Sweetened beverages intake, hyperuricemia and metabolic syndrome. The Mexico City Diabetes Study

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Abstract

Objective. To determine prevalence of hyperuricemia and its relation with intake of sweetened beverages (SB) and metabolic syndrome (MS) in low income urban Mexican population. **Materials and methods.** A cross-sectional analysis of The Mexico City Diabetes Study, a prospective population-based investigation (1 173 participants) was performed. We used logistic regression, adjusted by pertinent variables. We determined prevalence of hyperuricemia and explored associations of uric acid levels with MS and intake of SB. **Results**. Prevalence of hyperuricemia was 26.5 and 19.8% in males and females respectively. In an adjusted multivariate model, body mass index, waist circumference, and triglyceride were higher as uric acid quartiles increased (p<0.005-0.001). The odds ratio for MS was 1.48 for 3rd uric acid quartile and 2.03 for 4th quartile. Higher consumption of SB was associated with higher uric acid levels (p<0.001). **Conclusion.** Prevalence of hyperuricemia is high. Potential association with intake of SB, resulting in metabolic alterations should be considered.

Key words: hyperuricemia; beverages; metabolism; Mexico

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Resumen

Objetivo. Determinar prevalencia de hiperuricemia en población mexicana urbana de bajos ingresos, relación con ingesta de bebidas endulzadas y síndrome metabólico. **Material y métodos.** Análisis transversal del Estudio de la Diabetes en la Ciudad de México (1 173 participantes), utilizando regresión logística, ajustada por variables pertinentes. Se determinó prevalencia de hiperuricemia, se exploraron asociaciones de niveles de ácido úrico con síndrome metabólico y bebidas endulzadas. **Resultados**. La prevalencia de hiperuricemia fue 26.5 y 19.8%, hombres y mujeres, respectivamente. El índice de masa corporal, circunferencia de cintura y triglicéridos fueron más altos con cada cuartil de ácido úrico (p<0.005 - 0.001). La razón de momios para síndrome metabólico fue 1.48 para el tercer cuartil y 2.03 para el cuarto. Se encontró mayor consumo de bebidas endulzadas a mayores niveles de acido úrico (p<0.001). **Conclusión**. La prevalencia de hiperuricemia es alta. La asociación con bebidas endulzadas y las alteraciones metabólicas resultantes deben considerarse.

Palabras clave: hiperuricemia; bebidas; metabolismo; México

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The interest in serum uric acid (UA) has re-emerged due to its possible role as a cardiovascular risk factor. Moreover, hyperuricemia (HU) contributes to the development of renal disease, a cardiovascular risk factor.[1] The mechanism by which UA enhances these risks remains under investigation. Excessive dietary intake of fructose has recently emerged as a relevant association, since it is an ingredient in foods and beverages consumed in increasing quantities in Mexico.[2,3] In studies in healthy subjects, physiological increments in insulin concentration acutely decreased renal UA clearance jointly with an increased sodium reabsorption. Hence, the chronic hyperinsulinemia associated with insulin resistance imposes a chronic antiuricosuric and antinatriuretic pressure on the kidney, eventually influencing both UA and blood pressure levels.[4,5] Moreover, HU has been related to endothelial dysfunction and it is considered an independent risk factor for high blood pressure (HBP). The suggested mechanism is UA-mediated glomerular hypertension, cortical vasoconstriction, glomerular damage, and tubular ischemia. The intricacies and the specific sequence of pathophysiologic events remain still a matter of scientific investigation. Recent studies have shown that lowering serum UA by reducing fructose intake and/or the administration of allopurinol, results in improvement of the metabolic alterations.[6] In view of the high prevalence of the components of the metabolic syndrome (MS) in the Mexican population,[7] the high carbohydrate content in the Mexican diet,[8,9] and the significant consumption of sweetened beverages with high fructose content in Mexico[10,11] we explored the prevalence of HU, the possible role of sweetened beverage intake and its association with the MS components as elements possibly implicated in the chronic kidney disease epidemic in the country. We present the results of an analysis performed in the latest follow-up phase of the Mexico City Diabetes Study (MCDS).

