COMPARISON OF CRYTALLURIA IN PATIENTS DRINKING EITHER FREE OR CONTROLLED WATER INTAKE

B. Kacem[1], Z. Kaid-Omar[1], M. Daudon[2], A. Semmoud[3], B. Lacour[2], D. Bougeard[3] and A. Addou[1*]

[1]Laboratoire STEVA, Faculté des Sciences, University of Mostaganem (Algeria)
[2]Laboratoire de Biochimie A, Hôpital Necker, Paris, (France)
[3]Laboratoire de Spectrochimie Infrarouge et Raman (LASIR), Université des Sciences et Technologies, Villeneuve d'Ascq (France)

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ABSTRACT

In 223 stone formers, standardised daily water supply of 3 litres on average has enabled the reduction of crystalluria occurrence from 51.8% before to 23.3% following high water intake advice. After urine storage at +4°C for 48 hours, crystalluria occurred in 90.2% and 54.1% respectively. For comparison, spontaneous crystalluria was studied in 61 control subjects. It was present in 30% of the samples on direct examination and 60.7% after storage at +4°C. Interestingly, the occurrence of crystalluria in stone formers while on free water intake was varying from 46.6% to 60.6% of the urine samples according to the anatomic location of the stone. On standardised water supply conditions, crystalluria decreased in all patients, except patients with vesical lithiasis, but the number of the latter patients was in fact too low to draw tangible conclusions. Crystalluria of weddellite was the most frequent (69.5% of the cases), pure in 39.3% and associated to other crystals in 30.2%. Amorphous urates were present alone in 14.4% and associated in 26% of the crystallurias. Carbapatite was present always associated with other species in 13.5% of the cases in the same way as whewellite in 13.5% of the cases. Besides, the water intake has permitted the spontaneous evacuation of 34.1% of the stones in situ. The composition of the latter was mostly whewellite in 57.9% of the cases, carbapatite in 18.4%, and struvite in 6.6% of the cases. The expulsion kinetics study has shown that the maximum peak of stone evacuation is obtained after 30 to 45 days on diuresis treatment, 71.4% of the evacuations being observed within six weeks following the beginning of the treatment.

Key words : Crystalluria, Urolithiasis, Calcium Oxalate, Carbapatite, Diuresis.

INTRODUCTION

It is well known that increasing diuresis is the best medical advice to prevent calculi recurrence in stone former patients[1]. Epidemiological convincing studies have reported that the stone risk is significantly lower in patients who assume high daily water intake[2,3]. Similarly, in stone formers, high water intake significantly reduced the risk of stone recurrence[4,5]. The mechanism of a high diuresis in preventing stone formation is the decreased supersaturation of the urine which is presumably the main factor of crystal formation. Nevertheless, very few studies have investigated the occurrence of spontaneous crystalluria in various conditions of water intake[6]. On the other hand, medical advices such as permanent high diuresis to prevent stone recurrence are often difficult to follow by the patient for a long time period and visible results, for example disappearance of crystalluria, may be a substantial help to encourage the patients.

In order to accustom the lithiasic patients to more water consumption and to study the influence of the water intake on the development of crystalluria and expulsion ability of *in situ* stones, we followed crystalluria in 223 lithiasic patients while on free water intake (<1.3 litres a day) and and while on recommended high daily water intake of 3 litres. By comparison, spontaneous crystalluria was studied in 61 control subjects on free water intake.

MATERIAL AND METHOD

We studied spontaneous crystalluria in 1338 first morning urine voiding from 223 lithiasic patients including 100 men aged 34.6 years in average (range: 18-61 years) and 123 women aged

36.2 years in average (range: 16-60 years). Three urine samples were investigated in patients while on free water intake (<1.3 litres a day) and three other urine samples while on recommended high daily water intake of 3 litres. Hence a total of 600 samples were collected in men and 738 in women All patients presented *in situ* stones. By comparison, spontaneous crystalluria was studied in 140 first morning urine samples from 61 control subjects (42 men and 19 women) aged 35.1 years in average age was 35.1 years for men (limits: 14 and 60 years) and 30.5 years for women (limits: 16 and 54 years). The daily water intake in control subjects was ranged from 1 or 1.5 litre a day.

Each urine sample was set into a Malassez cell and crystalluria was analysed by optical polarised microscopy . Urine samples were kept at room temperature and examined first within two hours following collection (direct examination) and second after storing for 48 hours at +4°C. Measurement of urine pH was done systematically upon receiving the urine sample .

Water intake was evaluated by questioning each patient about the liquids consumption during the 24 hours prior to collection. The water consumed by the patient was systematically analysed for possible additional investigation.

