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ORIGINAL PAPER

Clinical and biochemical profile of patients with "pure" uric acid nephrolithiasis compared with "pure" calcium oxalate stone formers

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Abstract The purpose of the present study was to compare the clinical characteristics of "pure" uric acid (UA) stone formers with that of "pure" calcium oxalate (CaOx) stone formers and to determine whether renal handling of UA, urinary pH, and urinary excretion of promoters and inhibitors of stone formation were different between the two groups. Study subjects comprised 59 patients identified by records of stone analysis: 30 of them had "pure" UA stones and 29 had "pure" CaOx nephrolithiasis. Both groups underwent full outpatient evaluation of stone risk analysis that included renal handling of UA and urinary pH. Compared to CaOx stone formers, UA stone formers were older (53.3 ± 11.8 years vs. 44.5 ± 10.0 years; $P = 0.003$); they had higher mean weight (88.6 ± 12.5 kg vs. 78.0 ± 11.0 kg; $P = 0.001$) and body mass index (29.5 ± 4.2 kg/m^2 vs. 26.3 ± 3.5 kg/m^2; $P = 0.002$) with a greater proportion of obese subjects (43.3% vs. 16.1%; $P = 0.01$). Patients with "pure" UA lithiasis had significantly lower UA clearance, UA fractional excretion, and UA/creatinine ratio, with significantly higher serum UA. The mean urinary pH was significantly lower in UA stone formers compared to CaOx stone formers (5.17 ± 0.20 vs. 5.93 ± 0.42; $P < 0.0001$). Patients with CaOx stones were a decade younger, having higher 24-h urinary calcium excretion (218.5 ± 56.3 mg/24 h vs. 181.3 ± 57.1 mg/24 h; $P = 0.01$) and a higher activity product index for CaOx [AP (CaOx) index]. Overweight/obesity and older age associated with low urine pH were the principal characteristic of "pure" UA stone formers. Impairment in urate excretion associated with increased serum UA was also another characteristic of UA stone formers that resembles patients with primary gout. Patients with pure CaOx stones were younger; they had a low proportion of obese subjects, a higher urinary calcium excretion, and a higher AP index for CaOx.

Keywords Uric acid stones · Calcium oxalate stones · Urinary acidification · Stone former · Overweight · Urinary pH

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Introduction

Several studies have pointed out that in recent decades there has been an increasing prevalence of urolithiasis in many western countries [1, 2]. At the same time there has been an increasing progression of obesity in industrialized nations that has reached epidemic proportions [3, 4]. This temporal parallelism of obesity and increased stone formation has suggested a possible relationship between them. Several epidemiological studies have shown an association between body size and nephrolithiasis [5, 6] although some case control studies have given conflicting results depending on gender and age [7, 8]. Apart from this, whether obesity favors both uric acid (UA) stone formation as well as calcium oxalate (CaOx) stone formation or only one type of stone in particular has not been analyzed until recently. Daudon

et al. [9] has found evidence that overweight is associated with a high proportion of UA stones in patients less than 60 years of age.

Pure UA stones account for approximately 10% of all stones analyzed in the United States, it is 25% in Germany and as high as 39.5% in Israel [10–12]. The most prevalent and invariant feature among UA stone formers is low urinary pH [13, 14]. In an analysis of nearly 5,000 nephrolithiasis patients in the United States, a strong inverse relationship was found between urinary pH and body weight [15]. This association persisted after adjusting for urinary sulphate, a marker of animal protein intake, suggesting that dietary indiscretion is not the only variable responsible for the association, and that insulin resistance associated with high body mass index (BMI) might be the real link between them.

With respect to CaOx stone formers, a recent study has found overweight/obesity to be strongly associated with an elevated risk of stone formation in both genders, due only to an increased excretion of stone promoters [16]. Indeed Lemann et al. [17] had demonstrated many years ago that body size was the major determinant of urinary oxalate excretion.

The purpose of the present study was to compare the clinical characteristics of "pure" UA stone formers with those of "pure" CaOx stone formers, specially in relation to their weight and to determine if there were differences in these two groups in renal handling of UA, urinary pH and urinary excretion of promoters and inhibitors of stone formation.

