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ARTICLE

The positive association between serum uric acid, impaired fasting glucose, impaired glucose tolerance, and diabetes mellitus in the ELSA-Brasil study

Associação positiva entre ácido úrico sérico, glicemia em jejum alterada, tolerância glicêmica alterada e diabetes mellitus no estudo ELSA-Brasil

La asociación positiva entre ácido úrico sérico, glucosa alterada en ayunas, tolerancia a la glucosa alterada y diabetes mellitus en el estudio ELSA-Brasil

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Abstract

There is a conflict in the literature regarding the association between serum uric acid (SUA) levels and glycemic status. Therefore, we evaluated the association between SUA level and glycemic status – impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes mellitus – and insulin resistance, in a large Brazilian study. This is a cross-sectional, observational study with 13,207 participants aged 35-74 years, at baseline (2008-2010) of the Brazilian Longitudinal Study of Adult Health *(ELSA-Brasil). A multinomial regression analysis was performed to test the association between SUA and glycemic status (IFG, IGT, and newly diagnosed type 2 diabetes at the cohort baseline) after adjustments by age, sex, skin color, body mass index, physical activity, smoking, alcohol consumption, comorbidities, and medicines use. Logistic regression model was used to evaluate the association between SUA and insulin resistance by HOMA-IR. Stratified analyses by sex were performed. The mean age (standard deviation) was 51.4 (8.9) years, 55.2% of participants were women. There were 1,439 newly diagnosed diabetes. After all adjustments, higher SUA was associated with IFG, IGT, and diabetes, with odds ratio (OR) = 1.15 (95%CI: 1.06; 1.25), 1.23 (95%CI: 1.14; 1.33), and 1.37 (95%CI: 1.24; 1.51), respectively. There was association between SUA levels and insulin resistance with OR = 1.24 (95%CI: 1.13; 1.36). In analysis stratified by sex, higher SUA persisted independently associated with impaired glycemic status. Our results suggest that a higher SUA levels were significantly associated with glycemic status in a large Latin American population, mainly among women.*

Diabetes Mellitus; Uric Acid; Impaired Glucose Tolerance; Insulin Resistance

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Introduction

Diabetes mellitus is a public health problem. Being a highly prevalent condition that increases cardiovascular risk and associated morbimortality, diabetes is associated with high health expenditures and large economic impact on health systems [1]. About 463 million adults were diagnosed with diabetes worldwide by 2019 [2]. If effective interventions are not performed, diabetes will be present in over 700 million adults, by 2025 [1].

Several risk factors that contribute to the development of diabetes are well known, such as obesity and sedentary lifestyle [1]. Uric acid is the final product of purine metabolism under the action of the xanthine oxidase enzyme [3]. Higher serum uric acid (SUA) levels are associated with the development of gout, cardiovascular diseases, renal disease, and inflammatory process [3]. The association between elevated SUA levels and increased risk of hyperglycemia has been reported by some authors [4,5,6,7,8]. A meta-analysis showed that elevation of 1mg/dL in the SUA level was associated with a 17% risk increase of developing diabetes. Moreover, it was suggested that the increase of 1mg/dL on uricemia would be comparable to the increase of 1kg/m^2 in body mass index (BMI) for the development of type 2 diabetes [4]. In contrast, other studies, including some with genetic evaluation, have not shown positive association between higher uricemia and hyperglycemia [9,10,11]. Studies have found that urate is involved in oxidative stress, systemic inflammation, insulin sensibility, and intrahepatic fructose metabolism [12].

SUA test is an accessible and simple laboratorial test, and is a potentially modifiable factor. Investigating whether SUA levels are associated with diabetes, pre-diabetes status, and insulin resistance may be relevant for clinical and public health purposes. To date, these studies are lacking in a large mixed-race and multi-ethnic populations. Brazil is a developing country, with more than 210 million inhabitants distributed in the territory of continental dimensions, and with some epidemiological profile distinct from other countries. We did not find Latin America studies evaluating the association between uricemia and diabetes, and epidemiological studies about uricemia are scarce and small. Meta-analysis evaluated do not include studies with specifically Latin American populations.

Thus, we aim to investigate a possible association between SUA levels and impaired glycemic status; and between SUA and insulin resistance, at the baseline of a large Brazilian prospective study, the *Brazilian Longitudinal Study of Adult Health* (ELSA-Brasil).

