	<0.001	-0.2	0.87	-0.23	0.01
Triglycerides	0.33	<0.001	0.4	<0.001	0.24	<0.001
Meets many criteria of MS	0.3	<0.001	0.23	0.04	0.41	<0.001

Table 2: The correlation between the components of metabolic syndrome (MS) and uric acid.
Rho: Spearman´s Rho correlation coefficient.

In the overall sample, patients with hyperuricemia had twice the odds of MS as subjects without hyperuricemia (p=0.02) (Table 3). Additionally, patients with hyperuricemia also had higher odds of hyperglycemia (OR 3.1, p<0.001) and hypertriglyceridemia than did patients with normal uric acid levels (OR 2.1, p=0.02). When the results were stratified by gender, women showed almost 5 times the odds of hyperglycemia as men (OR=4.8, 95%CI=1.7 to 13.4).

Variables	With hyperuricemia	Without hyperuricemia	OR	95% CI	p
General					
MS (%)	49.3	32.8	2	1.1-3.6	0.02
Abdominal obesity (%)	40.6	35.1	1.3	0.7-2.3	0.44
Arterial hypertension (%)	464	38.1	1.4	0.8-2.5	0,25
Hyperglycemia (%)	36.2	14.9	3.2	1.6-6.4	<0.001
HDL Hypocholesterolemia (%)	58	61.2	0.9	0.5-1.6	0.66
Hypertriglyceridemia (%)	65.2	47.8	2.1	1.1-3.7	0.02
Men					
MS (%)	48.9	35.5	1.7	0.7-4.4	0.24
Abdominal obesity (%)	40.4	41.9	0.9	0.4-2.4	0.94
Arterial hypertension (%)	46.8	45.2	1.1	0.4-2.7	0.89
Hyperglycemia (%)	34	22.6	1.8	0.7-4.9	0.28

Table 3: Comparison of the prevalence of MS and its components in patients with or without hyperuricemia.

MS: metabolic syndrome, OR: odds ratio, proportions were compared using the Chi square test Abdominal obesity: waist circumference >88 cm (women) or >94 cm (men). Hypertension: SBP ≥ 135 mmHg or DBP >85. Hyperglycemia: fasting glucose ≥ 100 mg/dL. HDL Hypocholesterolemia: HDL cholesterol <50 mg/dL (women) or <40 mg/dL (men). Hypertriglyceridemia: triglycerides ≥ 150 mg/dL. Hyperuricemia: uric acid ≥ 7 mg/dL (men) or ≥ 6 mg/dL (women).

When comparing the prevalence of MS by quartiles, for-uric acid distribution, the quartile with the highest UA level (UA ≥ 6.3 mg/dL) had 3 times the odds of MS as the quartile with the lowest uric acid level (OR=3.1, 95% CI=1.4 to 7.1) (Table 4). We found a similar association in women but not in men.

Table 5 shows two models of multivariate analysis using binary logistic regression to investigate whether the UA level (independent variable) that was represented in a continuous scale (mg/dL) or according to an ordinal expression (quartiles) was associated with MS (dependent variable). When adjusted by gender in Model I, UA levels expressed in mg/dL were significantly associated with the presence of MS (OR=1.5, 95% CI=1.2 to 1.9). Once we assessed the results according to gender, the association between the UA level (mg/dL) and the presence of MS persisted. Uric acid was grouped into quartiles in Model II, and the fourth quartile (AU ≥ 6.3 mg/dL) showed a strong association with the presence of MS (OR=3.1, 95% CI=1.3 to 7.1) after the results were adjusted by gender. Additionally, age showed a weak association with CI values, with the results being very close to 1.

