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ORIGINAL PAPER

Clinical significance of uric acid dihydrate in urinary stones

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Abstract Uric acid crystallizes as an anhydrous compound (UAA), a dihydrate (UAD) or a mixture of both. A monohydrate form is very rare. About 20% of uric acid stones contain a significant amount (≥20%) UAD. It is believed that UAD crystallizes under highly acidic conditions (urine pH ≤ 5.0). Up to now, metabolic data on patients with UAD stones have not been reported in the literature. One hundred and fifty patients with pure uric acid calculi were studied. Stone analysis was performed using X-ray diffraction. According to the stone analysis, they were divided in two groups: 1. UAD (≥20% UAD), 2. UAA (<20% UAD). In all patients the following parameters were examined: age, sex, number of recurrences, body mass index (BMI); blood: creatinine, uric acid, calcium, sodium, and potassium; urine: pH-profiles, volume, calcium, uric acid, citrate, ammonia, and urea. Group 1 (≥20% UAD) consisted of33patientsand group 2 (<20% UAD) of 117 patients. Between these groups, there was a significant difference concerning the number of recurrences, the urine volume, and the urinary excretion of calcium. Patients with ≥20% dihydrate had a mean BMI of 31.6 ± 7.5, a mean number of recurrences of 0.24 ± 0.44, an urine volume of 2.6 ± 0.8 l/24 h, and a calcium excretion of 4.5 ± 2.2 mmol/24 h, whereas those with <20% dihydrate had BMI of 29.9 ± 5.0, 1.10 ± 1.42 recurrences, urine volume of 2.3 ± 1.2 l/24 h, and calcium excretion of 3.2 ± 2.4 mmol/24 h. All the other parameters tested were not significantly different. For the first time, our study shows metabolic data in uric acid patients with a significant amount of UAD. The comparison between this group and those patients with <20% UAD revealed that the first group is less prone to develop recurrences. This is a relevant difference concerning the necessity of metaphylactic measures. We could not confirm in patients with dihydrate if the urinary pH is more acid than in those with insignificant amounts of dihydrate. The higher 24-h urine volume, the higher excretion of calcium, and the higher BMI in the UAD group may be of pathophysiological relevance and requires further attention.

Keywords Uric acid · Uric acid dihydrate · Urolithiasis · Nephrolithiasis · Recurrence · Urinary calcium · Urine pH

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Introduction

Contrary to many other regions in Europe and Northern America, uric acid lithiasis is a very common type of stone disease in our region (Upper Franconia). About 25% of all stone patients treated in our hospital are uric acid stone formers [12]. Uric acid crystallizes as an anhydrous compound (UAA), a dihydrate (UAD) or a mixture of both. A monohydrate form is very rare [9]. The conditions of crystallization of the different types of uric acid stones are not completely understood [6]. About 20% of uric acid stones contain a significant amount (>20%) of UAD. UAA represents the more stable type, UAD readily transforms into the anhydrous salt. UAD is believed to crystallize under highly acidic conditions (urine pH ≤ 5.0) [7, 8].

Small organic molecules (molecular weight <20 kD) may also play a role in the formation of UAD [4].

It should be emphasized, however, that these are only hypotheses based on a very limited number of specimens and observations.

With respect to clinical significance, patient characteristics and underlying metabolic conditions of this uric acid compound, almost nothing has been reported in the literature.

Patients and methods

One hundred and fifty patients with pure uric acid calculi treated at the Department of Urology and Paediatric Urology, regioMed-Kliniken, Klinikum Coburg, Germany, were investigated. They were included in the study after their last stone episode. They were asked about previous stone episodes. The number of recurrences was calculated (total number of stone episodes minus one). At the time of this study, they were not on metaphylactic treatment.

Stone analysis was performed by X-ray diffraction using a two-circle diffractometer XRD 3003 (Seifert-FPM). For quantitative analysis, the program AUTOQUAN was used which is based on the Rietveld procedure. This method is an optimizing procedure using a model diffractogramme on the basis of known crystal structures being adapted to the measured diffractogramme.

The following parameters were determined in all patients: body mass index (BMI), urine pH profiles on 3 consecutive days at morning (fasting), noon (postprandial) and evening (postprandial). For urine pH measurements, dipsticks were used which allow pH measuring in 0.1 steps (Madaus GmbH, Cologne, Germany). The mean urinary pH was calculated in every patient. Patients were instructed to measure their urine pH by dip sticks. Measuring pH profiles allows for assessing the difference between fasting and postprandial pH. In a previous study, we could show that the means of pH profiles correlate with the pH measured in the 24-h urine specimen [10].

Blood was drawn to measure creatinine (Jaffé reaction, Dade Behring Marburg, Germany), sodium and potassium (atomic absorption), calcium (indirect ion sensitive electrode), and uric acid (modified uricase method, Dade Behring Marburg, Germany). A 24-h urine specimen was collected to determine the excretion of citrate (citrate lyase method, Boehringer Mannheim, Germany), creatinine (Jaffé reaction, Dade Behring Marburg, Germany), calcium (indirect ion sensitive electrode), uric acid (modified uricase method, Dade Behring Marburg, Germany), ammonia (modified glutamate dehydrogenase method using NADPH, test kit Ammonia Flex™, Dade Int., Newark, DE, USA), and urea (urease-glutamate dehydrogenase, Dade Behring Marburg, Germany).

For statistical analysis mean and standard deviations were calculated. In case of equal variance and Gaussian distribution Student's t test, otherwise the Mann–Whitney-test was used. Differences were called significant in case of $p < 0.05$. For these analyses, the program Prism 3.02 (GraphPad Software, San Diego, CA, USA) was used. Calculations were performed on a personal computer.

