

Serum uric acid and disorders of glucose metabolism: the role of glycosuria

J.A.M. Andrade¹, H.C. Kang², S. Greffin¹, M.L. Garcia Rosa³ and J.R. Lugon¹

¹Divisão de Nefrologia, Departamento de Medicina Clínica, Faculdade de Medicina, Universidade Federal Fluminense, Niterói, RJ, Brasil

²Departamento de Patologia, Faculdade de Medicina, Universidade Federal Fluminense, Niterói, RJ, Brasil

³Departamento de Epidemiologia e Bioestatística, Universidade Federal Fluminense, Niterói, RJ, Brasil

Abstract

Hyperuricemia has been associated with hypertension, diabetes mellitus, and metabolic syndrome. We studied the association between hyperuricemia and glycemic status in a nonrandomized sample of primary care patients. This was a cross-sectional study of adults ≥ 20 years old who were members of a community-based health care program. Hyperuricemia was defined as a value >7.0 mg/dL for men and >6.0 mg/dL for women. The sample comprised 720 participants including controls ($n = 257$) and patients who were hypertensive and euglycemic ($n = 118$), prediabetic ($n = 222$), or diabetic ($n = 123$). The mean age was 42.4 ± 12.5 years, 45% were male, and 30% were white. The prevalence of hyperuricemia increased from controls (3.9%) to euglycemic hypertension (7.6%) and prediabetic state (14.0%), with values in prediabetic patients being statistically different from controls. Overall, diabetic patients had an 11.4% prevalence of hyperuricemia, which was also statistically different from controls. Of note, diabetic subjects with glycosuria, who represented 24% of the diabetic participants, had a null prevalence of hyperuricemia, and statistically higher values for fractional excretion of uric acid, Na excretion index, and prevalence of microalbuminuria than those without glycosuria. Participants who were prediabetic or diabetic but without glycosuria had a similarly elevated prevalence of hyperuricemia. In contrast, diabetic patients with glycosuria had a null prevalence of hyperuricemia and excreted more uric acid and Na than diabetic subjects without glycosuria. The findings can be explained by enhanced proximal tubule reabsorption early in the course of dysglycemia that decreases with the ensuing glycosuria at the late stage of the disorder.

Key words: Hyperuricemia; Glycosuria; Diabetes mellitus; Prediabetes

Introduction

Elevated serum uric acid is an independent predictor of vascular complications and mortality in type 2 diabetes mellitus patients (1) and is associated with excess risk for development of diabetes (2,3).

The association between hyperuricemia and cardiovascular disease has been observed since the nineteenth century (4). This issue gained more attention in the late 1950s and since then several studies have stressed the correlation between uric acid and conditions such as arterial hypertension (5,6), diabetes mellitus (7), metabolic syndrome (8), atherosclerosis (9), and renal disease (10,11).

However, the relationship between diabetes mellitus and hyperuricemia is still subject to controversy. Although several studies have reported hyperuricemia as a risk factor for development of diabetes mellitus, especially in the context of insulin resistance, others have suggested that patients with recently diagnosed diabetes tend to have

lower serum uric acid than prediabetic or normoglycemic ones (12,13). Based on this information, we evaluated the association between uric acid and glycemic status in a nonrandomized sample of members of a community-based health care program.

Material and Methods

The study sample was derived from the CAMELIA (cardiometabolic renal) study, a cross-sectional observational study of familial aggregation of metabolic syndrome, conducted between July 2006 and December 2007 as a partnership between Universidade Federal Fluminense and the Niterói Healthcare Foundation. The protocol was approved by the Ethics Committee of the Faculdade de Medicina, Universidade Federal Fluminense, Niterói, RJ, Brazil, under the number 220/05.