Materials and methods

The MCDS is a population-based, prospective, investigation designed to characterize the prevalence, incidence and natural history of type 2 diabetes (T2D) and cardiovascular risk factors, in low-income urban inhabitants of Mexico City. The methodology and its results have been previously reported.[12,13] The baseline phase started in 1990 with 2 282 men and non-pregnant women (35 to 64 years). For the present analysis, we used the data corresponding to the latest follow-up (2008). In this phase, there were 1 174 participants, 463 (39%) men. One subject did not have UA determination. Therefore, the total cohort was 1 173 subjects. To estimate prevalence, we assumed that self-reported allopurinol users (n=13) had HU independently of their serum UA level. We excluded subjects who self-reported the use of thiazides, (n=39). For the association with MS, we further excluded allopurinol users (n=13) and subjects with incomplete information on metabolic markers (n=5). The final cohort therefore consisted of 1 116 subjects, 438 (39%) males. The Institutional Review Board of both the Instituto Nacional de Salud Pública and the Centro de Estudios en Diabetes approved the study protocol. Informed consent was obtained from the participating subjects in accordance with the ethical principles for medical research involving human subjects. All participants underwent a physical exam. Blood pressure (BP) was measured three times, using a calibrated sphygmomanometer, in the sitting position after five min of rest, the mean of the last two readings was used.[14] Height and weight were measured without shoes and upper garments. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Waist circumference (WC) was measured using standard methods. Participants previously diagnosed by a physician with HBP, and reporting use of antihypertensive medication were considered hypertensives regardless of their blood pressure values. For subjects that were not known as hypertensives, we used the criteria of the Joint Commission for The Diagnosis & Treatment of Hypertension (JNC VII).[15] Participants who self-reported that they had a previous diagnosis of T2D by a physician and were receiving pharmacologic treatment for diabetes, were considered to have T2D regardless of their blood glucose values. For subjects not known to be diabetic we used the American Diabetes Association diagnostic criteria (fasting glucose ≥126 mg/dL, or two-hour plasma glucose ≥200 mg/dL after a standard, 75-g oral glucose load).

We used the Food Frequency Questionnaire (FFQ) approach to estimate participant's usual diet. This instrument was applied at baseline, and it was previously validated in the Mexican population.[16,17] This method is useful to measure dietary patterns in long-term cohorts.[18] To determine the habitual sweetened beverages intake in this population, we established four categories: less than one bottle per week, one bottle per week to less than one bottle a day, one bottle per day and more than one per day. Smoking was defined by self-reporting as current, past smoker or never smoker. Fasting venous blood samples were taken for laboratory determination: Total cholesterol, triglycerides, glucose, creatinine, and uric acid were done in an auto-analyser.[19] HbA_{1c} was measured using ion-exchange chromatography all at the clinical laboratory of the ABC Hospital, Mexico City. Glomerular Filtration Rate (eGFR) was estimated using the Cockroft-Gault formula. HU was defined using the National Institutes of Health criteria (fasting concentra-

tions: ≥7mg/dL and ≥6mg/dL for men and women, respectively).[20] For each of the following four MS components, we used the criteria established in Adult Treatment Panel, (ATP-III): 1) Hyperglycemia (FPG ≥100 mg/dL or pharmacologic treatment for hyperglycemia), 2) Hypertriglyceridemia (fasting triglycerides levels ≥150mg/dl or current use of lipid lowering drugs), 3) Abdominal obesity (WC ≥102 cm and ≥88cm for males and females, respectively), and 4) HBP (blood pressure ≥130/85 mmHg or current use of antihypertensive drugs).[21] HDL was not used because it was not measured in this follow up. We classified participants as having none, only 1, any 2, any 3 or all 4 criteria, and defined MS with at least any of 3 of these components.

Data are presented as mean±SD, Student *t* test was used for group comparisons of continuous variables. For the prevalence estimates, we calculated 95% confidence intervals (CI) using the Agresti-Coull binomial confidence intervals for proportions. To explore the possible relationships between UA and the MS components, the population was divided into quartiles of UA concentrations including both male and female participants. To determine if there was an association between MS components and UA quartiles, we calculated odds ratios (OR) and 95% CI, using logistic regression models for the combination of at least three of the MS components. Tests for trend across quartiles were calculated by modelling UA quartiles linearly, using the median value of each quartile; a *p*-value of <0.05 was considered statistically significant. All models were gender and age adjusted. Additionally, we calculated another model adjusting by years of study, current smoking, glomerular filtration rate and sweetened beverage intake. All statistical analyses were performed using the Stata 12.0 software.