Patients	With MS n (%)	Without MS n (%)	OR	95% CI	p
General					
IV (≥ 6.30 mg/dL	29 (37.2)	24 (19.2)	3.1	1.4-7.1	0.006
III (5.5-6.29mg/dL)	22 (28.2)	30 (24.0)	1.9	0.8-4.3	0.013
II (4.6-5.49 mg/dL)	13 (16.7)	35 (28.0)	0.9	0.4-2.3	0.91
I (<4.6 mg/dL)	14 (17.9)	36 (28.8)	1	-	-
Men					
IV (≥ 6.30 mg/dL)	21 (61.8)	19 (43.2)	1.4	0.3-7.4	0.64
III (5.5-6.29 mg/dL)	7 (20.6)	10 (22.7)	0.9	0.2-5.5	0.94
II (4.6-5.49 mg/dL)	3 (8.8)	11 (25.0)	0.4	0.1-2.6	0.3
I (<4.6 mg/dL)	3 (8.8)	4 (9.1)	1	-	-
Women					
IV (≥ 6.30 mg/dL)	8 (18.2)	5 (6.2)	4.7	1.3-17.3	0.02
III (5.5-6.29 mg/dL)	15 (34.1)	20 (24.7)	2.2	0.8-5.7	0.11
II (4.6-5.49 mg/dL)	10 (22.7)	24 (29.6)	1.2	0.4-3.3	0.71
I (<4.6 mg/dL)	11 (25.0)	32 (39.5)	1	-	-

Table 4: Comparison of quartiles of uric acid in patients with and without metabolic syndrome MS: metabolic syndrome. OR: odds ratio. P=probability. n: number of subjects with the characteristic of interest.

Table 6 shows a multivariate analysis with hyperuricemia as the dependent variable. When analyzing the total sample after adjusting for age and other criteria for MS, both fasting hyperglycemia (OR=3.0, 95% CI=1.4 to 6.3) and male gender (OR=6.8, 95% CI 3.5 to 13.2) were identified as strong factors associated with hyperuricemia. However, when analyzing the results according to gender, there were no significant associations I men. Women, however, showed a strong association between fasting hyperglycemia and hyperuricemia (OR=4.8, 95% CI=1.7 to 13.4%).

Discussion

In our study, a direct relationship was observed between uric acid levels and the prevalence of MS, even after adjusting for potential confounders. One of the important findings in our study was the high prevalence of hyperuricemia (34%), which was higher than the estimates reported for some populations (8.4% among Iranian adults, and 14.4% among Chinese adults, 24.4% among Spanish adults, and 31.4% among other populations in Mexico) using the same definition of hyperuricemia [9,11,16,18]. It is noteworthy that nearly half (49.3%) of the subjects with hyperuricemia had MS. It should be noted that the size of the minimum sample was greatly exceeded.

When the results were stratified by gender, significant correlations between the level of UA and some of the components of MS such as waist circumference (only in women), triglycerides (both male and female) and fasting glucose (only in women) were found. Although significant epidemiological studies have established a close relationship between hyperuricemia and an

Variables	Unadjusted model		Adjusted model	
	OR (95%CI)	p	OR (95%CI)	p
Model I. Dependent variable: presence of MS				
General				
Uric acid, mg/dL	1.6 (1.2-2.1)	0.001	1.5 (1.2-1.9)	0.001
Age	1.03 (1.003-1.05)	0.03	1.03 (1.003-1.05)	0.03
Sex female	1.3 (0.6-2.6)	0.46	-	0.46
Men				
Uric acid, mg/dL	1.4 (1.01-23)	0.04	14 (1.01-2.0)	0.04
Age	1.0 (0.97-1.04)	0.63	-	0.63
Women				
Uric acid, mg/dL	1.7 (1.2-2.6)	0.007	1.7 (1.2-2.6)	0.007
Age	1.04 (1.006-107)	0.02	1.04 (1.006-1.07)	0.02
Model II. Dependent variable: presence of MS				
General				
Uric acid*	-	0.32	-	0.01
4.6 a 5.49 mg/dL	0.98 (0.4-2.4)	0.96	0.96 (0.4-2.4)	0.94
5.5 a 6.29 mg/dL	1.8 (0.8-4.2)	0.17	1.8 (0.8-4.1)	0.18
≥ 6.3 mg/dL	3.3 (1.3-8.3)	0.01	3.1 (1.3-7.1)	0.008
Age	1.03 (1.003-1.05)	0.03	1.03 (1.003-1.05)	0.03
Sex female	1.1 (0.6-2.2)	0.78	-	0.78

Table 5: Multivariate analysis using the presence of MS as the dependent variable
MS: metabolic syndrome. OR: odds ratio (obtained by logistic regression), Model I: Uric acid was introduced as a continuous variable, Model II: Uric acid was introduced as categorical variable. Reference category: uric acid<4.6mg/dL. The OR was not calculated for adjusted variables.

