Metabolic syndrome and associated urolithiasis in adults enrolled in a community-based health program

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Background. Urolithiasis is a common and recurrent disease, whose prevalence rate has recently increased in parallel to obesity pandemic.

Objectives. To estimate the prevalence of history of urolithiasis in a non-randomized sample of adults assisted by a community-based health program and to analyze its association with metabolic syndrome.

Methods. Cross-sectional study set in Niterói, Rio de Janeiro, Brazil, including adults (non-diabetic hypertensives, diabetics or controls). Participants were assessed through a standardized questionnaire and underwent clinical and laboratory evaluation, including blood and urine samples. The diagnosis of metabolic syndrome was based on harmonized criteria.

Results. A total of 740 adults were enrolled (M: F = 0.85; 43 ± 12 years; 30% white, and 70% non-white). Almost half of subjects (42.5%) had metabolic syndrome. The prevalence of urolithiasis in the sample was 10.1%. White skin colour, family history, and metabolic syndrome were independently associated with urolithiasis (P < 0.05). Subjects with the syndrome (excluding cases on diuretics) had more acidic urine (P = 0.014), increased natriuresis (P = 0.01) and higher uricosuria (P = 0.001) compared with non-affected ones. The prevalence of urolithiasis increased in proportion to the number of criteria for metabolic syndrome (P for trend <0.005).

Conclusions. Metabolic syndrome is a modifiable factor associated with urolithiasis in a way that the frequency of positive history increases proportionally to the number of its diagnostic criteria. These findings reinforce the recent suggested link between urolithiasis and cardiovascular risk factors.

Keywords. Diabetes mellitus, hypertension, metabolic syndrome X, uric acid, urolithiasis.

Introduction

The presence of metabolic syndrome increases cardiovascular morbimortality. An increased risk for urolithiasis has been noticed in parallel to the epidemic of metabolic syndrome. The worldwide prevalence of urolithiasis is estimated at 5–10%, with men being more affected than women. In this regard, data from developing countries, which carry the higher potential of increase in the obesity prevalence, are scarce. The aim of this study was to estimate the prevalence of history of urolithiasis and analyse its relationship with metabolic syndrome in a non-randomized sample of adults assisted by a community-based health program (the Family Doctor Program) of Niterói city, Rio de Janeiro, Brazil.

Methods

This study is derived from CAMELIA study, a cross-sectional observational study of familial aggregation of metabolic syndrome, conducted from July 2006 to December 2007 in a partnership between Universidade Federal Fluminense and Niterói Healthcare Foundation. A total of 1098 subjects assisted by the Family Doctor Program of Niterói city (in Rio de Janeiro, Brazil) were recruited following an initial selection of index cases. To be accepted as an index, 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 12–30 years, who would also enroll. Four groups of index cases were selected: non-diabetic hypertensives; non-hypertensive diabetics; diabetics and hypertensives; and controls, whose partners were also
neither hypertensive nor diabetic. Patients with immunodeficiency, malignancy, chronic renal failure (stage V), heart failure, coronary artery disease, stroke, severe peripheral vascular disease, pregnant women and users of immunosuppressive drugs (corticosteroids or cytostatics) were excluded. The protocol was performed according to the Declaration of Helsinki and has been approved by the Ethic Committee of the Medical School of Universidade Federal Fluminense. Written informed consent was obtained from all participants. Subjects were interviewed by trained investigators using a standardized questionnaire, which included a self-defined racial categorization among three options: white, black or mulatto (mixed-race). For the study, only subjects who were at least 20 years old (740 adults) were selected. Due to the low frequency of non-hypertensive diabetics, subjects were rearranged into three groups: non-diabetic hypertensives, diabetics, and controls. Data were analyzed in 2011.