Methods

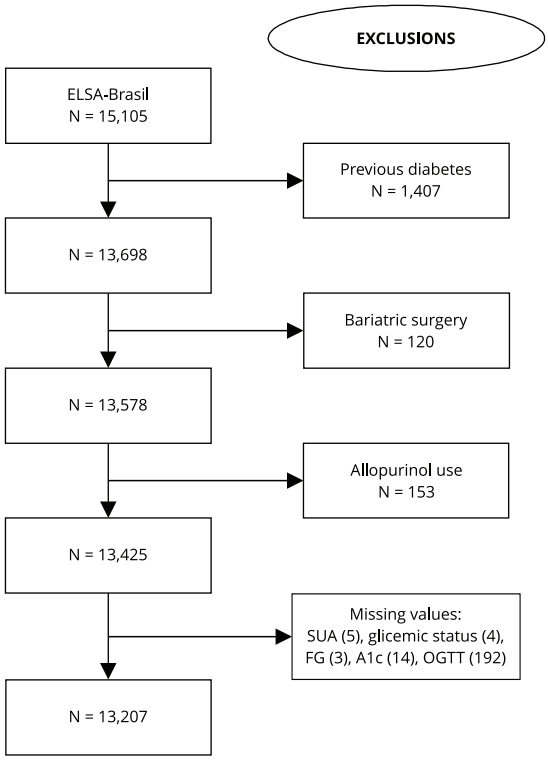
This is a cross-sectional study using ELSA-Brasil baseline data, collected from August 2008 to December 2010. The study population consisted of 15,105 participants aged 35-74 years. This multicenter Brazilian cohort study involves five public universities and one research institution, from three of the five major regions of the country. It aims to investigate epidemiological, clinical, and molecular aspects of chronic non-communicable diseases – mainly cardiovascular disease and diabetes [13,14].

Data collection started in 2008, according to study manuals and following international regulation for storage and data analysis. Interviews were performed after all participants signed the free consent form. Additional interviews, examinations, and laboratory tests were performed subsequently [13,14]. The ELSA-Brasil study was supported by the Brazilian Ministry of Health and the Brazilian Ministry of Science and Technology. More information is available at http://www.elsa.org.br/.

Our hypothesis is that there is a positive association between SUA levels and diabetes, impaired fasting glucose (IFG), and impaired glucose tolerance (IGT). For this analysis, the exclusion criteria were: participants with previous self-reported medical diagnosis of diabetes or in use of oral antidiabetic medications or insulin (n = 1,407); with reported bariatric surgery (n = 120) or allopurinol use (n = 153); without previous diabetes information status (n = 4); with missing values for fasting glucose (FG) (n = 3), glycated hemoglobin A1c (n = 14), oral glucose tolerance test (OGTT) (n = 192) and uric acid (n = 5). The final sample was composed of 13,207 participants (87.4%) (Figure 1).

Figure 1

Study population selection. ELSA-Brasil baseline (2008-2010).



A1c: glycated hemoglobin A1c; FG: fasting glucose; OGTT: oral glucose tolerance test; SUA: serum uric acid.

Laboratory tests

After overnight fasting, biological material samples were collected from all participants and were initially frozen and stored, and then transported to the central laboratory (University of São Paulo). All laboratory analysis were carried out in a single research center for better standardization [15].

The standard OGTT was performed in all participants of this study. Samples were collected for FG, after two hours of oral overload with 75g of anhydrous glucose [15].

Uric acid was measured by uricase method (enzymatic colorimetric) in the Siemens 1200 (Siemens Healthcare Diagnostics, Deerfield, Unites States). Hyperuricemia was defined on the basis of gender-specific cut-off points (> 7.2mg/dL for men, and > 6.0mg/dL for women) [15].

FG was measured by an enzymatic hexokinase (enzymatic colorimetric) method in Siemens 1200, glycated hemoglobin (A1c) by a high performance liquid chromatography (HPLC) in Bio-Rad Laboratories (Hercules, United States), and insulin by an immunoenzymatic assay, in Centaur Siemens equipment.

Triglycerides: Glycerol-phosphate peroxidase according to trinder (enzymatic colorimetric) and HDL cholesterol, in ADVIA 1200 Siemens equipment.

Creatinine measurement was based on the Jaffe's method in ADVIA 1200 Siemens equipment. The glomerular filtration rate (GFR) was estimated by serum creatinine, age, and sex, using the abbreviated form of *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI) [16].

Measures and definitions

"Glycemic status" was categorized into four categories: normoglycemia (normal FG and OGTT, and A1c < 5.7%), IFG (100mg/d/L ≥ FG < 126mg/dL and OGTT < 140mg/dL and A1c < 5.7%), IGT (140mg/dL ≥ OGTT < 200mg/dL and/or HbA1c > 5.7% and < 6.5%), and diabetes (FG ≥ 126mg/dL or OGTT ≥ 200mg/dL) or A1c ≥ 6.5%, according to the American Diabetes Association criteria [17]. Diabetes category means diagnosis of diabetes, at the baseline of the study, without previous diagnosis.

Insulin resistance was assessed by homeostasis model assessment of insulin resistance (HOMA-IR) by the [FG (mg/dL) x 0.0555 X plasma fasting insulin (mUI/L)] / 22.5. Insulin resistance was defined by HOMA-IR ≥ 90% percentile (P90) of the variable distribution [18].