Correspondence: J.R. Lugon, Rua Marques de Paraná, 303, 2^o andar, Centro de Diálise, 24033-900 Centro, Niterói, RJ, Brasil. Fax: +55-21-2629-9260. E-mail: jocerl@huap.uff.br

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A total of 1098 subjects who were enrolled in the Family Doctor Program of Niterói city, Rio de Janeiro, RJ, Brazil, were recruited following an initial selection of index cases. The present study included data from participants who were at least 20 years old. To be accepted as an index case, individuals were required to have a partner who agreed to participate in the study and to have at least one descendant with that partner, aged 12 to 30 years, who would also enroll. Four groups of index cases were initially selected. These were controls whose partners were also neither hypertensive nor diabetic, nondiabetic hypertensive patients, diabetic patients without hypertension, and diabetic patients who were hypertensive. Patients with immunodeficiency, malignancy, chronic renal failure (stage V), heart failure, coronary artery disease, stroke, severe peripheral vascular disease, pregnant women, or users of immunosuppressive drugs (corticosteroids or cytostatics) were excluded. Likewise, controls found to have a systolic blood pressure >140 mmHg and/or diastolic pressure >90 mmHg, or whose fasting glucose was ≥ 100 mg/dL were not included. Written informed consent was obtained from all participants. Subjects were interviewed by trained investigators using a standardized questionnaire.

Blood pressure was measured with an electronic sphygmomanometer (HEM-711AC Omron Co., Japan). Subjects whose reading was >140 mmHg (systolic) or >90 mmHg (diastolic) as well as those who reported using antihypertensive drugs were considered hypertensive. Body weight was measured by a digital electronic scale (PL80, Filizola, Brazil) and height by a portable digital stadiometer (Kirchner Wilhelm, Medizintechnik, Germany). The body mass index (BMI) was calculated as the ratio of weight in kilograms to height in meters squared. Waist circumference was assessed on three occasions using an inextensible tape measure, at the midpoint of the distance between the iliac crest and the last costal margin with the patient upright and at end expiration.

Participants whose fasting glucose was ≥ 126 mg/dL, and those who reported oral use of hypoglycemic agents and/or insulin were considered diabetic. Prediabetes was defined as fasting glucose between 100 and 125 mg/dL (American Diabetes Association) and hyperuricemia as plasma uric acid ≥ 6.0 mg/dL for women and ≥ 7.0 mg/dL for men. The diagnosis of metabolic syndrome was based on harmonized criteria (14). Subjects who met at least 3 of 5 of the following criteria were considered as having metabolic syndrome: 1) increased waist circumference - in Latin America >90 cm for men and >80 cm for women; 2) hypertriglyceridemia (triglycerides ≥ 150 mg/dL or use of lipid lowering drugs); 3) low HDL cholesterol ≤ 40 mg/dL in men and < 50 mg/dL in women; 4) systolic blood pressure ≥ 130 mmHg and/or diastolic ≥ 85 mmHg or use of antihypertensives, and 5) fasting glucose ≥ 100 mg/dL or use of antidiabetic agents.

Biochemical serum and urine samples were obtained after 8 h fasting. Analyses were performed with a Selectra

analyzer (NE Vital Scientific, Netherlands). Standard serum parameters included glucose, creatinine (Cr), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), triglycerides, and uric acid (UA). Urinary biochemical parameters were measured in a first morning urine sample and included Cr, albumin (Alb), sodium, and uric acid. Glycosuria was assessed semiquantitatively by dipsticks. We calculated the sodium excretion index (EINa) in mEq/g Cr, Alb:Cr ratio (ACR) in mg/g Cr, and fractional excretion of uric acid (FEUA) as a percentage. Microalbuminuria was defined as an ACR between 30 and 300 mg/g Cr. Glomerular filtration rate (eGFR) was estimated by CKD-EPI (the Chronic Kidney Disease Epidemiology Collaboration) formula, recommended as more appropriate for studies in the general population (15).

Continuous variables are reported as means \pm SD, categorical variables as frequencies. For continuous variables, differences between groups were tested using T-test for comparing two groups or, alternatively, one-way ANOVA complemented by the Duncan test; for frequencies, chi-square or the Fisher test was employed as appropriate. Values of $P < 0.05$ were considered to be significant. Statistical analyses were performed using SPSS (Statistical Package for Social Sciences, USA), version 18.0.

Results

A total of 720 patients were evaluated: controls ($n=257$) and euglycemic and hypertensive ($n=118$), prediabetic ($n=222$), and diabetic ($n=123$) patients. None of the subjects was using drugs for hyperuricemia. The general characteristics of the study population are shown in Table 1.

