Relationship of hyperuricemia with metabolic alterations and cardiovascular risk factors in a population of Mexican young adults

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Abstract

Introduction: Hyperuricemia is a risk factor for cardiovascular disease, but its impact has not been properly documented.

Objective: To assess the impact of hyperuricemia on metabolic parameters and cardiovascular risk factors (CRF) in apparently healthy Mexicans. **Method:** Cross-sectional study of 768 young adults. Association of hyperuricemia with alterations in metabolic parameters and CRF (hypertension, mixed dyslipidemia, metabolic syndrome) was sought. Log-linear and regression models were used to determine the influence of hyperuricemia. A multivariate analysis of variance was applied to observe the interaction of hyperuricemia and overweight or obesity with changes in metabolic parameters. **Results:** Metabolic parameters were higher in patients with hyperuricemia than with normal uric acid (all < 0.05). Hyperuricemia was significantly associated with hypertension (OR = 6.8, 95 % CI: 1.1-46), dyslipidemia (OR=2.5, 95% CI: 1.3-4.7) and metabolic syndrome (OR=2.3, 95% CI: 1.1-4.6). Hyperuricemia and overweight or obesity significantly predict changes in cardiovascular risk metabolic parameters (Wilks' λ =0.91, F (6.175)=3.1, p =0.007). **Conclusions:** Hyperuricemia is significantly associated with metabolic alterations and different CRF.

KEY WORDS: Uric acid. Cardiovascular risk. Hypertension. Dyslipidemia. Metabolic syndrome.

Introduction

Among the 10 leading causes of death in the world, cardiovascular diseases (CVD), such as ischemic heart disease and stroke, which cause more than 15 million annual deaths, have remained the main cause of death over the last 15 years.¹ In Mexico, CVD caused more than 135,000 deaths in 2016 and currently it is regarded as the leading cause of death in the country.² Therefore, the search for different markers associated with the risk of CVD has been crucial. One of these markers is uric acid (UA), an end-product of the metabolism of endogenous purines and of those consumed in the diet.³ Hyperuricemia can be

defined as the presence of UA serum values > 6 or 7 mg/dL in women and men, respectively.⁴ This clinical entity is common in individuals with CVD,⁵ but has also been associated with cardiovascular risk factors such as hypertension,⁶ obesity,⁷ metabolic syndrome,⁸ insulin resistance,⁹ dyslipidemia¹⁰ and atherogenic indices.¹¹ It is important noting that most studies that assess the relationship of hyperuricemia with metabolic parameters or cardiovascular risk factors have been carried out in specific populations with high risk for CVD, such as middle-aged adults or older adults, postmenopausal women, patients with kidney disease or with a history of CVD. Although analyses have been carried out in populations of children and adolescents, young adults aged between 18 and 22 years have not

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Table 1. Comparison of clinical characteristics, metabolic parameters and cardiovascular risk factors in individuals with and without hyperuricemia

Variable	Total (n = 768)		Normal uric acid (n = 579)		Hyperuricemia (n = 189)		p
	Mean ± SD		Mean ± SD		Mean ± SD		
Age (years)	18.8 ± 1.4		18.8 ± 1.4		18.8 ± 1.3		0.7
Weight (kg)	63.9 ± 13.5		62.2 ± 12.5		69.1 ± 15.1		< 0.0001
Height (m)	1.66 ± 0.56		1.66 ± 0.64		1.66 ± 0.08		0.9
Waist (cm)	82.6 ± 10.8		81.4 ± 9.8		86.2 ± 12.7		< 0.0001
BMI	23.6 ± 4.4		23.2 ± 3.7		25.1 ± 5.7		< 0.0001
Glucose (mg/dL)	88.5 ± 16.8		87.9 ± 17.5		90 ± 14.2		0.1
Total cholesterol (mg/dL)	165.3 ± 29.6		163.1 ± 28.9		171.9 ± 30.6		< 0.0001
Triglycerides (mg/dL)	116.2 ± 54.4		110.4 ± 50.2		134.1 ± 62.5		< 0.0001
HDL-C (mg/dL)	49.5 ± 12.9		50.3 ± 13.5		47.1 ± 10.9		0.003
LDL-C (mg/dL)	92.6 ± 24.8		90.8 ± 24.4		98 ± 25.2		0.001
VLDL-C (mg/dL)	22.9 ± 11.6		21.9 ± 11.2		26.9 ± 12.2		0.005
SBP (mm Hg)	115.7 ± 13.5		113.9 ± 13.3		121.5 ± 12.7		0.001
DBP (mm Hg)	70.9 ± 9.4		69.8 ± 9.8		74.7 ± 7.5		0.003
	n	%	n	%	n	%	
Women/men	466/302	61/39	380/199	66/34	86/103	46/55	< 0.0001
Abdominal adiposity	126	16.5	85	14.6	42	22	0.04
Overweight or obesity	237	30.9	154	26.6	83	43.9	< 0.0001
Hyperglycemia	20	2.6	10	1.7	10	5.3	0.01
Hypercholesterolemia	92	12	58	10	34	18	0.003
Hypertriglyceridemia	157	20.4	102	17.6	55	29.1	0.001
Low HDL-C	295	38.5	207	35.8	88	46.6	0.006
High LDL-C	175	22.8	117	20.2	58	30.7	0.002
High VLDL-C	155	20.2	94	16.2	65	34.6	0.006
Hypertension	25	3.3	8	1.4	18	9.3	0.03
Mixed dyslipidemia	44	5.7	23	4	21	11.1	0.001
Metabolic syndrome	37	4.8	18	3.1	19	10.1	< 0.0001

