Recurrence rates of urinary calculi according to stone composition and morphology

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Michel Daudon[1,2] · Paul Jungers[3] · Dominique Bazin[4,5] · James C. Williams Jr.[6]

Abstract

Few studies have examined the relative risk of recurrence of different stone types. The object of the present study was to evaluate the tendency for stone recurrence as a function of major mineral composition of the stones and morphological characteristics of the stones. This study was carried out using 38,274 stones for which we had data available to specify if the stone was from the first or a subsequent urinary stone episode. Stones were analyzed for morphology by stereomicroscope and for composition by infrared spectroscopy. Overall, 42.7% of stones were from patients who had had a previous stone event, with these being more frequent in men (44.4%) than in women (38.9%, $p < 0.0001$). Age of first stone occurrence was lowest for dihydroxyadenine (15.7 ± 16.6 years) and highest for anhydrous uric acid (62.5 ± 14.9 years), with the average age of first stones of calcium oxalate falling in the middle (40.7 ± 14.6 years for calcium oxalate dihydrate, and 48.4 ± 15.1 years for calcium oxalate monohydrate, COM). By composition alone, COM was among the least recurrent of stones, with only 38.0% of COM stones coming from patients who had had a previous episode; however, when the different morphological types of COM were considered, type Ic—which displays a light color, budding surface and unorganized section—had a significantly greater rate of recurrence, at 82.4% ($p < 0.0001$), than did other morphologies of COM. Similarly, for stones composed of apatite, morphological type IVa2—a unique form with cracks visible beneath a glossy surface—had a higher rate of recurrence than other apatite morphologies (78.8 vs. 39–42%, $p < 0.0001$). Stone mineral type alone is insufficient for identifying the potential of recurrence of the stones. Instead, the addition of stone morphology may allow the diagnosis of highly recurrent stones, even among common mineral types (e.g., COM) that in general are less recurrent.

Keywords Urinary stone · Stone analysis · Morphology · Recurrence

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Introduction

Epidemiological studies on rates of stone occurrence and recurrence in industrialized countries agree on two points: first, urinary stones strike men more often than women and, second, recurrence of at least one more stone occurs in 40–50% of affected persons [1–3]. However, few studies have examined the relative risk of recurrence of different stone types. It seems reasonable to state that cystine stone disease, because of its genetic basis, leads to greater stone recurrence than most other types of stone disease [4]. Similarly, uric acid stones in older patients are often quite recurrent [5]. However, it is not so clear what to say about the stones composed of calcium salts. For calcium oxalate, studies from some years ago suggest that weddellite (calcium oxalate dihydrate, COD) stones are more likely to recur than whewellite (calcium oxalate monohydrate, COM) stones [6], and that stones with a significant component of calcium

phosphate are more likely to recur than stones composed of pure calcium oxalate [7]. The object of the present study was to evaluate the tendency for stone recurrence as a function of the major mineral composition of the stones, but also to take into account the morphological characteristics of the stones and the sex of the patient.

Materials and methods

This study was carried out using 38,274 stones collected from all regions of France for which we have data on both stone recurrence and the patient's age at the first stone episode. The stones were analyzed for morphology and composition (by infrared spectroscopy, as previously described [8, 9]). Briefly, stones were examined using a stereomicroscope and each was classified according to the established morphological criteria [9, 10]. These criteria include the appearance of the stone surface but also the appearance of the stone interior after the stone was cleaved one or more times to reveal its presumed nidus. The main characteristics of the stones are summarized in Table 1 and some examples of stone types are given in Fig. 1. Following these visual observations, samples of stone material were dissected away for analysis by Fourier transform infrared spectroscopy. For each stone, patient data were available to specify if this was from the first or a subsequent stone episode. The results are expressed according to the principal constituent, morphological type, and structural characteristics of the stone, and separated according to the sex of the patient.

Statistical comparisons were carried out using ANOVA and Chi-squared tests, as appropriate, using NCSS software (NCSS, Kaysville, Utah, USA).

Results

Of the 38,274 stones, coming from 26,368 males (68.9%) and 11,906 females, 16,336 (42.7%) were from patients who had had a previous stone event. Of these patients with recurrent stones, 11,702 were male and 4634 female, illustrating the fact that recurrent stones were more frequent in men than in women (44.4 vs 38.9% of the total for each sex, $p < 0.0001$). The mean age of patients with recurrent stones did not differ between the sexes (45.0 ± 14.3 years old for men, 44.0 ± 14.8 for women).