Materials and methods

We selected from 180 stone analysis records those, which belonged to patients who had a simultaneous full stone risk analysis and had either "pure" UA or "pure" CaOx composition. Patients who did not have a simultaneous stone analysis record and full stone risk analysis were excluded. We also excluded patients with mixed composition stones. Stone composition in our laboratory was determined by crystallographic analysis using polarized light microscopy. The two groups of stone-forming patients left for analysis were: 30 patients with "pure" UA stones (UA stone formers; 28 males and 2 females), and 29 patients with "pure" CaOx nephrolithiasis (CaOx stone formers; 26 males and 3 females).

The full stone risk analysis consisted of two 24-h urine samples and a fasting venous blood sample obtained on the third day after the urine collections. Urine samples were refrigerated for measurements of total volume, creatinine, sodium, potassium, calcium, phosphorus, magnesium, UA, oxalate, and citrate. In blood samples we measured electrolytes, creatinine, urea nitrogen, calcium, phosphorus, magnesium, and UA. A spot urine sample after 8-h fasting in the morning of the third day was used for urine pH measurement. We used the International Obesity Task Force definition (IOTF reference) to define overweight and obesity (overweight/pre-obese: BMI between 25.0 and 29.9; obese BMI ≥30) [18].

Analytical procedures and calculations

Serum calcium was measured by ISE methodology with the Synchron CX3 Delta automated analyzer (Beckman, Beckman Instruments, Inc. Brea, CA, USA); the same methodology was used for urinary calcium determination (done in an acidified aliquot). Coefficient of variation was 1.3% at 8 mg/dl and 1.5% at 14 mg/dl. Serum and urine creatinine were measured by a Jaffe kinetic method using CCX spectrum automated analyzer (Abbott Laboratories, USA). Serum coefficient of variation was 7% at 0.8 mg/dl and 1.8% at 4.2 mg/dl. Urine CV was 2.9% at 43 mg/dl and 3% at 87 mg/dl. Phosphate was measured by UV (molybdate) using CCX Spectrum automated analyzer (Abbott Laboratories, USA). Urine CV was 2.9% at 43 mg/dl and 3% at 87 mg/dl and serum CV was 6.5% at 2.4 mg/dl and 2.8% at 4.5 mg/dl. Sodium and potassium were measured by Synchron CX3 autoanalyzer. UA (done in an alkalinized aliquot to prevent precipitation) was analyzed by the uricase method. (CV: 5% at 2.7 mg%, 3% at 7.0 mg% and 3% at 10mg%). Urinary pH was measured with a pH electrode in the second urine of the morning immediately post-voiding. Urinary citrate was determined enzymatically [19] using reagents from SIGMA-Aldrich Corp. (St Louis, MO, USA). Oxalate (done in an acidified aliquot) was determined enzymatically (Trinity Biotech, Bray Co., Wicklow, Ireland). The mean of the two urine samples were used in calculations. Risk of CaOx stone formation was determined using Tiselius's Index [20] in which the ion activity product was estimated by an index called Activity product CaOx index [AP (CaOx) index]:

$$\mathrm{AP(CaOx)index} = 1.9 \times \mathrm{Ca}^{0.84} \times \mathrm{Ox}^{1.0} \times \mathrm{Mg}^{-0.12} \times \mathrm{Cit}^{-0.22} \times \mathrm{V}^{-1.03}$$

where urinary excretions of calcium (Ca), oxalate (Ox), magnesium (Mg), and citrate (Cit) are expressed in mmol/l and urine volume (V) in liters.

Endogenous UA clearance and creatinine clearance were calculated from values for UA and creatinine in 24-h urine and fasting blood samples. The fractional excretion of urate was calculated as the ratio of UA clearance and the corresponding creatinine clearance.

Statistical analysis

Statistical analysis was performed using CSS: Statistica software (StatSoft, Inc, Tulsa, OK, USA). Results are expressed as mean ± standard deviation. Urinary values are the mean of the two urine samples. The level of significance was alpha <0.05. Comparisons between groups for continuous variables were analyzed by Student's unpaired *t*-test or Wilcoxon Rank Sum test depending on normality of their distribution. Dichotomic variables were analyzed by Chi-square test.