Student's t-test comparison for independent samples in continuous quantitative variables and by chi-square or Fisher's exact test for categorical variables.

BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SD = standard deviation, VLDL-C = very low density lipoprotein cholesterol.

been examined. Therefore, the purpose of this research is to assess the impact of hyperuricemia on metabolic parameters and cardiovascular risk factors in apparently healthy young Mexican adults.

Method

A cross-sectional study was carried out at the *Benemérita Universidad Autónoma de Puebla* from

August 2011 to May 2018. Mexican individuals aged between 18 and 22 years, without a medical history of metabolic alterations in the previous year, who were not receiving pharmacological treatment for chronic or metabolic diseases or with specific diet were included. Subjects without a fasting period longer than 12 hours, who referred metabolic alterations within the previous year or who decided not to participate were excluded; subjects in whom hemolyzed

or lipemic serum was obtained were removed from the study.

Individuals attended the facilities of the *Benemérita Universidad Autónoma de Puebla* Faculty of Medicine Department of Biochemistry, where they underwent somatometry (weight, height and waist circumference), history taking and clinical assessment (blood pressure), with a peripheral blood sample being obtained by venipuncture for biochemical analysis (VITROS DT60 II® analyzer, Ortho-Clinical Diagnostics, Raritan, NJ, United States), which included quantification of glucose, total cholesterol, triglycerides, UA and high (HDL-C), low (LDL-C) and very low density lipoprotein cholesterol (VLDL-C).

Alterations in body composition and metabolic parameters, as well as risk factors were categorized according to the Adult Treatment Panel Guidelines (ATP-III):¹²

- Waist circumference ≥ 80 cm in women or ≥ 90 cm in men, abdominal adiposity.
- Body mass index (BMI) ≥ 25 , overweight or obesity
- Hyperglycemia, fasting serum glucose ≥ 100 mg/dL.
- Hypertriglyceridemia, serum triglycerides (TGL) ≥ 150 mg/dL.
- Hypercholesterolemia, total cholesterol values ≥ 200 mg/dL.
- Decreased HDL-C, < 40 mg/dL in men or < 50 mg/dL in women.
- High LDL-C, > 100 mg/dL.
- High VLDL-C, ≥ 30 mg/dL.
- Hyperuricemia, serum UA > 6 and 7 mg/dL in women and men, respectively.
- Altered systolic blood pressure (SBP), ≥ 130 mm Hg.
- Altered diastolic blood pressure (DBP), ≥ 85 mm Hg.
- Hypertension, blood pressure values higher than 130/85 mm Hg.
- Dyslipidemia, TGL ≥ 150 mg/dL and total cholesterol ≥ 200 mg/dL.
- Metabolic syndrome, presence of three or more risk factors according to ATP-III.