Sex was categorized as male or female; the age was analyzed in years; the race /skin color was self-reported and categorized as black, brown, white, and others (including Asians and Indians); and the schooling was categorized in elementary, high school, and higher education. Diabetes in first-degree relatives was self-reported (family history of diabetes) [13].

Prevalent coronary heart disease was defined by the report of myocardial infarction and/or myocardial revascularization [13].

Anthropometry was performed by trained examiners using standardized techniques and equipment. BMI was calculated using weight (kg) divided by square of height (m^2). Health-related behaviors were assessed by the participants' self-report. Physical activity in leisure time was evaluated by the *International Physical Activity Questionnaire* (IPAQ) in the modified long version and participants were classified into three groups: low, moderately, or very active, according to the sum of the weekly metabolic equivalents – a combination of type, frequency, and duration of the physical activities performed [13]. Participants were classified as never smoked, ex-smokers, or smokers. Ex-smokers were those who smoked at least 100 cigarettes throughout a lifetime and current smokers, who still smoked at the time of the interview [13].

The intake of dairy, animal protein, fructose, and alcoholic beverages were assessed by a validated semi quantitative *Food Frequency Questionnaire* (FFQ) [19,20,21]. Frequency and the amount of dairy consumed were assessed, resulting in the evaluation of the intake categories in servings/day. Alcohol consumption was analyzed as grams/week and fructose as grams/24h [19].

Arterial hypertension was defined by a self-reported medical diagnosis of hypertension, use of anti-hypertensive drugs, or blood pressure ≥ 140x90mmHg at the moment of evaluation (sum of two measures, after five minutes of rest in the sitting position) [13].

Statistical analysis

Continuous variables were described by means and standard deviation (SD) or median value and interquartile range (IQR; 25th to 75th percentile), according to the distribution of the data. Categorical variables were described by frequencies and proportions. ANOVA test was used to compare means, and Kruskal-Wallis for the medians across glycemic status categories.

The association of variable glycemic status with SUA levels (continuous) and other explanatory variables was investigated by univariate analysis. All the variables with p-value < 0.20 and those clinically relevant, regardless of whether p < 0.20 in the univariate analysis, were pre-selected to enter multinomial logistic regression models with "glycemic status" as the response variable, and SUA levels as the variable of interest. A low number of participants had chronic kidney disease (n = 521). Sensitivity analysis showed that the exclusion of them did not affect the results. Therefore, we are presenting analysis with adjustment by GFR rather than with the exclusion of these participants.

Models were consecutively adjusted as follows: Model 1 – glycemic status, SUA (continuous), age (continuous), sex, race/skin color, schooling, family history of diabetes; Model 2 – Model 1 plus BMI, systolic and diastolic blood pressure, prevalent coronary heart disease, and glomerular filtration rate; Model 3 – Model 2 plus physical activity, smoking, alcohol and dairy intake, fructose and animal protein consumption, triglycerides, and HDL cholesterol; Model 4 – Model 3 plus use of medicines that may interfere with uricemia (diuretics, losartan, fenofibrate, acetylsalicylic acid, gout medications). Tests were conducted on whether uric acid levels and fructose intake were effect modifiers on the associations of glycemic status by multiplicative interaction terms between uric acid/fructose

intake. Additionally, tests were conducted on whether SUA and skin color were effect modifiers on the associations of glycemic status by multiplicative interaction terms between uric acid/skin color. We performed sensitivity analysis with categorical BMI, stratified into four categories according to nutritional status: underweight, eutrophic (reference), overweight and obesity.

The strength of the associations between the variables in the regression analysis was verified by odds ratio (OR) and confidence intervals (95%CI).

Logistic regression models were used to test the association between SUA levels and insulin resistance (yes/no), as the response variable, with the same adjustments and including multiplicative interaction terms between uric acid/fructose intake.

Sex-specific analysis were performed, and for the female sex we also included estrogens therapy used for postmenopausal, in Model 4.

All analyses were performed using the statistical software Stata 14 (https://www.stata.com) with a 5% significance level and the p-values were two sided.

The study was approved by the Research Ethics Committees of the six participating centers and the Brazilian National Commission for Ethics in Research (CONEP/MS 976/2006).

Results

Data from 13,207 participants were analyzed. The mean (standard deviation) age was 51.4 (±8.9) years, with 55.2% of females. Most participants had university degree (54%), and self-reported race/skin color as white (53.2%). A family history of diabetes was present in 37%. The mean SUA was 5.5mg/dL (±1.5), with 6.4mg/dL (±1.4) for men and 4.8mg/dL (±1.2) for women. The prevalence of hyperuricemia in the total sample was 18.4% (n = 2,430), 25.1% among men and 13.0% among women.