Results

The mean age of the population was 62.8±7 years. Overall, 120 men and 135 women met HU criteria, only 13 (5.3 %) of these subjects were receiving treatment for HU. The mean value of UA level was 5.3 mg /dL for the entire population (1 134 participants excluding thiazide takers). After excluding allopurinol users, the mean UA level was 8.1 ± 0.9 mg/dL and 7.1 ± 1.1 mg/dL for hyperuricemic men and women, respectively. There were no statistically significant differences between the diabetic and hypertensive subgroups as shown in table I.

Upon stratifying the study population by quartile of UA concentrations (table II), BMI, WC, and triglycerides were significantly higher as UA concentrations increased. Mean values for both systolic and diastolic blood pressure levels tended to be similar in all uric acid quartiles. Fasting, 2-hour glucose levels and HbA_{1c} tended to be high in all groups, reflecting the high prevalence of dysglicemia in this population. Surprisingly, glucose and HbA_{1c} levels decreased across UA quartile. Renal function, as estimated by serum creatinine levels or eGFR, was progressively worse at higher UA levels. The proportion of subjects with high intake of sweetened beverage (> 1 bottle/day) increased steadily with UA quartile ($p<.001$). We estimated that the intake of 1 bottle of sweetened beverage per day could provide 45.9% of total daily fructose intake.

Table I
Prevalence of hyperuricemia by age group, gender, and condition.*
The Mexico City Diabetes Study, third follow up (2008-2009)

Age group	*All*		*T2D*		*With HBP*		*Without HBP & T2D*	
	Males (n=452)	*Females (n=682)*	*Males (n=112)*	*Females (n=175)*	*Males (n=199)*	*Females (n=320)*	*Males (n=204)*	*Females (n=285)*
<64 years	25.1	16.0	28.0	10.7	24.8	14.7	22.1	18.4
(n=686)	(20-30)	(12.7-20)	(19.6-39.5)	(5.9-18.3)	(17.9-33.2)	(10.3-20.7)	(15.8-30)	(13.3-25)
≥ 65 years	29.1	25.1	20.0	27.8	20.5	24.8	38.3	22.0
(n=448)	(22-36)	(20.4-30.4)	(9.7-36.2)	(18.7-39.1)	(12.9-30.9)	(18.3-32.7)	(28-49.8)	(15.6-30.6)
Total HU	26.5	19.8	25.9	17.7	23.1	23.1	27.9	20.0
(n=255)	(22-30)	(17-23)	(18.6-34.7)	(12.7-24)	(17.7-29.5)	(17.8-29.5)	(22.2-34.5)	(15.7-25)

* Entries are % and 95% CI for 1 134 subjects, including allopurinol users (n=13) and excluding thiazide takers (n=39)

HU= hyperuricemia
HBP= high blood pressure
T2D= type 2 diabetes
Numbers could be representing a case twice due to the concurrent pathology

Table II

Clinical and metabolic characteristics by quartile of serum uric acid concentrations.*
The Mexico City Diabetes Study, third follow up (2008-2009)