The variables are presented as the mean $\pm$ standard deviation and as frequencies and proportions. A normality test was performed by means of the Kolmogorov-Smirnov statistic. Parametric statistics were obtained in the comparison of quantitative continuous variables using Student's t-test. Non-parametric comparisons in independent categorical variables were performed using the chi-square test and nominal

variables strength of association was obtained with Cramer's V. Different log-linear and logistic multivariate regression models were applied to observe interactions and influence of overweight or obesity-adjusted hyperuricemia and other confounding variables. Finally, a multivariate analysis of variance (MANOVA) was applied to assess the effect of hyperuricemia and overweight or obesity on changes in metabolic parameters of cardiovascular risk. A p-value < 0.05 was taken as a statistically significant value. All analyses were performed using the SPSS program, version 21 (IBM, Armonk, NY, USA).

Results

The study population included 768 individuals, 466 women and 302 men. Average age of the study sample was 18.8 ± 1.4 years, and BMI was 23.6 ± 4.4 ; the somatometry results and the biochemical profile were found within reference values. The presence of central adiposity was low and only 30 % of the population was overweight or obese. The least frequent metabolic alteration was hyperglycemia ($n = 20$, 2.6 %), while the most common was low HDL-C ($n = 295$, 38.5 %). The prevalence of hypertension ($n = 25$, 3.3 %), dyslipidemia ($n = 44$, 5.7 %) and metabolic syndrome ($n = 37$, 4.8 %) was low.

When individuals with normal UA ($n = 579$) were compared with those who had hyperuricemia ($n = 189$), weight, BMI and waist circumference were observed to be higher in subjects with hyperuricemia; similarly, the metabolic profile showed higher values. The proportions of altered metabolic parameters were higher in subjects with hyperuricemia than in those who had normal UA, which indicated a statistically significant association of hyperuricemia with an increase in cardiovascular risk factors ($p < 0.01$). The strength of association allowed measuring the relationship between nominal data and, in all metabolic alterations, there was a low but statistically significant relationship with hyperuricemia: hyperglycemia, $V = 0.09$, $p = 0.008$; hypercholesterolemia, $V = 0.11$, $p = 0.003$; hypertriglyceridemia, $V = 0.12$, $p = 0.001$; low HDL-C, $V = 0.095$, $p = 0.008$; high LDL-C, $V = 0.11$, $p = 0.003$; high VLDL-C, $V = 0.2$, $p = 0.003$; hypertension, $V = 0.2$, $p = 0.01$; mixed dyslipidemia, $V = 0.13$, $p < 0.0001$; metabolic syndrome, $V = 0.14$, $p < 0.0001$ (Table 1).

Different log-linear models were constructed to analyze the type of relationship between overweight or obesity and hyperuricemia with different metabolic parameters and cardiovascular risk factor alterations.

Table 2. Multivariate logistic regression models for metabolic alterations and cardiovascular risk factors

	Univariate model			Adjusted model*		
	OR (95% CI)	SE	p	OR (95% CI)	SE	p
Model for hyperglycemia						
Hyperuricemia	3.2 (1.3-7.7)	0.46	0.01	2.7 (1.1-6.9)	0.47	0.03
Overweight or obesity	1.8 (1.2-2.7)	0.22	0.007	2.4 (0.9-5.9)	0.46	0.06
Model for hypercholesterolemia	1					
Hyperuricemia	.9 (1.2-3.1)	0.24	0.004	1.8 (1.1-2.9)	0.24	0.01
Overweight or obesity	1.5 (1.2-2.1)	0.15	0.004	1.2 (0.8-1.9)	0.23	0.3
Model for hypertriglyceridemia						
Hyperuricemia	1.9 (1.3-2.8)	0.19	0.001	1.6 (1.1-2.3)	0.2	0.03
Overweight or obesity	2 (1.6-2.6)	0.22	0.0001	2.3 (1.6-3.3)	0.18	0.0001
Model for low HDL-C						
Hyperuricemia	1.6 (1.1-2.2)	0.17	0.009	0.9 (0.7-1.4)	0.19	0.9
Overweight or obesity	2.5 (1.9-3.4)	0.14	0.0001	2.6 (1.8-3.7)	0.18	0.0001
Model for high LDL-C						
Hyperuricemia	1.8 (1.2-2.5)	0.19	0.003	1.6 (1.1-2.3)	0.19	0.02
Overweight or obesity	1.8 (1.3-2.6)	0.17	0.001	1.5 (1.1-2.2)	0.18	0.02
Model for high VLDL-C						
Hyperuricemia	2.7 (1.3-5.4)	0.35	0.004	1.5 (0.7-3.3)	0.39	0.3
Overweight or obesity	3.9 (2-7.6)	0.34	0.0001	3.8 (1.9-7.6)	0.35	0.0001
Model for hypertension						
Hyperuricemia	7.1 (1.3-40)	0.89	0.03	6.8 (1.1-46)	0.96	0.04
Overweight or obesity	3.1 (0.6-17)	0.88	0.2	2.6 (0.4-16)	0.91	0.3
Model for mixed dyslipidemia						
Hyperuricemia	3 (1.6-5.6)	0.31	0.0001	2.5 (1.3-4.7)	0.33	0.006
Overweight or obesity	3.2 (2.1-4.9)	0.22	0.0001	2.6 (1.4-4.9)	0.32	0.003
Model for metabolic syndrome						
Hyperuricemia	3.5 (1.8-6.8)	0.34	0.0001	2.3 (1.1-4.6)	0.36	0.02
Overweight or obesity	6.7 (3.7-12)	0.31	0.0001	5.5 (2.6-12)	0.38	0.0001