Results

Patient's clinical characteristics

Characteristics of the study patients are shown in Table 1. UA stone formers were older than CaOx stone formers. The age of the patients considered refers to the time of the urine collection and stone composition analysis. The mean weight, BMI (in kg/m^2) and 24-h urinary creatinine excretion were higher in UA stone formers than in CaOx stone formers. The percentage of obese patients was significantly higher among patients with "pure" UA lithiasis, and 84% of UA patients had a BMI greater than 26.

Patient's biochemical profile

Renal handling of UA and urinary acidification in both groups are shown in Table 2. UA patients had significantly lower UA clearance, UA fractional excretion and UA/creatinine ratio, with significantly higher serum UA. Most patients with UA stones (88%) have a normal 24-h UA excretion (males up to 800 mg/24 h and females up to 750 mg/24 h), similar to patients with CaOx stones (83.9%). Mean urinary volume was similar in both groups but mean urinary pH was significantly lower in the pure UA stone formers compared to pure CaOx stone formers.

With respect to the rest of the urinary analytes, patients with UA stones had greater 24-h excretion of phosphate and sodium (Table 3) while patients with CaOx stones have higher 24-h excretion of urinary calcium and AP (CaOx) index.

Table 1 Demographic and anthropometric characteristics of patients with uric acid and calcium oxalate lithiasis

	UA lithiasis, $n = 30$	Ca/Ox lithiasis, $n = 29$	*P*-value
Age (years)	53.3 ± 11.8	44.5 ± 10.0	0.003
Height (m)	1.74 ± 0.06	1.70 ± 0.06	0.02
Weight (kg)	88.6 ± 12.5	78.0 ± 11.0	0.001
BMI (kg/m^2)	29.5 ± 4.2	26.3 ± 3.5	0.002
Obese (%)	43.3	16.1	0.01

Table 2 Biochemical parameters of uric acid handling and urine pH in patients with uric acid and calcium oxalate lithiasis

	UA lithiasis, $n = 30$	Ca/Ox lithiasis, $n = 29$	*P*-value
Uric acid clearance (ml/min)	6.86 ± 2.86	8.76 ± 3.06	0.01
Serum uric acid (mg/dl)	6.26 ± 1.43	5.32 ± 0.98	0.004
Uric acid (mg/24 h)	597.5 ± 248.4	646.4 ± 191.5	0.40
Fractional excretion uric acid	0.068 ± 0.05	0.087 ± 0.02	0.01
Uric acid/creatinine ratio	0.295 ± 0.13	0.438 ± 0.28	0.021
Urinary pH	5.17 ± 0.20	5.93 ± 0.42	<0.0001

Table 3 Urinary excretion of analytes in patients with uric acid and calcium oxalate lithiasis

24-h urine	UA lithiasis, $n = 30$	Ca/Ox lithiasis, $n = 29$	*P*-value
Calcium (mg)	181.3 ± 57.1	218.5 ± 56.3	0.01
AP (CaOx) index	0.75 ± 0.37	1.2 ± 0.98	0.03
Phosphate (mg)	954.3 ± 303.2	715.2 ± 246.5	0.001
Creatinine (mg)	1,852.9 ± 397	1,626.7 ± 306	0.01
Na (mEq)	207.2 ± 70.9	148.4 ± 60.2	0.001
Citrate (mg)	579.1 ± 290.8	531.7 ± 197.2	0.46
Oxalate (mg)	28.9 ± 7.2	30.0 ± 6.0	0.33
Magnesium (mg)	88.1 ± 28.9	101.0 ± 37.7	0.14
Volume (ml)	2,048 ± 623	1,946 ± 927	0.52

Correlations

Analyzing all the patients together, we found a negative correlation between body weight ($r = 0.44$; $P < 0.00001$), BMI ($r = 0.32$), urinary creatinine ($r = 0.31$) height ($r = 0.31$) and age ($r = –0.30$) with urinary pH. In the multiple linear regression analysis only weight persisted significantly associated with urinary pH ($B = –0.33$; Multiple $R = 0.51$).