Group	*1* *mg/dL* *median (IQR)* *3.7(1.44-4.29)*	*2* *mg/dL* *median (IQR)* *4.8(4.30-5.25)*	*3* *mg/dL* *median (IQR)* *5.8(5.26-6.27)*	*4* *mg/dL* *median (IQR)* *7.2(6.28-11.86)*	*P*‡
Number*	279	279	281	277	
Gender (male)	19/279	87/279	124/281	174/277	<0.001
Age (years)	62.1 (±7.5)	63.7 (±7.9)	62 (±7.3)	63.4 (±8.1)	0.318
Schooling (years)	5.5 (±3.2)	5.7 (±3.9)	6.1 (±3.8)	5.9 (±4.2)	0.612
BMI (kg/m^2)	28.6 (±4.4)	29.2 (±5.3)	29.3 (±4.5)	30.4 (±4.9)	<0.001
Waist circumference (cm)	97.6 (±11.5)	99.9 (±14.1)	101.2 (±10.1)	102.8 (±11.3)	<0.001
Systolic BP (mmHg)	130 (±17.1)	128.3 (±16.9)	129.2 (±16.8)	131.3 (±16.6)	0.256
Diastolic BP (mmHg)	79.5 (±8.9)	78.2 (±8.0)	79.2 (±8.9)	80.1 (±8.9)	0.263
Fasting glucose (mg/dL)	128.3 (±74.2)	109.4 (±45.3)	108.1 (±44.5)	105.8 (±39.7)	0.299
2-hour glucose (mg/dL)	141.2 (±93.2)	132.3 (±54.4)	136.1 (±55.6)	137.7 (±57.4)	0.015
HbA^{1c} (%)	8.2 (±3.2)	7.5 (±2.3)	7.2 (±1.8)	7.1 (±1.7)	0.007
Triglycerides (mg/dL)	151.5 (±66.9)	162.5 (±80.9)	193.5 (±137.6)	190 (±100.3)	<0.001
Total cholesterol (mg/dL)	195.4 (±36.6)	197.6 (±35.3)	197.1 (±39.2)	197.6 (±37.9)	0.763
Creatinine (mg/dL)	0.76 (±0.1)	0.80 (±0.2)	0.90 (±0.3)	1.00 (±0.4)	<0.001
eGFR (ml/min)	85 (±24)	83 (±24)	84 (±25)	78 (±25)	0.01
Sweetened beverage intake (>1/day) (%)	19 (7.7%)	43 (16.8%)	54 (20.5%)	63 (24.5%)	<0.001

* entries are mean (±SD) or n (%) for 1 116 subjects excluding allopurinol (n=13) and thiazide takers (n=39)
‡ P for trend

BMI= body mass index
BP= blood pressure
eGFR= estimated glomerular filtration rate
HbA^{1c}= glycosylated hemoglobin
IQR= interquartile range
Categorical data were analyzed by $\chi 2$ test

The proportion of individual MS components in the UA quartiles is shown in table III. The prevalence of obesity (BMI ≥30 kg/m^2) was higher with each incremental level as was the proportion of subjects with high waist circumference. The proportion of individuals with high triglycerides rose above 60% in the top two UA quartiles. We explored the association of various MS components with UA quartiles by gender. There were 402 women with a mean UA concentration of 4.9±0.6 mg/dL who had less than three MS components, and 275 women with a mean UA level of 5.1±0.08 mg/dL presenting more than three components (p=0.09). In men, 313 individuals with a mean UA of 5.9±0.8 mg/dL had less than three MS components, while 125 subjects with a mean UA of 6.3±0.13 mg/dL had more than three components (p=0.008) (data not shown in table III).

We evaluated the association between UA quartile, MS risk (three or more components) and sweetened beverage intake by means of logistic regression (table IV). In model 1 adjusting for age and gender, we found a 62% increased risk for the highest quartile. In model 2, after also adjusting for smoking and schooling, the associations between uric acid quartiles and MS did not change significantly. When entering eGFR (model 3), MS risk was increased at the 3rd UA quartile (OR=1.48; 95% CI 1.02-2.14, p< 0.036), and the 4th quartile (OR=2.03; 95% CI 1.37-3.00, p<0.001). Finally, when adding sweetened beverage intake (model 4), the association between MS and UA remained statistically significant (p<0.002). However we did not demonstrated an additional effect, moreover the p value decreased, remaining statistically significant.