The overall prevalence of hyperuricemia in the study population was 8.9%. The influence of gender and age upon the frequency of hyperuricemia can be observed in Figure 1. Despite the adoption of different reference values for each gender, young males tended to be more hyperuricemic than young females at every age range but statistical significance was reached only in those 40-49 years of age. Above the age of 50 years, gender differences were no longer present, meaning that the increase of frequency of hyperuricemia in females with aging was more substantial. In both genders, the highest frequency of hyperuricemia was seen above 60 years of age.

Data from the four study groups are shown in Table 2. The frequency of hyperuricemia was statistically higher in both prediabetic and diabetic patients than in controls. The following parameters were uniformly higher in the three patient groups than in controls: age, frequency of male gender, body mass index, and frequency of diuretic use. In contrast, mean eGFR values were statistically higher in the controls compared with the other groups. Some additional statistically significant differences were found between groups: diabetic subjects were older than the participants of other groups, had lower eGFR than

Table 1. General features of 720 participants.

Age (years)	42.4 ± 12.5
Gender (male/female), f%	45/55
Race (white/non-white), f%	30/70
Body mass index (kg/m ²)	27.2 ± 5.6
Creatinine (mg/dL)	0.87 ± 0.23
Uricemia (mg/dL)	4.6 ± 1.5
Hyperuricemia ^a , f%	8.9
Controls, f (f%)	257 (35.7)
Euglycemic hypertension, f (f%)	118 (16.4)
Prediabetes, f (f%)	222 (30.8)
Hypertension	117 (53.0)
Diabetes, f (f%)	123 (17.1)
Hypertension	107 (87.0)
Metabolic syndrome ^b , f (f%)	299 (42.5)
Diuretic use ^c , f (f%)	132 (18.3)
ACE inhibitor use ^c , f (f%)	145 (20.1)
eGFR (mL·min ⁻¹ ·1.73 (m ²) ⁻¹)	94.7 ± 20.1

Data are reported as means ± SD or as otherwise indicated. ^aUric acid >6.0 mg/dL for females and >7.0 mg/dL for males; ^baccording to the tripartite consensus criteria (14); ^cregular use in the last 3 months. f: frequency; ACE: angiotensin converting enzyme; eGFR: estimated glomerular filtration rate as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI).

prediabetic patients, and higher frequency of microalbuminuria than every other group. The frequency of diuretic use was lower in prediabetic patients than in those with hypertension and euglycemia. The use of angiotensin converting enzyme (ACE) inhibitors was higher in hypertensive

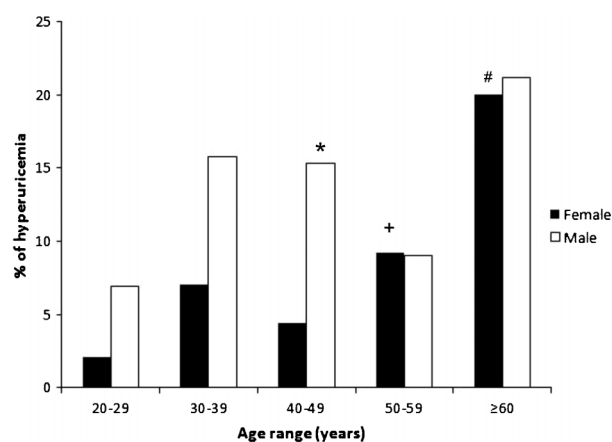


Figure 1. Frequency of hyperuricemia in males (M) and females (F) at 5 age ranges, in years: 20-29 (n=154, 96F/58M), 30-39 (n=109, 71F/38M), 40-49 (n=233, 135F/98M), 50-59 (n=176, 76F/100M), ≥60 (n=48, 15F/33M). *P<0.05, comparison between groups for the same age range (two sample T-test); P<0.05, comparisons within the female group: + vs 20-29 years; # vs 40-49 years (one-way ANOVA complemented by the Duncan test).

euglycemic and diabetic patients than in either controls or prediabetic subjects. The difference between these two last groups also reached statistical significance in favor of prediabetic participants. Only four participants, all in the prediabetic group, were being treated with an A1-receptor blocker (Losartan).