*Adjusted for age and gender.

HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SE = standard error, VLDL-C = very low density lipoprotein cholesterol.

The results yielded by each model indicated that hyperglycemia ($p = 0.01$), hypercholesterolemia ($p = 0.005$), hypertriglyceridemia ($p = 0.01$) low HDL-C ($p = 0.0001$), high LDL-C ($p = 0.01$), elevated VLDL-C ($p = 0.04$), hypertension ($p = 0.02$), mixed dyslipidemia ($p = 0.004$) and metabolic syndrome ($p = 0.006$) are dependent only on hyperuricemia, since the presence of overweight or obesity together with hyperuricemia did not impact on the frequencies expected for each model.

With the logistic regression models, the influence of hyperuricemia and overweight or obesity on different metabolic parameter and cardiovascular risk factor alterations was sought, but prior to applying the multivariate models, bivariate correlation analyses between UA and all metabolic parameters were performed, adjusting for the presence of hypertension, dyslipidemia, and metabolic syndrome, in order to rule out collinearity between variables. The results of the

bivariate correlations indicated that there were no statistically significant correlations between variables belonging to each cardiovascular risk factor (SBP and DBP for hypertension, triglycerides and cholesterol for mixed dyslipidemia, and waist circumference, glucose, triglycerides, HDL-C, SBP and DBP for metabolic syndrome) and UA.

Different univariate and multivariate models were constructed for each metabolic alteration. In the univariate models, hyperuricemia and overweight or obesity were used. Hyperuricemia was identified, in a univariate manner, as an influence factor in all cardiovascular risk parameters, as also were overweight or obesity, except in hypertension. When the data were adjusted by gender and age, hyperuricemia was the factor with the highest influence on metabolic alterations; only in the model for low HDL-C and for high VLDL-C, this influence was not statistically significant (Table 2).

The impact of hyperuricemia, overweight and obesity on the changes in metabolic parameters of cardiovascular risk was assessed by means of MANOVA. The results indicated that hyperuricemia alone does not significantly predict changes in the eight metabolic parameters (Wilks $\lambda = 0.93$, $F[6,175] = 2.14$, $p = 0.05$), while overweight and obesity ($BMI > 25$) predicts changes in all eight metabolic parameters (Wilks $\lambda = 0.89$, $F[6,175] = 3.36$, $p = 0.04$). The interaction between hyperuricemia and overweight and obesity can significantly predict changes in all eight metabolic parameters of cardiovascular risk (Wilks $\lambda = 0.91$, $F[6,175] = 3.1$, $p = 0.007$).

The F multivariate test indicated that the main differences between metabolic parameters in individuals with hyperuricemia were observed in SBP and DBP, and in overweight or obese individuals, in glucose, TGL, SBP and DBP. The interaction between hyperuricemia and overweight or obesity mainly affects the cholesterol, LDL-C and SBP values ($p < 0.05$).