Table III

PROPORTION OF METABOLIC SYNDROME COMPONENTS BY URIC ACID QUARTILES. THE MEXICO CITY DIABETES STUDY, THIRD FOLLOW UP (2008-2009)

Group	*1 mg/dL median (IQR) 3.7(1.44-4.29)*	*2 mg/dL median (IQR) 4.8(4.30-5.25)*	*3 mg/dL median (IQR) 5.8(5.26-6.27)*	*4 mg/dL median (IQR) 7.2(6.28-11.86)*	‡p value
Number*	279	279	281	277	
BMI ≥30 kg/m2	100/279 (35.8%)	113/279 (40.5%)	126/281 (44.8%)	128/277 (46.2%)	0.007
WC ≥102 cm males	15/53 (28.3%)	23/87 (26.5%)	53/124 (42.8%)	80/174 (46.0%)	0.001
WC ≥88cm females	178/226 (78.8%)	170/192 (88.5%)	140/157 (89.2%)	93/103 (91.2%)	0.001
BP ≥130/85 mmHg	134/279 (48%)	118/279 (42.3%)	127/281 (45.2%)	140/277 (50.5%)	0.438
TG ≥150 mg/dL	113/279 (40.5%)	136/279 (48.7%)	170/281 (60.5%)	169/277 (61.0%)	<0.001
FPG ≥100 mg/dL	89/279 (31.9%)	72/279 (25.8%)	70/281 (24.9%)	74/277 (26.7%)	0.167
Number of MS components					
None	30/279 (10.8%)	30/279 (10.8%)	21/281 (7.5%)	22/277 (7.9%)	0.134
Only 1	65/279 (23.3%)	67/279 (24%)	58/281 (20.6%)	62 /277 (22.4%)	0.599
Any 2	88/279 (31.5%)	90/279 (32.3%)	97/281 (34.5%)	85 /277 (30.7%)	0.994
Any 3	73/279 (26.2%)	61/279 (21.9%)	74/281 (26.3%)	69 /277 (24.9%)	0.932
All 4	23/279 (8.2%)	31/279 (11.1%)	31/281 (11%)	38 /277 (13.7%)	0.05
At least any 3 MS criteria	96/279 (34.4%)	92/279 (33.0%)	105/281 (37.4%)	107/277 (38.6%))	0.159

* Entries are n (%) for 1 116 subjects excluding allopurinol (n=13) and thiazide takers, (n=39)
‡ P for trend

IQR= interquartile range
BMI= body mass index
WC= waist circumference
BP= Blood Pressure
TG= Triglycerides
FPG= Fasting Plasma Glucose
MS= Metabolic Syndrome
Categorical data were analyzed by $\chi 2$ test

Table IV

MULTIPLE LOGISTIC REGRESSION MODELS TO ASSESS ASSOCIATION OF METABOLIC SYNDROME RISK WITH SERUM URIC ACID QUARTILES. THE MEXICO CITY DIABETES STUDY, THIRD FOLLOW UP (2008-2009)

	Model 1			*Model 2*			*Model 3*			*Model 4*		
	OR	*95%CI*	*p value*	*OR*	*95%CI*	*p value*	*OR*	*95%CI*	*p value*	*OR*	*95%CI*	*p value*
Q1, 3.74 (1.44-4.29)	1.00	-	-	1.00	1.00	-	-	-	-	1.00	-	-
Q2, 4.79 (4.3-5.25)	0.99	0.69-1.41	0.968	0.99	0.70-1.42	0.999	1.01	0.69-1.46	0.950	1.06	0.71-1.58	0.773
Q3, 5.75 (5.26-6.27)	1.34	0.95-1.92	0.104	1.33	0.93-1.90	0.112	1.48	1.02-2.14	0.036	1.47	0.99-2.18	0.059
Q4, 7.19 (6.28-11.86)	1.62	1.11-2.34	0.012	1.59	1.09-2.31	0.015	2.03	1.37-3.00	<0.001	1.88	1.23-2.87	0.003
p for trend		0.004			0.005			<0.001			<0.002	
Age, years	1.01	0.99-1.02	0.154	1.00	0.98-1.01	0.882	1.04	1.02-1.07	<0.001	1.05	1.02-1.07	<0.001
Gender, male vs. female	0.50	0.39-0.67	<0.001	0.56	0.42-0.75	<0.001	0.44	0.32-0.60	<0.001	0.46	0.32-0.65	<0.001
Smoking, current	-	-	-	0.83	0.45-1.52	0.548	0.79	0.42-1.49	0.472	0.84	0.44-1.61	0.597
Schooling, years	-	-	-	0.94	0.90-0.98	0.004	0.94	0.90-0.98	0.004	0.94	0.90-0.98	<0.001
Glomerular filtration rate (mL/min)	-	-	-	-	-	-	1.02	1.01-1.03	<0.001	1.03	1.02-1.04	<0.001
Sweetened beverage intake (1/week-<1/day)	-	-	-	-	-	-	-	-	-	1.07	0.72-1.57	0.737
Sweetened beverage intake (1/day)	-	-	-	-	-	-	-	-	-	1.38	0.88-2.15	0.157
Sweetened beverage intake (>1/day)	-	-	-	-	-	-	-	-	-	1.36	0.83-2.23	0.227