The mean FG was 101.6mg/dL (±16.3) in total sample, 104.9mg/dL (±19.2) among males, and 98.8mg/dL (±12.8) among females. The median OGTT was 118.7mg/dL (IQR: 101.3-140.8). The mean BMI was 26.7kg/m^2 (±4.6). There were 1,439 participants with newly diagnosed diabetes at the baseline cohort, and the prevalence of coronary disease was 2.5%. The median HDL cholesterol was 55mg/dL (IQR: 47-65). Among these participants, 91% consumed less than 175g alcohol/week, and the median dairy consumption was 3.4 (IQR: 2.0-5.4) servings/day. The median fructose intake was 21.6g/day (IQR: 14.9-31.0). The mean GFR was 85.9mL/min/1.73m^2 (±14.9).

Insulin resistance was defined by HOMA-IR value of 4.18, which corresponds to P90. Insulin resistance was evidenced in 1,327 participants, 10% of the final sample, most of them male.

In Table 1, data of the sample study is depicted according to the glycemic status. After all adjustments, higher SUA levels were significantly associated with impaired glycemic status. For each 1mg/dL increase in SUA levels, the odds of IFG, IGT and diabetes, was, respectively, 15%, 23% and 37% higher (Table 2). In the overall sample, we adjusted for the waist-to-hip ratio and there was no relevant change in OR (data not shown). Table 2 shows the sensitivity analysis, stratified by sex. The positive association between SUA levels and altered glycemic status remained significant after stratification. After sensitivity analysis with categorical BMI, the OR of IFG, IGT and diabetes was 1.17 (95%CI: 1.08; 1.27), 1.25 (95%CI: 1.16; 1.35) and 1.40 (95%CI: 1.26; 1.54), respectively, maintaining the positive association. The association between higher SUA levels and altered glycemic status was stronger among women. SUA levels were positive and significantly associated with insulin resistance in the general population OR = 1,24 (95%CI: 1.13; 1.36) and after stratification by sex (Table 3). Higher SUA had a strong association with insulin resistance, mainly among women.

Table 1

Characteristics of the study population according to glycemic status. ELSA-Brasil at baseline (2008 to 2010) (N = 13,207).

Characteristics	Normal glycemia (n = 4,936)	IFG (n = 2,790)	IGT (n = 4,042)	Diabetes mellitus (n = 1,439)	p-value
Sociodemographic					
Age [mean (SD)]	48.9 (8.4)	52.0 (8.6)	52.8 (9.1)	55.1 (8.3)	0.062
Sex [n (%)]					0.083
Male	1,738 (35.2)	1,588 (56.9)	1,806 (44.7)	789 (54.8)	
Female	3,198 (64.8)	1,202 (43.1)	2,236 (55.3)	650 (45.2)	
Schooling [n (%)]					< 0.001
Elementary	331 (6.7)	351 (12.6)	553 (13.7)	307 (21.3)	
High school	1,667 (33.8)	878 (31.5)	1,435 (35.5)	558 (38.8)	
Higher education	2,938 (59.5)	1,561 (55.9)	2,054 (50.8)	574 (39.9)	
Race/Skin color [n (%)]					0.001
Black	656 (13.4)	328 (11.9)	706 (17.7)	318 (22.4)	
Brown	1,355 (27.7)	771 (28.0)	1,126 (28.2)	421 (29.6)	
White	2,743 (56.1)	1,551 (56.4)	2,026 (50.7)	624 (43.9)	
Others	134 (2.8)	102 (3.7)	137 (3.4)	59 (4.1)	
Family history of diabetes mellitus [n (%)]	1,573 (32.2)	1,003 (36.5)	1,558 (39.1)	640 (45.3)	0.034
Health-related behaviors					
Smoking status [n (%)]					0.418
Never	3,143 (63.7)	1,535 (55.0)	2,239 (55.4)	695 (48.3)	
Ex-smoker	1,198 (24.3)	892 (32.0)	1,219 (30.2)	522 (36.3)	
Smoker	595 (12.0)	363 (13.0)	584 (14.4)	222 (15.4)	
Alcohol consumption (grams/week) [n (%)]					0.854
< 175	4,660 (94.4)	2,440 (87.5)	3,694 (91.4)	1,224 (85.1)	
≥ 175 < 350	208 (4.2)	266 (9.5)	238 (5.9)	144 (10.0)	
≥ 350	68 (1.4)	84 (3.0)	110 (2.7)	71 (4.9)	
Physical activity [n (%)]					0.001
Intensive	422 (8.7)	223 (8.1)	259 (6.5)	55 (3.8)	
Moderate	769 (15.9)	484 (17.5)	621 (15.5)	209 (14.7)	
Low	3,645 (75.4)	2,052 (74.4)	3,113 (78.0)	1,163 (81.5)	
Dairy products [median (IQR P25-75)]	3.5 (2.1-5.5)	3.3 (1.9-5.3)	3.3 (1.9-5.3)	3.1 (1.7-5.1)	0.0001
Animal protein consumption [median (IQR P25-75)]	78 (58-105)	80 (60-109)	80 (57-112)	84 (60-119)	0.0001
Fructose intake [median (IQR P25-75)]	21.1 (14.7-29.8)	21.2 (14.8-31.1)	22.3 (15.1-31.8)	23.1 (15.7-34.3)	0.0001
Laboratory tests and comorbidities					
Uric acid (mg/dL) [mean (SD)]					
Male	6.1 (1.3)	6.4 (1.3)	6.6 (1.4)	6.8 (1.5)	< 0.001
Female	4.4 (1.0)	4.9 (1.1)	5.0 (1.2)	5.5 (1.2)	0.385
GFR [mean (SD)]	88.4 (14.6)	84.9 (14.3)	85.0 (15.2)	82.2 (15.0)	0.070
HDL-C (mg/dL)					
Male	51 (44-58)	49 (43-57)	48 (43-56)	48 (42-55)	1.000
Female	62 (54-73)	60 (51-71)	59 (50-69)	56 (49-65)	1.000
Triglycerides (mg/dL) [median (IQR P25-75)]	94 (70-131)	118 (85-168)	123 (88-173)	149 (105-218)	< 0.001
Hypertension [n (%)]	980 (19.9)	898 (32.2)	1,527 (37.8)	811 (56.4)	< 0.001
BMI (kg/m^2) [median (IQR P25-75)]	24.8 (22.6-27.4)	26.3 (24.0 -29.1)	26.9 (24.2-30.1)	28.6 (25.6-31.9)	0.001
Waist-to-hip ratio [mean (SD)]	0.85 (0.1)	0.90 (0.1)	0.90 (0.1)	0.94 (0.1)	0.001
Coronary disease [n (%)]	68 (1.5)	64 (2.5)	121 (3.2)	54 (4.0)	0.627