Mean age at first stone as a function of stone mineral

We first consider the data on patients' initial stone events, looking at the age of first stone occurrence for the different crystalline species. The data are shown in Table 2, where, for each majority stone component, the mean age of the patients is given for each sex, with the stone components listed according to the increasing mean age of first occurrence. It is striking that the first five compositions listed in Table 2—that is, the stone types occurring at the earliest ages—are crystalline species that are relatively rare, representing < 5% of all stones [10, 11]. We are aware that the small number of samples in these groups is a limiting factor for the significance of the data regarding these stones. However, as expected, due to their inherited origin, the first groups of calculi are dihydroxyadenine and cystine. The crystalline species occurring at the youngest age is dihydroxyadenine. The second species is cystine, followed by octacalcium phosphate and whitlockite, then ammonium urate. Coming next in the table are more common types of stone, the first of which is COD, the calcium-dependant type of calcium oxalate [12–14]. The mean age at which this crystalline species appeared as a stone was 40 years, eight years younger than the mean age for COM stones, the other form of calcium oxalate. The distribution of calcium oxalate stones according to the crystalline phase and the patient's age and gender at the onset of the disease is illustrated in Fig. 2.

Between COD and COM are four forms of phosphate stone. Finally, the species appearing latest in life are the two forms of uric acid. The distribution of uric acid stones according to the patient's age and gender at the onset of the disease is shown in Fig. 3.

Frequency of stone recurrence as a function of principal component

Table 3 shows the proportion of patients having a recurrent stone episode (that is, the second or later stone episode for the patient) for each principal stone component. Within this, the stone components are ranked according to the increasing proportion of recurrent stones. Among the stone mineral types that have the lowest percentage of recurrence, two are phosphate stones, including struvite. However, among the seldom-recurring stones is also COM, the constituent most commonly found in urinary stones [10, 15, 16]. All the stone compositions that follow struvite in the table—with the exception of COD in men and women, and carbapatite and octacalcium phosphate in women—are more recurrent than the average percentage for all stones. Among these more-recurrent compositions, the two forms of uric acid appear at the head with a percentage of recurrence above 50%, significantly higher than the average percentage for all stones. Finally, the three species at the bottom of Table 3 are particularly recurrent, apparently all forms of stone caused by very active metabolic processes: These are brushite, cystine, and dihydroxyadenine.

For stones of calcium oxalate, brushite and cystine, we have also recorded the number of stone episodes in the

Table 1 Morphoconstitutional classification of urinary calculi (from [9, 10])

Morphological type	Subtype	Main components	Main morphological characteristics (for more details, see [9, 10])	
			Surface	Section
I	Ia	Whewellite	Mammillary, brown	Concentric, radiating organization, brown
	Ib	Whewellite	Rough and mammillary, brown	Unorganized, brown
	Ic	Whewellite	Budding, cream to pale yellow–brown	Poorly organized, cream to pale yellow–brown
	Id	Whewellite	Smooth, beige or pale brown	Concentric, compact, beige
	Ie	Whewellite	Locally budding and mammillary, pale yellow–brown to brown	Locally unorganized, locally radiating organization, pale yellow–brown to brown
II	IIa	Weddellite	Bipyramidal crystals aggregated, with sharp angles and ridges, pale yellow	Loose radial organization, pale yellow
	IIb	Weddellite ± whewellite	Bipyramidal crystals aggregated, with blunted angles and ridges, pale yellow	Unorganized, pale yellow
	IIc	Weddellite	Rough, grey-beige	Thin layers in periphery, unorganized core, grey-beige
III	IIIa	Uric acid	Smooth, ochre to orange	Concentric, radiating organization, orange
	IIIb	Uric acid	Embossed, rough and porous, beige to orange	Unorganized or poorly organized and porous, orange
	IIIc	Various urates	Rough, locally porous, beige to greyish	Unorganized with porous areas, beige to greyish
	IIId	Ammonium urate	Embossed, rough and porous, grey-brown	Alternated layers, thick and brownish, thin and greyish
IV	IVa1	Carbapatite	Rough or slightly embossed, cream to beige	Poorly organized, whitish to cream
	IVa2	Carbapatite	Embossed, glazed with cracks, yellow–brown	Alternated layers, thick and yellow–brown, thin and cream
	IVb	Carbapatite	Heterogenous, both embossed and rough. Heterogenous color, cream to brown	Alternated layers, thick and cream, thin and yellow–brown
	IVc	Struvite	Amalgamate crystals with blunted angles and thick ridges, whitish	Crude radial crystallization, whitish
	IVd	Brushite	Finely rough or aggregated rods, cream to beige	Concentric, radiating organization, cream to beige
V	Va	Cystine	Rough or grainy, yellowish	Poorly organized, loose radiating organization, yellowish
	Vb	Cystine	Smooth, cream to pale yellowish	Concentric in periphery, unorganized core, cream to yellow
VI	VIa	Proteins	Smooth, cream to pale brown	Unorganized, cream to pale brown
	VIb	Proteins	Rough and flaked off, dark brown to black	Crude and diffuse foliated structure, dark brown to black
	VIc	Proteins	Homogenous, smooth, dark brown	Soft concentric dark-brown shell, unorganized beige core
Main mixed types				
Ia + IIa and Ia + IIb	Whewellite + weddellite			
IIa + IVa1 and IIb + IVa1	Weddellite + carbapatite			
Ia + IIa + IVa1	Whewellite + weddellite + carbapatite			