When diabetic patients were stratified by the presence of glycosuria and compared with respect to several selected variables (Table 3), several significant differences were found. Patients with glycosuria showed null prevalence of hyperuricemia, higher FEUA, higher E1Na, and a higher prevalence of microalbuminuria than those without glycosuria. Age, gender distribution, eGFR, frequency of diuretic use, and prevalence of arterial hypertension did not differ between these two diabetic groups. Of note, the frequency of hyperuricemia in prediabetic subjects (14%) was found to be very similar to that of diabetic patients without glycosuria (15.1%, P=0.860), yet significantly different from those with glycosuria (0%, P=0.037).

Discussion

The association between hyperuricemia and diabetes mellitus is controversial, possibly due to peculiarities in the excretion of glucose and uric acid in these patients. Some studies have suggested that diabetics, especially those recently diagnosed, tend to have lower serum uric acid than prediabetic and normoglycemic patients (12,13).

In the present study, we evaluated 720 subjects from a community-based health care program to assess their serum levels of uric acid, dividing them into 4 groups according to their glycemetic status and blood pressure: 1) absence of either hypertension or diabetes (controls), 2) hypertension but not dysglycemia, 3) prediabetes (with or without hypertension), and 4) diabetes (also with and without hypertension). As far as we know, this is the first study in the literature to address hyperuricemia in these 4 groups of patients extracted from a single population. It is also unique in that we simultaneously collected serum and urine samples for evaluation.

The overall prevalence rates of hyperuricemia and metabolic syndrome in the study population were 8.9 and 42.5%, respectively (Table 1). These values certainly overestimate the prevalence of these disorders in the general Brazilian population, whose rates of hypertension and diabetes are lower than those of this nonrandomized sample (16). Consistent with other studies (17,18), hyperuricemia was more common in males and tended to increase with age (Figure 1).

Mean BMI values were higher in the three groups of patients than in the controls (Table 2), confirming the association of obesity with both hypertension and serum glucose disorders (19). The prevalence of hyperuricemia increased in an almost linear manner from controls (3.9%) to euglycemic hypertension (7.6%) and prediabetic status (14.0%). Diabetic patients exhibited a slightly lower

Table 2. Comparison of clinical data, and plasma and urinary biochemical parameters in controls, euglycemic hypertension (EH), prediabetes and diabetes.

	Controls (n = 257)	EH (n = 118)	Prediabetes (n = 222)	Diabetes (n = 123)
White race (f%)	30.3	24.1	35.0	27.6
Serum uric acid (mg/dL)	4.1 ± 1.3	4.8 ± 1.3*	5.0 ± 1.6*	4.8 ± 1.6*
Hyperuricemia ^a (f%)	3.9	7.6	14.0*	11.4*
Age (years)	35 ± 12	45 ± 11*	45 ± 11*	50 ± 9*+ [#]
Male gender (f%)	37.0	49.2*	49.5*	52.0*
Body mass index (kg/m ²)	25.0 ± 4.5	28.3 ± 5.8*	28.1 ± 5.6*	29.2 ± 5.8*
Metabolic syndrome (f%)	4.5	39.7*	67.3* ⁺	77.7* ⁺
Diuretic use ^b (f%)	0.4	36.4*	23.9* ⁺	28.5*
ACE inhibitor use ^b (f%)	0.4	42.4*	19.8* ⁺	40.7* [#]
Serum Cr (mg/dL)	0.82 ± 0.19	0.87 ± 0.28	0.91 ± 0.22*	0.93 ± 0.23*
eGFR (mL·min ⁻¹ ·1.73 (m ²) ⁻¹)	102.9 ± 19.4	94.0 ± 19.2*	90.1 ± 18.5*	86.6 ± 19.4* [#]
FEUA (%)	5.8 ± 3.6	5.1 ± 3.6	5.9 ± 3.5	7.3 ± 4.3* [#]
EINa (mEq/g Cr)	120.5 ± 76.5	141.0 ± 109.3	144.6 ± 116.5	178.0 ± 127.2*
Microalbuminuria (f%)	3.5	5.9	6.8	15.4* ⁺ [#]