Discussion

This study was undertaken to characterize patients with "pure" UA nephrolithiasis and to compare them with patients having pure CaOx stones. We identified these patients by records of stone analysis. Of the three defects

that can produce "pure" UA stones, hyperuricosuria, acidic urine pH, and low urinary volume [21], only low urine pH was invariably present in our UA stone patients. "Pure" CaOx stone formers had higher urinary excretion of calcium and a higher activity product index for CaOx.

Pak et al. [14] have suggested that the biochemical features of UA stone formers might be unique, possibly similar to the pathophysiologic disturbances underlying primary gout. In primary gout urinary pH is low, causing UA stones, and fractional excretion of urate is reduced, contributing to the development of hyperuricemia [22, 23]. In his study Pak et al. took considerable care in the selection of study subjects, and the UA group was matched with the control group according to age, BMI, and gender. The reason for this matching was that high BMI could cause insulin resistance [24], which then could influence urinary pH and urate excretion [25]. In our study, we did not match UA patients with CaOx patients, as we wanted to see their demographic and anthropometric characteristics. Our results show that the UA patients are older than CaOX stone formers, with a high proportion of obese subjects (nearly 50% of them).

Maalouf et al. [6] had found a strong graded negative inverse association between urinary pH and body weight that persisted after adjustment for age and urinary creatinine. As UA stone formers in our study had significantly higher body weight than CaOx patients, not surprisingly they had significantly lower urine pH.

Zechner et al. [26] have studied the epidemiologic and metabolic aspects of idiopathic UA lithiasis. Of the 264 patients with urolithiasis, those with pure UA or urate stones were compared to those with other types of calculi for differences in epidemiologic factors and UA, calcium, and phosphate metabolism. They showed that patients with UA stones were predominantly older men as we showed in our study. These patients had comparatively lower incomes and spent less money on food but consumed more alcohol. The urinary pH was lower than in the other groups. Bollack et al. [27] have shown that in Alsace, France, where urate lithiasis accounted for 32.7% of cases of lithiasis requiring hospitalization, 59% of patients were hyperuricaemic (but only 10% had typical gout), 14.6% were hyperuricosuric but all had low urine pH. Patients with this disorder were males in three fourth of the cases, over the age of 50 and were associated with marked obesity (mean weight 81.5 kg). All these characteristics were seen in the population we studied. In our sample we could not analyze the male/female ratio, because not all of the patients that came to our clinic had their stone analysis performed at the same time they had a stone risk analysis done, particularly females.

With respect to "pure" CaOx stone formers overweight/obesity was not prevalent among our patients and their increased risk of stone formation was mainly due to an increased urinary calcium excretion with increased relative supersaturation of CaOx. Contrary to our findings, in a recent large cohort of CaOx stone formers from Germany, overweight and obesity were present in 59.2% of men and in 43.9% of women [16]. Multiple linear regression analysis revealed a significant positive correlation between BMI and urinary UA, sodium, ammonium, and phosphate excretion and an inverse correlation between BMI and urinary pH in both men and women, whereas BMI was associated with urinary oxalate excretion only among women and with urinary calcium only in men.

Daudon et al. recently analyzed the type of stone produced by large body seize subjects [9]. They found that in males, the proportion of calcium stones was lower in overweight and obese groups than in normal BMI group, whereas the proportion of UA stones gradually increased with BMI, from 7.1% in normal BMI to 28.7% in obese subjects ($P < 0.0001$). The same was true with females, with a proportion of UA stones rising from 6.1% in normal BMI to 17.1% in obese patients ($P = 0.003$). In addition, the proportion of UA stones markedly rose with age in both genders ($P < 0.0001$). The average BMI value was significantly higher in UA stone formers aged <60 years than in all other groups, whereas it did not differ from other groups in those aged ≥60 years.

The present study had two main limitations: (1) As we included in the study only the patients that had a simultaneous stone composition analysis and a stone risk analysis the number of patients studied was small; (2) for the same reason the number of women studied was very small.

We conclude that in this predominantly male population that we studied, low urine pH associated with overweight/obesity and older age were the principal characteristics of "pure" UA stone formers. Impairment in urate excretion associated with increased serum UA was also another characteristic of UA stone formers, which resembles patients with primary gout. Patients with "pure" CaOx stones were younger; they had a low proportion of obese subjects, a higher urinary calcium excretion and a higher activity product index for CaOx.

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