patients with recurrent stones. The patients who produced calcium oxalate stones had a mean of 3.5 stone episodes, while that number exceeded 7.5 for both brushite and cystine. This number is probably even higher for patients with uric acid stones, but it is difficult to evaluate with precision, as these patients often repeatedly form sand and/or

Fig. 1 Photographs of the stone surface for the main morphological types of urinary calculi. Photographs **a– d** pure COM stones. Photograph **e** pure COD stone. Photograph **f** COD (75%)+COM (25%). Photographs **g** and **h** pure uric acid stones. Photograph **i** pure ammonium urate stone. Photograph **j** calcium phosphate stone made of a mixture of carbapatite (80%) and of amorphous carbonated calcium phosphate (20%). Photograph **k** nearly pure calcium phosphate stone: carbapatite (95%)+COD (5%). Photograph **l** carbapatite (50%)+struvite (40%)+amorphous carbonated calcium phosphate (10%). Photograph **m** struvite (90%)+carbapatite (10%). Photograph **n** brushite (90%)+COD (5%)+carbapatite (5%). Photograph **o** mixture of COM (70%) and COD (30%)
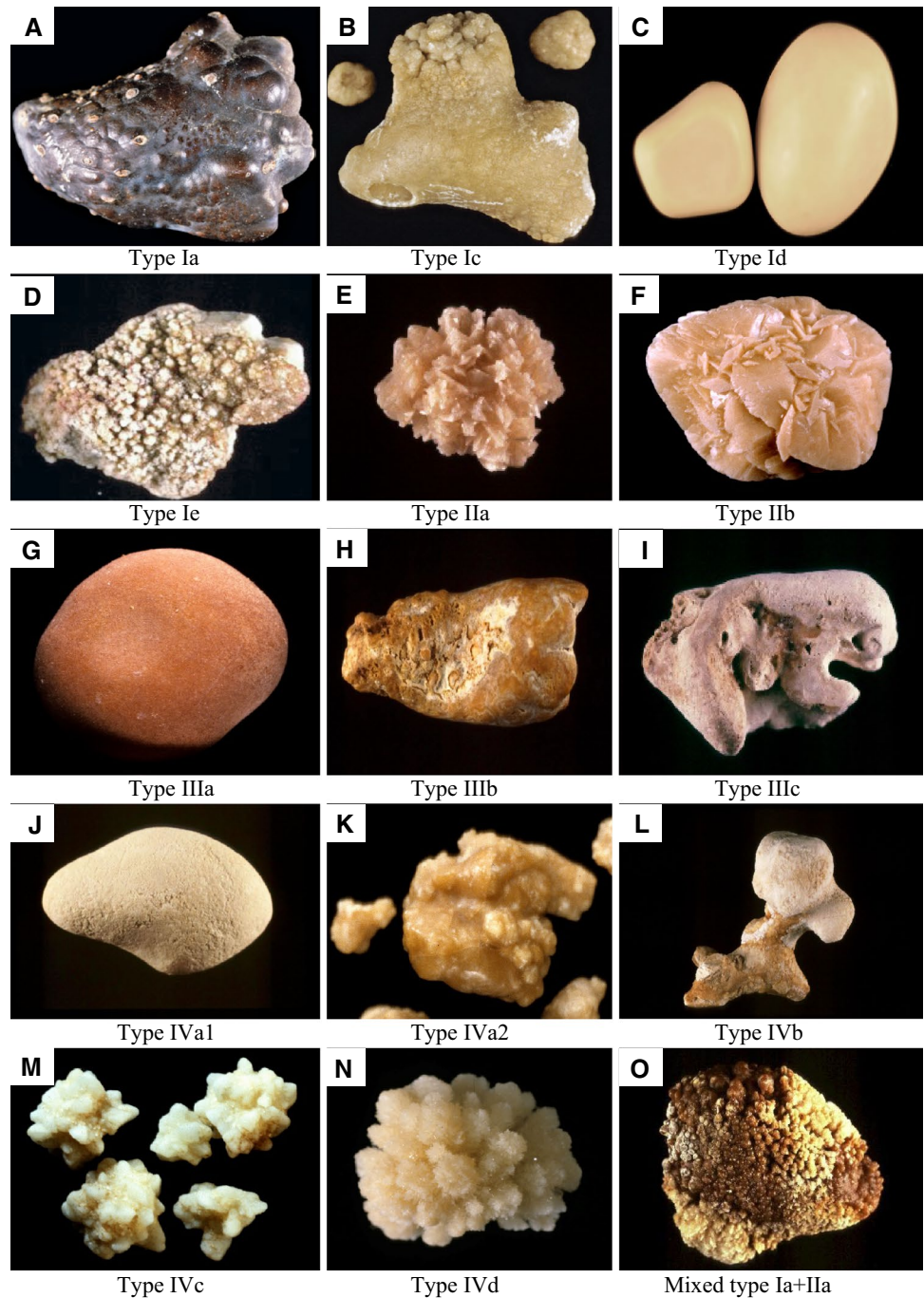
very small stones that are passed spontaneously with limited clinical symptoms. Moreover, in contrast to other crystalline species, stones composed of uric acid can be dissolved by urinary alkalization [17].