Results

Figure 1 shows a histogramme with the distribution of UAD percentage in our patients. There were no patients with stones exclusively consisting of UAD.

33 patients ($n = 20$ males, $n = 13$ females) had a uric acid stone containing more than 20% dihydrate (group 1). The majority of UAD containing stones (17/34) showed a share of 20–39%.

117 patients ($n = 88$ males, $n = 29$ females) had less than 20% dihydrate (group 2), the majority (104/117) containing less than 10%.

According to the histogramme, showing a trough at 15–20% UAD, patients were divided into two groups:

1. UAD (≥20% dihydrate)
2. UAA (<20% dihydrate)

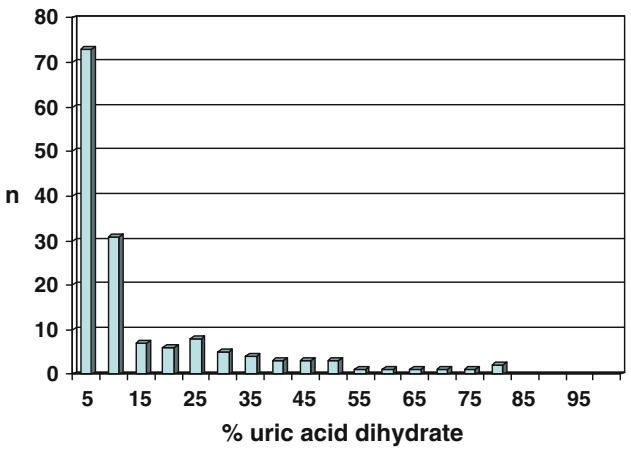

Fig. 1 Distribution of the percentage of uric acid dihydrate in 150 patients with pure uric acid stones

Table 1 Body parameters and recurrences (mean ± standard deviations)

	Age (years)	BMI (kg/m^2)	No. Recurr.
UAD	59.5 ± 13.3	31.6 ± 7.5	0.24 ± 0.44
UAA	62.9 ± 11.1	29.9 ± 5.0	1.00 ± 1.29
Significance	ns	$p = 0.0023$	$p = 0.0027$

Table 2 Serum (S) parameters (mean ± standard deviations)

	Crea (mg/dl)	UA (mg/dl)	Ca (mval/l)	Na (mmol/l)	K (mmol/l)
UAD	1.2 ± 0.3	5.9 ± 1.5	4.5 ± 0.2	138 ± 3	4.1 ± 0.5
UAA	1.4 ± 0.6	6.3 ± 1.8	4.7 ± 0.2	137 ± 9	4.2 ± 0.4
Significance	ns	ns	ns	ns	ns

Table 3 Urine (U) parameters (mean ± standard deviations)

	U-Vol (l/day)	U-pH	U-Ca (mmol/day)	U-Citr (mmol/day)	U-UA (mmol/day)	U-Urea (mmol/day)	U-Amm (mmol/day)
UAD	2.6 ± 0.8	5.8 ± 0.2	4.5 ± 2.2	1.7 ± 1.4	4.2 ± 1.6	418 ± 154	46 ± 27
UAA	2.3 ± 1.2	5.9 ± 0.3	3.2 ± 2.4	1.3 ± 1.2	3.7 ± 2.7	370 ± 176	43 ± 52
Significance	$p = 0.0273$	ns	$p = 0.039$	ns	ns	ns	ns

Regarding personal parameters, the BMI was significantly higher, the recurrence rate significantly lower in group 1 (UAD). There was no difference in age between the two groups (Table 1).

Serum parameters were also not different between the two groups (Table 2).

Twenty-four hour volume and calcium excretion were significantly higher in group 1 (UAD) when compared with group 2 (UAA). All the other urine parameters were not significantly different (Table 3).

Discussion

Thirty-three out of 150 patients (22%) with uric acid calculi showed more than 20% UAD. This is in accordance with data reported previously [8].

For the first time, however, our examinations show data on the natural history and metabolic evaluation in UAD patients. The most important fact is that UAD stone formers have a significantly lower recurrence rate (0.24 ± 0.44) than patients with stones containing less than 20% UAD (1.00 ± 1.29). This has an important clinical implication concerning the necessity of metaphylactic measures.

The reasons for the lower recurrence rate are not completely understood. Potentially, the higher 24-h urine volume does play a role. Investigations in calcium stone formers demonstrated that increasing the diuresis results in a lower recurrence rate [2, 3]. The same may be true for uric acid lithiasis as well.

On the other hand, BMI was higher in UAD patients. High BMI is regarded as a risk factor for uric acid stone formation [1, 5]. Our own studies in uric acid stone patients, however, are in accordance with the findings of this examination showing no significant correlation between BMI and stone frequency [11].

From a physicochemical standpoint, Hesse et al. [7, 8] postulated a lower urine pH for the formation of UAD. Our metabolic evaluation, however, did not confirm that in patients with UAD the urine pH is more acidic than in those with insignificant amounts of UAD.

Small organic molecules (molecular weight < 20 kD) may also play a role in the formation of UAD.

Last, the higher excretion of the calcium in the dihydrate group may be of pathophysiological relevance and requires further attention.

Summing up, this is the first report on metabolic data on a series of UAD patients reported in the literature. The most striking observation is that UAD patients have a significantly lower recurrence rate than patients with UAA. This is of clinical relevance regarding the necessity of special metaphylactic measures.

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