Blood pressure was measured with an electronic sphygmomanometer (HEM-711 AC Omron Co., Japan) following VII Joint protocol. Subjects whose reading was higher than 140 mmHg (systolic) or 90 mmHg (diastolic) and those who reported to be under antihypertensive drugs (corticosteroids or cytostatics) were excluded. Vascular disease, pregnant women and users of immunosuppressive drugs (corticosteroids or cytostatics) were excluded. The diagnosis of metabolic syndrome was based on harmonized criteria. Subjects who met at least three of five criteria were considered as having metabolic syndrome, namely: (i) increased waist circumference—in Latin America ≥90cm for men and ≥80cm for women; (ii) hypertriglyceridemia (triglycerides ≥150 mg/dl or use of lipid lowering drugs); (iii) low High-density lipoprotein-cholesterol (HDL-C) <40 mg/dl in men and <50 mg/dl in women; (iv) systolic blood pressure ≥130 mmHg and/or diastolic ≥85 mmHg or use of antihypertensive; and (v) fasting glucose ≥100 mg/dl or use of anti-diabetic agents.

Participants whose fasting glucose was equal to or above 126 mg/dl, and those who reported oral use of hypoglycemic agents and/or insulin were considered diabetic.

Body weight was measured by electronic digital scale (PL80, Filizola S/A, 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) and squared height (in metres). 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 expiration.

Biochemical serum and urine analysis was obtained after 8h of fasting, with Selectra analyzer, NE Vital Scientific, Netherlands. Standard serum parameters included glucose, urea, creatinine, total cholesterol, Low-density lipoprotein-cholesterol, HDL-C, triglycerides and uric acid. The urine excretion of sodium, calcium and uric acid were estimated by calculation of the ratios of sodium/creatinine (in mEq/g), calcium/creatinine (in mg/g) and uric acid/creatinine (in mg/g), respectively. Urine specific gravity and pH were measured through dipstick analysis.

Results were expressed as mean ± standard deviation, median, minimum and maximum values, percentiles, absolute (n) or relative (%) frequencies as appropriate. Categorical variables were compared using Pearson's chi-square or Fisher's exact test. Unpaired t-test was applied to compare numeric variables with normal distribution and Wilcoxon–Mann–Whitney or Kruskal–Wallis tests for non-normal distribution. The dependent variable was the history of urolithiasis. Independent variables included sex, age, skin colour, family income, metabolic syndrome, smoking, sedentary, diuretic use, family history of urolithiasis, BMI, diabetes, hypertension, serum levels of total cholesterol, uric acid, creatinine, glucose, urine determinations of glucose, specific gravity, pH, calcium/creatinine, uric acid/creatinine and sodium/creatinine ratio.

The association of history of urolithiasis in the survey with the independent variables was tested in a multivariate analysis. Considering familial clustering, the analysis was performed using the model of generalized estimating equations, suitable for non-independent observations. Only non-collinear variables with a high probability of association in the initial analysis (P < 0.10) were included in the model. Jonckheere–Terpstra test for trend was applied to check for association between the number of metabolic syndrome criteria and the frequency of history of urolithiasis. Statistical significance was assumed if the P-value was less than 0.05.

All statistical analysis was performed using SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA), version 18.0.

**Results**

Clinical and laboratorial characteristics of the study population are shown in Table 1. The overall prevalence of urolithiasis was 10.1%, without gender disparity (11.3% in men versus 9.2% in women, P = 0.21). From the 75 subjects who reported kidney stones, 63 (84%) also reported positive imaging or spontaneous elimination of calculi. Low-back pain was the predominant complaint reported (90.7%). Gross hematuria
was present in 40% of cases. When asked about the number of distinct episodes of renal colic, 65.3% of patients reported a single episode and 28% had recurrent disease. There was no difference in the recurrence frequency among metabolic syndrome carriers when compared with the others (26.1 versus 31%, respectively; \( P = 0.656 \)), even after excluding diuretic users (32.1% versus 31.0%, respectively; \( P = 0.928 \)). In diabetics, non-diabetic hypertensives and controls the prevalence was 14.0%, 10.2% and 8.6%, respectively. Using mathematical extrapolation, after adjustment of the data for the Brazilian age range (64% \( \geq 20 \) years of age) and for the prevalence of diabetes (8.8%) and non-diabetic hypertensives (19.0%) in the country approached 6.0%.4,5