RESULTS AND DISCUSSION

The clinical interest of crystalluria studies remains controversial[7] although a number of studies have provided evidence that crystalluria is more frequent and often more abundant or presenting with larger crystals and/or aggregates in stone formers than in healthy subjects[8-11]. In a previous report, we were able to provide evidence that high fluid intake may significantly reduce crystalluria when compared to stone formers who declined medical advice to increase diuresis[6]. In the present study, among 669 urine samples from stone formers while on free water supply conditions, 338 urine samples, *i.e.* 50.5%, had crystalluria upon direct examination. After storing at + 4°C, as is shown in Table -1, this proportion reaches 90.2% (604 positive crystalluria cases out of 669, $p < 0.0001$), showing evidence of a high supersaturating level and the metastable state of the urine samples[12-14].

The same patients while on 3 litres water intake per day did not present more than 23.3% positive crystalluria cases at room temperature, i.e. 156 cases out of 669 ($p < 0.0001$). After keeping urine at + 4°C, the crystallisation risk had clearly decreased compared to free water intake since crystalluria was only affecting 54.1% of the urine samples (i.e. 362 samples out of 669, $p < 0.0001$).

In the control subjects, crystalluria was observed upon direct examination in only 30% of the samples (*i.e.* 42 positive crystalluria cases out of 140 samples). The results were in agreement with previous reports showing that crystalluria was more frequent in idiopathic calcium stone formers than in healthy subjects[9,10].

The difference was highly significant with respect to stone-former patients under free water intake conditions ($p<0.0001$), but not significant with respect to the patients under standardised high diuresis treatment. The occurrence of crystalluria increased to 60.7% in controls (85 positive crystalluria cases out of 140 samples) after keeping urine at + 4°C. The difference remained highly significant relative to urine samples kept at + 4 °C of the lithiasic patients on free water intake conditions ($p< 0.0001$).

As shown in Table -2, crystalluria frequency while on free water intake was not significantly different according to the location of the stones and their laterality: 50.9% in case of bilateral lithiasis and 51.3% in case of unilateral lithiasis, which suggests that the seriousness of lithiasis as referred to its bilaterality, is not linked to a somewhat more active lithogenic process than in the case of unilateral lithiasis.

One can imagine that in the majority of the cases, stone bilaterality can be explained either by a longer development of the lithiasic disease or by

Table - 1 : Frequency of crystalluria in lithiasic patients before and after water supply

Water intake conditions	Direct examination (%)		Total (%)	Examination after storing at + 4°C		Total (%)
	Men	Women		Men	Women	
Free	50.3	52.8	51.8	91.6	89.1	90.2
Standardized	21	25.2	23.3	55.3	53.1	54.1

Table - 2 : Crystalluria development versus site of *in situ* stones

Location	Frequency of crystalluria while on free water intake conditions (%)		Frequency of crystalluria while on standardized water intake conditions (%)	
Bilateral lithiasis	50.9	(168/330)	18.4[1]	(61/330)
Left kidney	47.6	(60/126)	27.8	(35/126)
Right kidney	50.0	(60/120)	22.5[2]	(27/120)
Left ureter	61.1	(11/18)	38.9	(7/18)
Right ureter	53.2	(33/62)	32.25	(20/62)
Bladder	46.15	(6/13)	46.15	(6/13)

[1] $p < 0,01$ and [2] $p < 0,05$ versus left ureter

Indiquer entre parenthèses ou dans une colonne supplémentaire les effectifs pour chaque localisation. La différence entre uretères droit et gauche est-elle significative sous 3 litres de diurèse?

predisposing anatomic factors without, strictly speaking, urinary tree malformations.

Under standardised water intake conditions, direct examination of crystalluria showed a decrease down to 23.3%. Contrary to what was observed under free water intake conditions, crystalluria varied from 32.25% in the case of right ureter lithiasis to 46.15% in the case of vesical lithiasis, the difference being significant for bilateral stones in comparison with left ureter stones.

We have compared the nature of observed crystalluria upon direct examination under free water intake conditions in the stone patients and control subjects (Table -3). In stone formers,

Table - 3 : Types of crystalluria observed under free water intake conditions

Name of observed crystals	Direct examination of crystalluria in lithiasic patients (%)	Direct examination of crystalluria in control subjects (%)
C2	39.3	47.6
CAU + C2	16,5	-
CAU	14.4	9.5
CCAP ± CA	6.3	7.1
C1 + CAU	5.5	-
C2 + C1	3.4	-
C2 + CAU + C1	2.9	2.4
C2 + ACCP ± CA	2.6	11.9
Str	2.3	-
Br + C2 ± CA	1.7	-
UAD	1.5	2.4
Str + UAA	1.5	-
C2 + ACCP + C1 ± CA	1.1	-
C2 + Br	0.3	2.4
Str + C2 + UAA	0.3	-
AU	0.3	-
Br	-	14.3
C2 + UAD	-	2.4
Overall crystalluria	51.8	30.0