Frequency of stone recurrence as a function of stone morphology

The frequency of stone recurrence varied with morphological type (Table 4; Fig. 4). This was especially apparent in calcium oxalate stones where the recurrence rate varied among morphological types from 27 to 82%, and in calcium phosphate stones, where the recurrence rate varied from 39 to 79% among the different morphological types. Overall, the recurrence rate of COM was relatively low (Table 3), but the morphological types Ie, and especially Ic, had higher rates of recurrence (Fig. 4). Thus, recognition of these morphological types of COM in a patient could alert the physician to the possibility of a greater chance of stone recurrence.

Table 2 Mean age (years ± SD) at the first stone episode according to the stone composition

Main component	Males		Females		All		p value M vs F
	N	Age	N	Age	N	Age	
Dihydroxyadenine	15	7.2 ± 9.3	6	29.0 ± 17.3	21	15.7 ± 16.6	< 0.01
Cystine	43	26.5 ± 20.1	51	27.7 ± 16.3	94	27.1 ± 18.2	NS
Octacalcium phosphate pentahydrate	16	25.6 ± 18.4	18	31.0 ± 13.2	34	28.6 ± 15.9	NS
Whitlockite	21	25.1 ± 19.2	22	37.4 ± 16.3	43	31.4 ± 18.4	< 0.05
Ammonium hydrogen urate	48	25.4 ± 27.1	35	43.7 ± 19.8	83	33.1 ± 26.1	< 0.001
Weddellite (COD)*	3440	41.0 ± 14.0	1039	39.7 ± 16.1	4469	40.7 ± 14.6	< 0.05
Brushite	162	42.8 ± 16.8	59	38.2 ± 16.2	221	41.6 ± 16.9	NS
Carbapatite	1064	39.4 ± 22.9	1702	43.1 ± 16.9	2766	41.7 ± 19.6	< 0.001
Amorphous carbonated calcium phosphate	17	37.7 ± 30.1	29	44.4 ± 25.1	46	41.9 ± 27.1	NS
Struvite	157	44.2 ± 26.5	205	47.2 ± 21.3	362	45.9 ± 23.7	NS
Whewellite (COM)*	7890	48.8 ± 14.4	3383	47,4 ± 16.5	11,273	48.4 ± 15.1	< 0.01
Uric acid dihydrate	192	58.3 ± 12.9	40	62.9 ± 14.0	232	59.1 ± 13.3	NS
Uric acid anhydrous	1080	62.8 ± 14.6	366	61.8 ± 15.1	1446	62.5 ± 14.9	NS