BMI: body mass index; GFR: glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; IQR: interquartile range; SD: standard deviation.

Note: statistical test ANOVA and Kruskal Wallis.

Table 2

Association between glycemic status and uricemia in the general population and stratified by sex. ELSA-Brasil baseline (N = 13,207).

	Unadjusted model * OR (95%CI)	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)
Study population					
IFG					
Uric acid	1.48 (1.43; 1.53) **	1.34 (1.28; 1.39) **	1.21 (1.16; 1.27) **	1.14 (1.09; 1.20) **	1.15 (1.06; 1.25) **
IGT					
Uric acid	1.45 (1.40; 1.49) **	1.46 (1.40; 1.51) **	1.31 (1.26; 1.37) **	1.24 (1.18; 1.29) **	1.23 (1.14; 1.33) **
Diabetes					
Uric acid	1.80 (1.72; 1.87) **	1.74 (1.66; 1.83) **	1.48 (1.40; 1.57) **	1.31 (1.23; 1.39) **	1.37 (1.24; 1.51) **
Male					
IFG					
Uric acid	1.23 (1.17; 1.30) ***	1.23 (1.16; 1.29) ***	1.12 (1.05; 1.19) ***	1.07 (1.00; 1.14) ***	1.15 (1.02; 1.29) ***
IGT					
Uric acid	1.33 (1.27; 1.40) ***	1.33 (1.26; 1.40) ***	1.19 (1.12; 1.26) ***	1.13 (1.06; 1.21) ***	1.15 (1.02; 1.29) ***
Diabetes					
Uric acid	1.49 (1.40; 1.59) ***	1.48 (1.39; 1.58) ***	1.23 (1.14; 1.32) ***	1.10 (1.01; 1.19) ***	1.20 (1.04; 1.39) ***
Female					
IFG					
Uric acid	1.53 (1.43; 1.63) ***	1.44 (1.36; 1.54) ***	1.30 (1.20; 1.40) ***	1.20 (1.11; 1.30) ***	1.19 (1.02; 1.38) *** 1.19 (1.02; 1.38) ***,#
IGT					
Uric acid	1.70 (1.62; 1.80) ***	1.60 (1.51; 1.69) ***	1.45 (1.36; 1.55) ***	1.35 (1.26; 1.44) ***	1.29 (1.14; 1.47) *** 1.30 (1.15; 1.48) ***,#
Diabetes					
Uric acid	2.43 (2.26; 2.62) ***	2.16 (1.99; 2.33) ***	1.93 (1.76; 2.12) ***	1.66 (1.51; 1.83) ***	1.70 (1.41; 2.04) *** 1.70 (1.42; 2.05) ***,#

95%CI: 95% confidence interval; HDL-C: high density lipoprotein cholesterol; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; OR: odds ratio.

* The associations are for a 1mg/dL difference;

** $p < 0.001$;

*** $p < 0.05$;

Adjusted for estrogens therapy used for postmenopausal women.