In a multivariate analysis, the association of metabolic syndrome with urolithiasis was adjusted by non-colinear significant factors from Table 2 (\( P < 0.10 \), namely, skin colour, age and family history. Metabolic syndrome, white skin colour and family history were independently associated with urolithiasis (\( P < 0.05 \)), irrespective of adoption of the standard or the strict criterion (Table 3).

After excluding the ones who were regularly taking diuretics, fasting urine samples of subjects without and with metabolic syndrome were compared. Urine parameters that were found to be different in this analysis are represented in Fig. 1. Metabolic syndrome carriers had more acidic urine (\( P = 0.014 \)), higher sodium excretion index (\( P = 0.01 \)) and higher uric acid/creatinine ratio (\( P = 0.001 \)). Calciuria was not found to be different.

In order to better explore the relationship between metabolic syndrome and urolithiasis, patients were grouped according to the number of positive criteria for metabolic syndrome (0, 1, 2, 3, 4 or 5). There was a progressive increase on the frequency of urolithiasis according to the number of positive criteria: from 6.0% in patients without any criterion to alarming 22.7% in those with five criteria; \( P \) for trend \( = 0.003 \) (Fig. 2). The same pattern was observed when the strict criterion was adopted, with the extremes ranging from 4.8% to 19.0% (\( P \) for trend \( = 0.004 \)).

### Discussion

The worldwide prevalence of metabolic syndrome is increasing and its presence has been associated with an increased risk of urolithiasis. In this study we evaluated the prevalence of urolithiasis in a Brazilian non-randomized sample comprised of non-diabetic hypertensives, diabetics and controls in a community-based health program. In addition, the factors associated with urolithiasis were analyzed. Data were derived from a population study initially designed to address familial clustering of cardiovascular risk factors.

A crude prevalence of urolithiasis of 10.1% was obtained, a number that sits in the top rates reported from the general population in different countries.6–8 Such high prevalence is certainly due to the non-randomized nature of the study population in which diabetics and hypertensives were over-represented. Using adjustments for the prevalence of diabetics and non-diabetic hypertensives in the country and taking the Brazilian age–population pyramid in consideration, a national prevalence estimate of urolithiasis of 6% was obtained. Even with the inherent limitation of a mathematical inference, the number is comparable to that reported in other international studies.

Factors associated with urolithiasis were analysed in the study sample. Previous epidemiologic studies point to male sex, ethnicity, family history, age, climate, occupation, diabetes mellitus, hypertension and obesity as risk factors for urolithiasis.9–11 In the present study, stone
formers were predominantly white and had more frequent family history, repeating previous reports. On the other hand, a male preponderance was not found. Of note, increased prevalence rates of urolithiasis in women narrowing male-to-female urolithiasis prevalence ratio have recently been published. One could question whether this phenomenon is related to the metabolic syndrome pandemic among females.

In order to ascertain the relationship of metabolic syndrome and urolithiasis a multivariate analysis was performed. Metabolic syndrome emerged as an independent factor for urolithiasis even after adjustment for age, skin colour, and family history. It should be stressed that among the independent factors found to associate with urolithiasis in the present study, metabolic syndrome is the only modifiable one.