*COM = calcium oxalate monohydrate − COD = calcium oxalate dihydrate
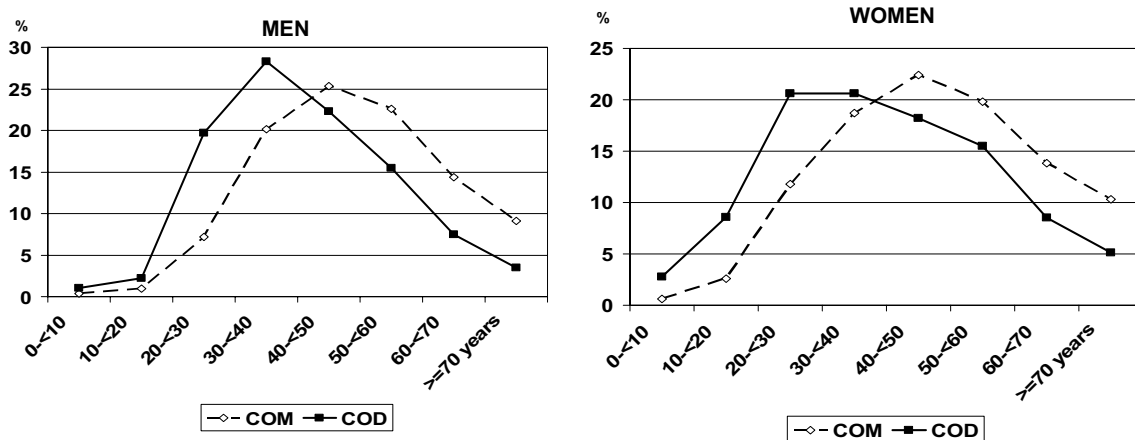
Fig. 2 Age distribution of patients at the onset of COM or COD stone disease in both genders

For stones containing mainly COD (type II), the percentage of stones that were recurrent was generally not different from the mean of all stones, except for type Ia + IIb (mixture of COM and COD) which were less recurrent and type IIa + IVa1 (COD and carbapatite) stones which were significantly more recurrent.

Regarding stones composed primarily of forms of calcium phosphate, types IVa1 and IVa2 (both types of carbapatite) were very different, the latter being significantly more recurrent than the mean of all stones from men and women, suggesting the possibility of more active metabolic processes driving this morphological form. Type IVd (brushite) was also significantly more recurrent in both sexes, consistent with the high recurrence rate of this stone type reported in American studies [18–20].

Stones composed of uric acid of type IIIb (not type IIIa, often related to stasis) or cystine were significantly more recurrent than the mean for all stones, consistent with these stones resulting from metabolic processes more active than those that drive the formation of common calcium stones.

Influence of Randall's plaque (RP)

As seen in Table 5, calcium oxalate stones developed from RP actually seem to exhibit a slight tendency to be more recurrent than stones formed by other mechanisms ($p = 0.02$), with a significant difference according to the gender of patients. In men, 41% of stones with an RP were recurrent by comparison with 38.6% of stones without any RP ($p < 0.01$). No significant difference was found in stones
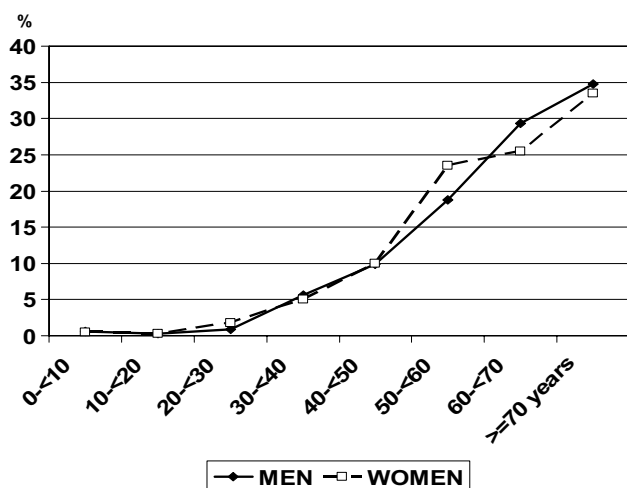
Fig. 3 Age distribution of patients at the onset of uric acid stones in men and women