Note: Model 1 = adjustment by age, gender, family history of diabetes, education and race/skin color; Model 2 = Model 1 + body mass index, systolic and diastolic blood pressure, coronary artery disease and glomerular filtration rate; Model 3 = Model 2 + health-related behaviors, HDL-c e triglycerides, animal protein consumption and dairy products; Model 4 = Model 3 + use of medicines.

Table 3

Association between insulin resistance assessed by homeostasis model assessment of insulin resistance (HOMA-IR ≥ P90) and uricemia in the general population and stratified by sex. ELSA-Brasil baseline (2008-2010) (N = 13,207).

	Unadjusted model * OR (95%CI)	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)
General population					
Uric acid	1.56 (1.50; 1.61) **	1.59 (1.52; 1.66) **	1.28 (1.22; 1.36) **	1.19 (1.12; 1.26) **	1.24 (1.13; 1.36) **
Male					
Uric acid	1.45 (1.37; 1.52) ***	1.43 (1.36; 1.51) ***	1.16 (1.09; 1.24) ***	1.10 (1.03; 1.18) ***	1.19 (1.05; 1.35) ***
Female					
Uric acid	1.95 (1.82; 2.09) ***	1.91 (1.77; 2.06) ***	1.55 (1.42; 1.69) ***	1.36 (1.23; 1.50) ***	1.34 (1.12; 1.61) *** 1.36 (1.13; 1.63) ***,#

95%CI: 95% confidence interval; HDL-C: high density lipoprotein cholesterol; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; OR: odds ratio.

* The associations are for a 1mg/dL difference;

** p < 0.001;

*** p < 0.05;

Adjusted for estrogens therapy used for postmenopausal women.

Note: Model 1 = adjustment by age, gender, family history of diabetes, education and race/skin color; Model 2 = Model 1 + body mass index, systolic and diastolic blood pressure, coronary artery disease and glomerular filtration rate; Model 3 = Model 2 + health-related behaviors, HDL-c e triglycerides, animal protein consumption and dairy products; Model 4 = Model 3 + use of medicines.

Discussion

This study investigated the association between glycemic status and SUA levels in men and women at the baseline of a large cohort of Brazilian adults. After adjusting for demographic, anthropometric, health conditions, laboratory variables, and for the intake of some food groups, alcoholic beverages, and use of medicines, it was observed that higher SUA levels were independently associated with abnormal glycemic status and insulin resistance. These results were demonstrated in both genders, with higher association among female participants, and without influence of estrogenic drugs used for hormonal postmenopausal therapy.

Some authors have demonstrated an association between higher SUA levels and hyperglycemia. Prospective data from the original *Framingham Heart Study*, showed there was a high independent risk of future diabetes development in those with higher uricemia, in a positive linear progression; including in young adults, reaching a 20% higher risk for each 1mg/dL increase in SUA [22].

Our findings were consistent with the literature. Kramer et al. [6] investigated the incidence of diabetes in individuals with normal glycemia, IFG, and IGT, with mean age of 63.3 years. The risk of diabetes increases by 60% for each 1mg/dL higher baseline SUA, after several adjustments. The SUA cut-off of 5.35mg/dL had a 100% negative predictive value for incident diabetes, after almost two decades of follow-up.

However, in contrast to this study, other researchers did not find an association between SUA and altered glycemic status. A study with American adults from the third *National Health and Nutrition Examination Survey* [10] found an inverse association between higher SUA levels and diabetes, but there is no mention about adjustments for drugs such as allopurinol. A Chinese cohort [9] with more than 4,400 participants also evaluated the association between SUA, xanthine oxidase activity, and diabetes development. There was an association between SUA and diabetes, but this association was lost after adjustment for xanthine oxidase activity. The authors concluded that elevated xanthine oxidase activity, but not SUA, has been associated with an increased risk of developing diabetes.

Another study [11] evaluated the association between SUA levels and diabetes among more than 24,000 participants of eight European countries. Although a positive association between the increase

in SUA level and risk of diabetes was found, there was no causal relationship between the variables after analysis by Mendelian randomization, using a genetic score with 24 uric acid associated loci. Other studies have also shown an association between SUA and incident diabetes. Mendelian randomization, however, did not provide evidence for a causal link between them [23,24].

A meta-analysis emphasized that urate plays an important role in insulin resistance; and higher SUA was associated with an increased risk of developing diabetes [4]. Hyperuricemia reduces the bioavailability of nitric oxide – fundamental for the cellular uptake of glucose – which could be a mechanism that would, partially, explain insulin resistance [3,25]. On the other hand, hyperinsulinemia leads to an increase in SUA due to a reduction in uric acid secretion; since insulin stimulates the expression of the urate transporter 1 (URAT1), which increases renal urate reabsorption, generating accumulation of plasma uric acid [3,25]. The rapid hepatic synthesis of uric acid from fructose(a sugar commonly added to beverages, soft drinks, and processed foods) causes mitochondrial oxidative stress, via activation of NADPH oxidase, which stimulates insulin resistance and fat accumulation regardless of excessive caloric intake [12]. The likely mechanism in which fructose induces hyperuricemia is due to the increased degradation of adenosine triphosphate to adenosine monophosphate, a precursor of uric acid [12].