Data are reported as means ± SD or as otherwise indicated. f: frequency; ^aUric acid >7.0 mg/dL for males and >6.0 mg/dL for females; ^bregular use of diuretics in the last 3 months. ACE: angiotensin converting enzyme; Cr: creatinine; eGFR: estimated glomerular filtration rate as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI); FEUA: fractional excretion of uric acid; EINa: sodium excretion index. *P<0.05 vs controls; ⁺P<0.05 vs euglycemic hypertensives; [#]P<0.05 vs prediabetics (one-way ANOVA complemented by the Duncan test).

prevalence than prediabetic patients (11.4%) but the difference did not reach statistical significance. Prediabetic subjects, who had a 53% prevalence of hypertension, and reported lower frequency of diuretic use, tended to have a higher prevalence of hyperuricemia than euglycemic hypertensive patients (P=0.111), despite similar BMIs. This finding by itself suggests that an explanation other than

diuretic use was behind the hyperuricemia of prediabetic participants. In addition, in contrast to euglycemic hypertensive patients, prediabetic participants had a significantly higher frequency of hyperuricemia than controls. Despite the statistically significant differences in the mean values of eGFR among the 4 groups, at least three reasons led us to think that these dissimilarities could not be blamed for the

Table 3. Plasma and urinary biochemical parameters in diabetic patients with and without glycosuria.

	Diabetes (n = 123)		P
	With glycosuria (n = 30)	Without glycosuria (n = 93)	
Hyperuricemia ^a (%)	0	15.1	0.024
FEUA (%)	10.2 ± 3.7	6.4 ± 4.0	<0.001
EINa (mEq/g Cr)	234.2 ± 125.6	159.9 ± 123.0	0.006
Age (years)	50.5 ± 9.0	47.8 ± 9.1	0.171
Male gender (f%)	50.0	52.7	0.798
Body mass index (kg/m ²)	28.8 ± 6.0	29.3 ± 5.8	0.697
Diuretic use ^b (f%)	16.7	32.3	0.100
ACE inhibitors use ^b (f%)	37.6	50.0	0.231
Hypertension (f%)	73.3	74.2	0.926
eGFR (mL·min ⁻¹ ·1.73 (m ²) ⁻¹)	91.5 ± 20.9	85.0 ± 18.7	0.108
Microalbuminuria (f%)	33.3	9.7	0.002

Data are reported as means ± SD or as otherwise indicated. f: frequency; ^aUric acid >7.0 mg/dL for males and >6.0 mg/dL for females; ^bregular use in the last 3 months. FEUA: fractional excretion of uric acid; EINa: sodium excretion index; Cr: creatinine; ACE: angiotensin converting enzyme; eGFR: estimated glomerular filtration rate as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). The two sample T-test was used to analyze continuous variables and the Fisher test was used to analyze frequencies.

observed disparities in the prevalence of hyperuricemia. Firstly, the mean eGFR values were close to the normal range in every group; secondly, the differences among groups were minor; and thirdly, the prevalence of hyperuricemia did not change along with the mean eGFR values.

Increased proximal tubule reabsorption has been reported in either experimental animals (20) or patients with metabolic syndrome (21) and is thought to be a major determinant of Na and urate retention, which are linked to hypertension and hyperuricemia (22,23). Dysglycemia, a manifestation of insulin resistance associated with obesity, is a common finding in metabolic syndrome. Previous studies have reported that serum levels of uric acid are positively correlated with blood glucose levels (after an oral glucose tolerance test) up to a concentration of about 140-180 mg/dL (12,24,25). The mechanism to explain this link between hyperglycemia and hyperuricemia may reside in the proximal tubule. The nephron hypertrophy that takes place in the early course of dysglycemia (26,27) may represent an adaptive process to prevent glucose loss. On the other hand, the increased proximal reabsorption of glucose may favor the serum glucose perturbation and exacerbate urate retention. Most glucose reabsorption is accomplished by Na-coupled transport through the SGLT2 molecules located at the luminal membrane of the proximal tubule, which are known to be overexpressed in dysglycemic experimental animals (28) and humans (29). Interestingly, the resulting reduced distal delivery of Na has already been suggested as implicated in the early increase in the glomerular hyperfiltration in dysglycemic conditions through tubular glomerular feedback (26,27). In this context, urate reabsorption could be an epiphenomenon accompanying augmented glucose reabsorption, given that the main urate transporter from proximal tubule cells into the blood is SCL2A9, a protein also involved in glucose transport in the proximal tubule (30). It should also be mentioned that high insulin levels, which are common in insulin resistance states, might have a role in Na and urate retention by acting at more distal sites along the nephron (31,32).