AUA = anhydrous uric acid; UAD = uric acid dihydrate; Br = brushite; CA = carbapatite; ACCP= amorphous carbonated calcium phosphate; C1 = whewellite; C2 = weddellite; Str = struvite; AU = Ammonium hydrogen urate ; CAU = complex amorphous urates weddellite (C2) was the most frequent species (69.5%), pure in 39.3% of the cases and associated with other crystalline species in 30% of the cases. The complex amorphous urates (CAU) were pure in 14.4% and in association in 26 % of the crystalluria cases. Carbapatite was present in 13.5% of the cases, always associated. ACP was pure or associated with carbapatite in 6.3%, and associated with other crystalline species in 4.9% of the cases. Whewellite (C1) was observed in 13% of the crystalluria cases, always associated with other crystalline species. Brushite was present in 2% of cases, always in association with other species, especially weddellite. Struvite was identified as pure in 2.3% of cases and associated in 1.7%. In control subjectss, predominance of weddellite (66.7%) was also observed, pure in 47.6% of the crystalluria cases and associated in 19.1% of them without any significant difference when compared with stone formers, in agreement with previous data [4].

Pure complex amorphous urates were present in 9.5% of the cases and associated with other species in only 2.4%. A somewhat high brushite frequency was noted, but almost always not very significant and hence unlikely to give rise to stone formation [13,15]. Finally, whewellite, which indicates hyperoxaluria[16,17], was observed in association with other crystalline species, in 2.4% of the positive samples against 13% in stone formers, the difference being significant ($p = 0.01$).

Besides, standardised diuresis treatment has allowed the spontaneous evacuation of 76 stones, i.e. 34.1 % of the *in situ* stones
The chemical composition of the stones is summarized in Table - 4.

Table - 4 : Frequency of main components in expelled stones

Main component	Frequency (%)
Whewelite	57.9
Carbapatite	18.4
Weddellite	13.1
Struvite	6.6
Uric acid anhydrous	2.6
Uric acid dihydrate	1.3

Whewellite was the major constituent in 57.9%, carbapatite in 18.4%, weddellite in 13.1%, and struvite in 6.6% of the cases. The spontaneously passed stones had an average size of 6 mm. The stones where calcium or magnesium phosphate was the major constituent were often larger than the others. On the other hand, the weddellite stones were often expelled in the form of fragments and small crystalline aggregates. The relationships between stone composition and crystalluria were reported in a previous study and were in good agreement for most crystalline species, underlined the interest of crystalluria studies in case of calculi are not available for analysis[18].

The supervision of patients under standardised water intake conditions has allowed the monitoring of the stone expulsion kinetics. The results are reported in Table -5.

Table - 5:
Expulsion kinetics of the *in situ* stones

Time elapsed for expulsion (days)	Frequency of expelled stones (%)		
7	4.3	41.4%	71.4%
15	5.7		
30	21.4		
45	30.0		
60	8.6		
90	5.7		
120	2.9		
> 120	11.4		

It can be noticed that the maximum expulsion peak of the stones is observed at 45 days and that 71.4% of the expulsions took place within the first six weeks after the beginning of the diuresis treatment. We then notice a regular decrease of the expulsion ability, either because the *in situ* stones are no longer mobilised by the forced diuresis treatment (stones too large or enclosed), or by reason of a weaker compliance of the patients relative to the water intake advice.

Besides, the study of the location of the stones in situ before and after water intake has shown that the ureter and bladder stones were evacuated in 51.8% and 40% of the cases respectively, and those of the kidney in 31.4% of the cases without significant difference according to laterality.

Conclusion

High water intake proved its ability to make an originally fairly high crystalluria become negative in a significant proportion of the lithiasic patients, and to have 34.1% of the in situ stones evacuated spontaneously. The occurrence of crystalluria as a function of location of stone suggests other factors that higher supersaturation are involved in bilateral stones when compared to unilateral calculi. This study confirms the importance of the diuresis treatment not only in the prevention of the crystallization risk, but also in the expulsion of a number of urinary stones when not invasive urological means such as ESWL are not yet available to all patients.

The study of crystalluria is a simple and cheap technique, non-invasive and easy to process, which proves to be very useful for taking charge lithiasic patients. It represents an excellent supervision test for monitoring the patients and assessing the efficiency of dietetic or therapeutic measures intended to decrease urine supersaturation and its crystallogenetic potential.

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