As a next step, biochemical particularities in the urine of metabolic syndrome subjects were investigated. From the literature, stone formers with metabolic syndrome are known to have a higher proportion

### Table 3
Multivariate analysis to evaluate variables associated with urolithiasis including (standard criterion) or non-including (strict criterion) cases with non-confirmed urolithiasis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Standard criterion</th>
<th>Strict criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR (CI 95%)</td>
<td>PR (CI 95%)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>1.76 (1.07–2.88)</td>
<td>1.95 (1.14–3.33)</td>
</tr>
<tr>
<td>Skin colour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2.64 (1.31–5.29)</td>
<td>2.54 (1.21–5.35)</td>
</tr>
<tr>
<td>Mulatto</td>
<td>1.62 (0.80–3.29)</td>
<td>1.55 (0.73–3.29)</td>
</tr>
<tr>
<td>Black</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (1.00–1.03)</td>
<td>1.01 (0.99–1.03)</td>
</tr>
<tr>
<td>Family history</td>
<td>2.68 (1.61–4.46)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mean ± SD.
<sup>b</sup>Median (12.5%–87.5%).
of uric acid calculi. In this regard, higher urinary acidity and hyperuricosuria are mechanisms implied on higher risk of uric acid stones formation. Insulin resistance, responsible for impaired ammoniagenesis and increased excretion of organic acids, seems to be a major subjacent factor creating a favourable environment for uric acid precipitation in those patients. A recent study showed that the increased risk of calcium oxalate precipitation in metabolic syndrome was not independently associated with increasing features of the syndrome after adjustment for confounding variables such as age, gender, urine sodium and urine sulfate. Consistent with previous reports, in our study, subjects with metabolic syndrome had lower fasting urine pH, higher uric acid excretion and higher sodium excretion compared with healthy ones. Calciuria was equivalent in both groups. Those findings are consistent with the concept that metabolic syndrome is preferentially associated with uric acid stones rather than with calcium stones.

Finally, the cumulative influence of the diagnostic criteria of metabolic syndrome upon the prevalence of urolithiasis was assessed. Consistent with the National Health and Nutrition Examination Survey III report (NHANES III) report, a progressive increase in the frequency of stone formers accompanied the increase of positive criteria for the syndrome. The association of metabolic syndrome with increased risk of adverse cardiovascular outcomes is well known. Recent data also point to a higher risk of myocardial infarction among kidney stone formers. If control of alterations present in metabolic syndrome will reduce the risk of renal stones as it does with cardiovascular morbimortality remains to be determined.

This study portrays some limitations. Considering the high cost of a large epidemiologic survey, urolithiasis was assessed from personal history and not from evidentiary examinations. Nevertheless, more than 80% of subjects who reported previous urolithiasis also reported positive imaging and/or spontaneous elimination of calculi. These data suggest that the history of urolithiasis in the...
survey was reliable. Unfortunately, as far as we could know, none of those stones were analysed, reflecting the unavailability of this diagnostic tool in our public health system. Also, it is known that urinalysis in 24-hour collection is considered the gold standard in the investigation of metabolic abnormalities and dietary inferences. The higher cost of this procedure and lack of practicality of its application in population studies led us to resort to fasting spot urine samples, in which sodium/creatinine, calcium/creatinine and uric acid/creatinine ratios were used as surrogate markers of their daily excretion. Apart from restrictions, these measures are useful to compare individuals. Urinary citrate and oxalate were not measured. Evaluation of urine pH by colorimetric method and the use of specific gravity as an indirect estimate of urinary osmolality were adopted for similar reasons. Despite that, this study was able to detect particularities in the urinary profile of patients with metabolic syndrome using quick and inexpensive tools that could be routinely applied at primary care level.

Conclusions

In summary, white skin colour, positive family history and metabolic syndrome were independently associated with urolithiasis. The urine of subjects with metabolic syndrome was more acidic and contained more sodium and uric acid than the urine of non-affected ones. The prevalence of stones increased with the number of positive criteria for metabolic syndrome. These findings reinforce the recent suggested link between urolithiasis and potentially modifiable cardiovascular risk factors.

Declaration

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Ethical approval: Ethic Committee of the Medical School of Universidade Federal Fluminense.

Conflict of interest: none.

References