Variables	Unadjusted model		Adjusted model	
	OR (95%CI)	p	OR (95% CI)	p
Dependent variable: presence of hyperuricemia				
General				
Abdominal obesity	0.9 (0.5-1.9)	0.83	-	0.88
Arterial hypertension	1.02 (0.5-2.1)	0.96	-	0.93
Hyperglycemia	2.7 (1.2-6.1)	0.02	3.0 (1.4-6.3)	0.005
HDL Hypocholesterolemia	1.04 (0.5-2.2)	0.91	-	0.69
Hypertriglyceridemia	1.6 (0.8-3.2)	0.21	-	0.19
Sex male	6.8 (3.4-13.5)	<0.001	6.8 (3.5-13.2)	<0.001
Age	1.0 (0.96-1.02)	0.93	-	0.94
Men				
Abdominal obesity	0.8 (0.3-2.3)	0.74	-	0.89
Arterial hypertension	0.9 (0.3-2.7)	0.93	-	0.89
Hyperglycemia	1.6 (0.5-5.6)	0.42	-	0.28
HDL Hypocholesterolemia	0.9 (0.3-2.7)	0.91	-	0.61
Hypertriglyceridemia	1.7 (0.6-4.6)	0.32	-	0.21
Age	0.99 (0.95-1.02)	0.6	-	0.77
Women				
Abdominal obesity	0.9 (0.3-2.6)	0.79	-	0.84
Arterial hypertension	1.2 (0.4-3.4)	0.71	-	0.63
Hyperglycemia	4.4 (1.4-13.7)	0.01	4.8 (1.7-13.4)	0.003
HDL Hypocholesterolemia	13 (0.4-4.1)	0.68	-	0.55
Hypertriglyceridemia	1.6 (0.5-4.5)	0.4	-	0.28
Age	1.01 (0.97-1.05)	0.69	-	0.62

Table 6: Multivariate analysis using the presence of hyperuricemia as a dependent variable
OR: odds ratio (obtained by logistic regression).
Hyperuricemia: uric acid ≥ 7 mg/dL (men) or ≥ 6 mg/dL (women).
The OR was not calculated for adjusted variables.

increased prevalence of MS components, including glucose levels in plasma, triglycerides/HDL-cholesterol, obesity and hypertension [16,19] the results of this study only showed an association with hyperglycemia in women.

In the multivariate model, when the results were adjusted for confounding factors such as age and gender, a greater presence of hyperuricemia was observed in men. These results are consistent with the studies conducted in China and Iran [4,12,18].This was a cross-sectional study; therefore, there were no dependent or independent variables, because both were measured concurrently, and it could not be guaranteed that the temporary criteria were met. This is the reason we used different models for different dependent variables [8].

The underlying mechanism of gender regarding the levels of UA and the risk for MS has not been elucidated to date [5]. A study conducted in American women showed that natural and surgical menopause was independently associated with hyperuricemia, while the use of replacement hormones was associated with low levels of UA in [19].

Surprisingly, according to our results, no criteria for MS were associated with hyperuricemia in men; only a weak association with triglycerides was found in the correlation matrix. This finding was not ratified in the multivariate model. These results differ from those of another study in a population of middle-aged and elderly individuals who reported a close relationship between the UA and triglyceride levels in men, with a better lipid index associated with hyperuricemia in men then in women [20,21].

In contrast, it must be noted that in our analysis, the presence of hyperglycemia was strongly associated with hyperuricemia (almost five times) in women. These results are consistent with those obtained by

Viazzi and collaborators [21],where the UA levels was a powerful predictor of type 2 diabetes mellitus in primary hypertension, especially in women [21].

The prevalence of both gout and hyperuricemia remains substantial and may have increased over the past 2 decades, which is likely related to increasing frequencies of adiposity and hypertension [22]. Furthermore, emerging evidence suggests that gout is strongly associated with metabolic syndrome [23] and may lead to myocardial infarction [24-26], type 2 diabetes mellitus [27], and premature death [23,28].

The non-response rate was 35.1%. However, since the prevalence found in our study was consistent with that reported in Mexico, we consider the risk to be low. There were other factors that could have influenced the level of UA such as eating and lifestyle habits, and other comorbidities [29].

Conclusions

Our results show that high concentrations of uric acid are associated with metabolic syndrome and suggest that the presence of fasting hyperglycemia is strongly associated with hyperuricemia in women.

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