A review article evaluated uricemia as a marker of metabolic syndrome. It was observed that the association between hyperuricemia, cardiovascular disease, and elevation of proinflammatory cytokines implicated in the development of atherosclerosis [26]. Increased levels of markers and mediators of inflammation are related to changes in blood glucose and in insulin sensitivity. Uric acid may induce oxidative stress on adipocytes, by inflammatory cytokines synthesis via NADPH oxidase, generating insulin resistance [12]. Interleukin-6 and tumor necrosis factor α (TNF-α) appear to interfere with insulin, signaling pathways and beta cell function. TNF-α facilitates serine phosphorylation of the insulin receptor substrate 1, altering the phosphatidylinositol 3-kinase pathway and reducing insulin sensitivity [12,27].

Inhibition of β-cell function by SUA may occur through several insulin signaling pathways, such as the adenosine monophosphate-activated protein kinase pathway. This is due to the overproduction of reactive oxygen species and oxidative damage, causing inhibition of proliferation and growth of β-cells. The kinase pathway is regulated by extracellular signaling and the nuclear transcription factor kappa B [28,29].

The pathogenesis of diabetes is complex and multifactorial, in which overweight, sedentary lifestyle, dietary habits, genetic factors, and age are highly relevant factors [1,17]. Despite all the knowledge about these factors, the prevalence of diabetes has increased in a worrisome way, with Brazil being the fifth country with the largest number of individuals with diabetes [1,2].

The population of this study, according to the data presented, shows a high risk of insulin resistance and altered glycemic status development, since most participants were middle-aged, with the mean BMI of 26.7kg/m^2 (±4.6), and reported a sedentary behavior. We adjusted for BMI to avoid confusion bias due to the causal relationship between obesity and diabetes. Even after conducting a sensitivity analysis with categorical BMI, stratified into four categories according to nutritional status, the association between SUA and impaired glycemic status remained positive.

The most relevant positive aspects of our study are the rigor in the collection and processing of data and the large sample size, which allowed the analysis of men and women, separately. It has been shown that there are strong sex-specific effects in the genetic basis of urate production and excretion [8,30]. We adjusted it in females using hormonal postmenopausal therapy, as there is evidence that estrogen exerts an uricosuric effect, interfering with uricemia [31]. Other positives aspects are the fact that it is a multicenter study carried out in different Brazilian regions, with diverse genetic profile. We adjusted for important confounding factors, such as skin color, glomerular filtration rate, and use of interfering drugs. Another significant adjustment was dietary intake of dairy products and animal protein recognized as factors that can be protective or increase the risk of hyperuricemia and diabetes, respectively [12,32]. We also tested whether SUA and skin color were effect modifiers on glycemic status associations by multiplicative interaction terms between uric acid/skin color, with no change in OR. A positive, statistically significant, association persisted after we tested for effect modification by fructose intake, a sugar associated with the rapid uric acid hepatic synthesis, insulin resistance, and hyperglycemia [12].

Finally, this is a cross-sectional study and it is not possible to show a causal relation between explanatory variables and the outcomes assessed. No residual confounding factors were considered, such as the xanthine oxidase activity and genetic profile.

Our work is innovative because we approach the association of SUA and altered glycemic status in the Latin American population, in a large sample, with almost 14,000 participants. With an estimated population of 50% white and 43% black and brown, this study proves to be remarkably diverse from the studies that addressed the topic, essentially with a Caucasian or Asian population.

We also made adjustments and an interaction term for the fructose intake and the consumption of dairy products, which may be related to SUA levels and glycemia.

Despite being a cross-sectional analysis, this study is related to a large Latin American sample, and Brazil has the fifth largest diabetes population in the world [2], many still without diagnosis and treatment.

In sum, despite all current scientific knowledge of pathogenesis, diagnosis, and therapy, the high incidence of type 2 diabetes – and all the consequences of its diagnosis – remain a major focus on public health, with worldwide interest. In our study, we sought to clarify the association between SUA, a low cost, simple and accessible biomarker, and hyperglycemia, trying to better understand a residual factor that influences the development of diabetes. There was a positive, independent, and significant association between SUA levels and altered status of glycemia, diabetes, and insulin resistance, mainly in women.

SUA is an accessible and simple laboratorial test, and a potentially modifiable factor. Investigating the SUA levels, especially in patients diagnosed with pre-diabetes and insulin resistance, may be relevant for clinical and public health purposes. Further studies can be developed to answer challenging questions about this association in populations with diverse genetic background.