Discussion

The sample of this study was collected over an eight-year period and obtaining a thorough medical history was necessary to determine that the individuals were apparently healthy and that therefore could be included. Although there were more women who had normal UA, the proportion of women and men who had hyperuricemia was similar. Body composition and metabolic parameters were observed to be statistically higher in subjects with hyperuricemia than in those with normal UA but, even in subjects with hyperuricemia, the values were within the reference limits. This finding is interesting because it provides evidence regarding one of the main issues around UA effects on the development of cardiovascular diseases, since many authors have suggested that it is unknown which alteration occurs first, whether cardiovascular alterations or hyperuricemia.¹³⁻¹⁶ In this study, we observed that, on average, in a population of relatively healthy young adults, there are individuals with hyperuricemia who have not yet developed metabolic alterations but have higher values than those with normal UA, which suggests, with the limitations inherent to a cross-sectional study, that subjects with hyperuricemia could develop metabolic disorders in the future.

There are different demographic (gender, ethnicity) and clinical factors (medications, comorbidities) that affect UA levels,¹⁷ and this aspect was therefore considered in the methodological design: all included

subjects were of Latin-American mestizo ethnicity and referred not having any comorbidity, or chronically consuming any medication. These sample selection criteria were necessary, given that a large part of research is focused on middle-aged adults or specific patient groups, since the inclusion of adult subjects with any cardiovascular risk factor, such as hypertension, who might be using diuretic drugs such as thiazides, which induces increases in UA, cholesterol and glucose,¹⁸ or adult populations with hyperinsulinemia, a common feature in metabolic syndrome and source of renal urate, sodium reabsorption and anti-uricosuric effects,¹⁹ involves biases that influence the interpretation of results. Therefore, we tried to control for most confounding factors of the UA-CVD interaction.

Several studies have been conducted where UA is associated with cardiovascular disease^{4,20} and even with death from cardiovascular events,²¹⁻²⁴ although some of them do not demonstrate a full causal effect because they do not address causality criteria;²⁴ in most of them, ORs or associations are indicated without reporting the strength of association. In this research, the strength of association was calculated using Cramer's V, which showed that UA has a low but statistically significant strength of association with all metabolic alterations and cardiovascular risk factors.

On the other hand, the investigations that have associated UA with any cardiovascular risk factor²⁵ mainly point out an important univariate association, but in the adjusted models there is loss of statistical power; in addition, no analyses were found that controlled for variables' collinearity. Since a strong correlation between UA and metabolic parameters, mainly in metabolic syndrome, has been reported,⁸ this would indicate that, in multivariate models, where the association of UA with any cardiovascular risk factor is sought, there would be significant results thanks to the same collinearity, given that the studies are carried out in middle-aged populations where the metabolic alteration has been present for longer time in the individual. In this work, we tried to control for said collinearity with hypertension, dyslipidemia and metabolic syndrome-adjusted correlation analyses, with no previous correlation being found of the independent variable (UA) with the parameters of the response variable (hypertension, dyslipidemia, metabolic syndrome). Among the main results, we identified a dependence of all metabolic and cardiovascular risk parameters on hyperuricemia, which was not determined by overweight or obesity, both of which have been described in the genesis of any metabolic alteration and CVD.²⁶

In the Mexican population, research on UA effects has been carried out mainly in children²⁷ or adults with broad age ranges.^{28,29} Only one study was found in Mexican population³⁰ that obtained similar results to those herein presented, where a high prevalence of metabolic disorders was also found in individuals with hyperuricemia, as well as higher risk of metabolic syndrome (OR = 1.78, 95% CI = 1.2-2.6, $p = 0.003$) in those with hyperuricemia with regard to those who had normouricemia; in said study, metabolic syndrome was the only cardiovascular risk factor that was analyzed, while in this investigation, hyperuricemia was associated with several other factors and adjustment was made for different confounding variables, in addition to looking for interactions of UA with overweight and obesity for assessment of changes in metabolic parameters.

The main limitation of this study was its methodological design, since although statistical evidence suggests causal association of hyperuricemia with cardiovascular alterations, we cannot ensure that they had a chronological development subsequent to the presence of hyperuricemia; prospective observational analyses will have to be carried out to corroborate this hypothesis.

It can be concluded that hyperuricemia is significantly associated with metabolic disorders and different cardiovascular risk factors such as hypertension, mixed dyslipidemia and metabolic syndrome, an association that is independent from overweight or obesity, which reveals that hyperuricemia in young adults is a marker of a future CVD.

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