When analyzing the impact of glycosuria on the presence of hyperuricemia in diabetic patients, we found that those testing positive for glucose in the urine did not have any serum uric acid concentrations above the reference value. Strikingly, this finding took place in a setting in which age, gender distribution, eGFR, BMI, frequency of diuretic use, and frequency of hypertension were not different between diabetic patients testing positive or negative for glucose in the urine. This finding is consistent with previous studies that reported higher mean serum uric acid values in prediabetic patients than in recently diagnosed diabetics (12,13), who are conceivably more prone to test positive for glucose in the urine. Accordingly, the frequency of hyperuricemia in prediabetic subjects and in diabetic patients without glycosuria proved to be very similar in the present study.

Glycosuria was accompanied by higher FEUA, higher EIna, and elevated frequency of microalbuminuria. Given the simultaneous increase in the urinary excretion of both sodium and uric acid in diabetic patients with glycosuria, it is tempting to think that a nonspecific mechanism is behind the alterations. In this regard, osmotic diuresis emerges as a natural candidate to account for the findings. However, this line of thinking does not find support in the literature, at least as the only explanation. In a study in which the acute effects of equimolar infusion of glucose and mannitol on the renal clearance of purine metabolites were evaluated, increased renal clearance of uric acid was only seen with glucose infusion (33). Nonetheless, an effect of osmotic diuresis cannot be ignored, given that an exceeding glucose load could saturate specific membrane transporters involved with Na, glucose, and urate reabsorption along the nephron and account for differences in the composition of the osmotic diuresis induced by the two compounds. In fact, this hypothesis is in line with the reported hypouricemic effect of dapagliflozin, a renal sodium-glucose cotransporter inhibitor recently tested in humans to improve serum glucose control in diabetic patients (29). In this regard, it would be interesting to have information as to serum uric acid levels in patients with renal familial glycosuria, but these data could not be found in the published literature.

Of note, our diabetic patients with glycosuria had increased albuminuria compared with those testing negative for urinary glucose. This finding could be a reflection of more advanced glomerular disease (more albumin crossing the filtration barrier) or another consequence of reduced proximal tubule reabsorption, but our data do not allow a definite conclusion in this regard.

Our study has some limitations. Patients were only seen once; consequently all laboratory analyses were carried out on one biological sample. In addition, 24-h urine collection, which is considered the gold standard for investigation of metabolic abnormalities, was not performed. The higher cost and lack of practicality of this procedure in population studies led us to resort to monitoring morning spot urine samples, in which the sodium/creatinine ratio in urine and fractional excretion of uric acid were used as surrogate markers of their excretion. Apart from these restrictions, these measures are thought to be useful for making comparisons among individuals. In addition, inevitable differences were seen between groups, such as age, BMI and use of diuretics or ACE inhibitors use. However, most of the dissimilarities were intrinsically related to the health status of the participants or to their treatment, and should not be statistically treated as confounders.

In summary, we found that subjects at the early stage of development of glucose disorders had a significantly higher frequency of hyperuricemia than both controls and euglycemic hypertensive participants. On the other hand,

diabetic patients with glycosuria had a null prevalence of hyperuricemia and higher urine excretion of sodium, uric acid, and albumin than that observed in those without glycosuria. These findings probably reflect enhanced proximal tubule reabsorption in the kidney in the early course of dysglycemia, which is mitigated when manifest glycosuria becomes present due to saturation of the glucose transport at this nephron segment in association

with perturbation of uric acid reabsorption along the nephron.

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