Q= Quartiles. Entries Mean (range)
OR= Odds Ratio
CI= Confidence Interval

Discussion

The biochemical pathway linking fructose metabolism to UA is known. Fructose phosphorylation by fructokinase depletes intracellular ATP, thereby pushing both UA synthesis (via inosine-monophosphate) and triglyceride formation (via glycerol-3-phosphate).[22] Experimental evidence in laboratory animals and humans has confirmed that excessive fructose ingestion raises UA levels inducing features of metabolic syndrome.[23, 24]

The prevalence of HU was found to be 26.5% (95%CI, 22.7-30.8) in men and 19.8% (95%CI, 17-23) in women. Although others have reported a relatively high prevalence of HU in the Mexican population, we find higher rates as compared with other estimates. This might be due to age structure differences of the study population, ours being older (62.8±7.7 years).[25, 26] Alarmingly, in a small sample of medical students, 17 to 23 years old, the prevalence of HU was 19.8%.[27] Similar figures are seen in other countries: In 1 661 Brazilian individuals (25-64 years old), prevalence of HU was of 13.2% (95%CI, 11.4-15%), statistically higher in men 16% (95%CI, 14-18%) than women 10.7% (95%CI, 9-12%).[28] In a subsample of approximately 9 000 US adults a 18.9% prevalence of HU has been found.[29]

Most HU cases were undiagnosed; consequently, few were under medical treatment. Since the majority of participants (98%) had healthcare access, lack of medical management suggests insufficient public and professional awareness. The previously reported high prevalence of the various components of the MS, as well as its consequences,[30] makes undiagnosed HU a significant finding. In fact, HU likely enhances risk for chronic kidney disease (CKD)[31] in a population already with a high prevalence of nephropathy, as implicated by the frequent occurrence of microalbuminuria.[32-34]

Overall, MS (at least three MS components) was present in one third of our cohort, with most of MS components (BMI, WC and triglycerides) increasing in frequency across increasing UA quartiles. The association between UA and the MS components in our population is so consistent, as to suggest HU as an additional component of MS, contributing along with disglycemia, hypertension, and dislipidemia[35] and even other nephrotoxic agents such as lead[36] to both cardiovascular and renal damage. Perhaps a more robust public health intervention to prevent CKD and atherosclerotic cardiovascular disease in México, could be to deal with this cluster of conditions in a comprehensive approach.

The reduction in glycemia and A1C levels across the uric acid quartiles parallels the reduction in renal function, as estimated by creatinine and eGFR. These are related phenomena since it is known that the kidney plays an important role in insulin metabolism and a diminution in renal capability is also a reduction in insulin metabolism resulting in higher insulin effect, which is reflected in decrements in glycemia and glycohemoglobin values. This is a cohort effect, since the participants in this phase of the MCDS are older adults.

In our population, sweetened beverage intake is high.[37] We found that its consumption increases across UA quartiles, suggesting at least a possible role in the differences seen in the prevalence of HU. Our results support findings of a recent study[38] demonstrating the association of sweetened beverage intake with the prevalence of HU and CKD.[39]

We recognize several limitations in our study; namely: The diet assessment was obtained at baseline only, without taking into account possible modifications during follow-up. The estimate of sweetened beverage intake was done using a FFQ. We did not include HDL as part of the metabolic syndrome because it was not measured in this follow up. A potential cohort effect might explain the high prevalence of diabetes, hypertension and dyslipidemia in our population. However, our findings coincide with others and likely reflect a growing health problem in Mexico.

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Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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