Contributors

A. I. R. Galvão wrote the manuscript, designed the study and the study's analytic strategy, analyzed the data, and conduct the literature review. A. M. R. Beleigoli designed the study and the study's analytic strategy, analyzed the data, and helped with the statistical analysis of the data. P. G. Vidigal and S. L. Appleton critically reviewed and edited the manuscript for important intellectual content. B. B. Duncan, M. I. Schmidt, and S. M. Barreto helped with the statistical analysis of the data and critically reviewed and edited the manuscript for important intellectual content. M. F. H. S. Diniz designed the study and the study's analytic strategy, analyzed the data, conduct the literature review, and critically reviewed and edited the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Additional informations

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Resumo

Há uma controvérsia na literatura a respeito da associação entre níveis de ácido úrico sérico (AUS) e glicemia. Portanto, avaliamos a associação entre AUS e glicemia (glicemia em jejum alterada, intolerância glicêmica e diabetes mellitus), além da resistência insulínica, em uma amostra grande no Brasil. O estudo transversal observacional incluiu 13.207 participantes com idade entre 35 e 74 anos na linha de base (2008-2010) do Estudo Longitudinal de Saúde do Adulto *(ELSA-Brasil). Foi realizada análise de regressão multivariada para testar a associação entre AUS e glicemia (glicemia em jejum alterada, intolerância glicêmica e diagnóstico novo de diabetes tipo 2 na linha de base da coorte) depois de ajustar para idade, sexo, cor, índice de massa corporal, atividade física, tabagismo, consumo de álcool, comorbidades e uso de medicação. O modelo de regressão logística foi usado para avaliar a associação entre AUS e resistência insulínica por HOMA-IR. Foram realizadas análises estratificadas por sexo. A média de idade (DP) foi 51,4 (8,9) anos, e 55,2% dos participantes eram mulheres. Houve 1.439 novos diagnósticos de diabetes. Depois de todos os ajustes, o AUS esteve associado à glicemia em jejum alterada, intolerância glicêmica e diabetes, com odds ratio (OR) = 1,15 (IC95%: 1,06; 1,25), 1,23 (IC95%: 1,14; 1,33) e 1,37 (IC95%: 1,24; 1,51), respectivamente. Houve uma associação entre níveis de AUS e resistência insulínica, com OR = 1,24 (IC95%: 1,13; 1,36). Na análise estratificada por sexo, persistiu a associação independente entre AUS elevado e glicemia. Os resultados sugerem que níveis elevados de AUS estão associados de maneira significativa com a glicemia em uma população latino-americana grande, sobretudo entre mulheres.*

Diabetes Mellitus; Ácido Úrico; Intolerância à Glucose; Resistência à Insulina

Resumen

Hay un conflicto en la literatura respecto a la asociación entre los niveles de ácido úrico sérico (AUS) y el estado glucémico. Por eso, evaluamos la asociación entre el nivel AUS y el estatus glucémico: glucosa alterada en ayunas (GAA), tolerancia a la glucosa alterada (TGA) y diabetes mellitus (diabetes), comparados con la resistencia a la insulina en un amplio estudio en Brasil. Se realizó un estudio transversal, observacional con 13.207 participantes, con edades comprendidas entre los 35-74 años, en la base de referencia del Estudio Longitudinal de Salud entre Adultos brasileños *(2008-2010) (ELSA-Brasil). Se realizó un análisis de regresión multinomial para probar la asociación entre AUS y el estado glucémico (GAA, TGA y de nuevo la diabetes tipo 2, diagnosticada en la cohorte como base de referencia) tras los ajustes por edad, sexo, color de piel, índice de masa corporal, actividad física, fumar, consumo de alcohol, comorbilidades, uso de medicinas. Se usó el modelo de regresión logística para evaluar la asociación entre AUS y la resistencia a la insulina por el HOMA-IR. Se realizó también un análisis estratificado por sexo. La media de edad (desviación estándar) fue 51,4 (8,9) años, un 55,2% de los participantes eran mujeres. Hubo 1.439 nuevos casos de diabetes diagnosticados. Tras todos los ajustes, una AUS más alta estuvo asociada con GAA, TGA y diabetes, con odds ratio (OR) = 1,15 (IC95%: 1,06; 1,25), 1,23 (IC95%: 1,14; 1,33), y 1,37 (IC95%: 1,24; 1,51), respectivamente. Hubo asociación entre los niveles AUS y la resistencia a la insulina con OR = 1,24 (IC95%: 1,13; 1,36). En el análisis estratificado por sexo, una AUS más alta persistía independientemente asociada con un estado glucémico alterado. Nuestros resultados sugieren que unos niveles más altos de AUS estuvieron significativamente asociados con el estado glucémico en una amplia población latinoamericana, principalmente entre mujeres.*

Diabetes Mellitus; Ácido Úrico; Intolerancia a la Glucosa; Resistencia a la Insulina

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