from women. However, differences exist regarding the stone type. For example, COM stones of type Ia developed from an RP appear significantly more recurrent than COM stones of type Ia without RP in men (38.1 vs 33.5%, $p < 0.001$) with only a trend in women (32.1 vs 28%, $p = 0.07$). In addition, stones of mixed types I + II and II + I are significantly more recurrent than type Ia stones in men in both groups of stones with and without RP and in women in the group of stones without RP.

Discussion

Stone disease is a very common finding in industrialized countries and is constantly increasing as revealed by epidemiological studies [21–23]. In most cases, it is a consequence of dietary imbalance and/or chronically insufficient water intake. In general, the correction of these factors should prevent stone recurrence. However, among stone diseases, metabolic forms exist that expose the patient to multiple recurrences of calculi with the possible consequence of altering the kidney function and, sometimes, inducing end-stage renal failure. These may result from inherited or acquired pathologies, the diagnosis of which is of crucial importance to treating them and reducing the risk of stone recurrence and crystallization in the kidney. Stone analysis at the first episode is one method for the early detection of stone diseases which are prone to recur. As shown in the present study, there are great differences in terms of stone recurrence risk according to both stone composition and morphology.

Onset of stones

The mean age at the onset of the disease, as revealed by a stone episode, varied in relation to the stone composition. The earliest component found was dihydroxyadenine, which corresponds to an adenine phosphoribosyltransferase deficiency, an inherited autosomal disease

Table 3 Frequency of stone recurrence according to the stone composition

Component	Males		Females		Total	
	N	%	*N*	%	*N*	%
ACCP[(1)]	8	32.0	13	30.2	21	30.9
Whitlockite	10	32.3	14	38.9	24	35.8
Whewellite (COM)	5241	39.5***,e	1768	34.1e	7013	38.0e
Struvite	143	47.0**	121	36.7	264	41.6
Presence of struvite	492	44.9***	526	36.5	1018	40.1
Ammonium Urate	28	36.8	32	47.1	60	41.7
Weddellite (COD)	2883	45.2***	625	37.2	3508	43.5a
Carbapatite	1022	48.8***,e	1143	39.9	2165	43.6a
Uric acid anhydrous	1193	52.1*,e	329	46.8c	1522	50.9e
Uric acid dihydrate	198	50.6 a	50	55.6b	248	51.6c
Octacalcium phosphate	28	63.6*,a	15	45.5	43	55.8
Brushite	479	75.7e	143	70.8e	622	74.5e
Cystine	378	90.9e	293	86.7e	671	89.0e
Dihydroxyadenine	19	95.0d	7	100b	26	96.3e
All stones	11,702	44.4***	4634	38.9	16,341	42.7

[(1)]ACCP = amorphous carbonated calcium phosphate

*$p < 0.05$; **$p < 0.01$; ***$p < 0.00001$ vs females

a$p < 0.05$; b$p < 0.01$; c$p < 0.001$; d$p < 0.0001$; e$p < 0.00001$ vs mean recurrence for a given gender or by comparison to the whole series

Table 4 Frequency of stone recurrence according to the morphological type of the stone

Morphological type[1]	Males		Females		Total	
	N	%	N	%	N	%
Calcium oxalates						
Ia	1735	35.9***,e	499	29.8d	2234	34.3e
Ib	58	26.1c	25	30.9	83	27.4d
Ic	29	85.3e	13	76.5b	42	82.4e
Id	66	40.0	43	46.2	109	42.3
Ie	44	54.3	26	48.2	70	51.9
Ia + IIa	424	41.7	147	38.6	571	40.8
Ia + IIb	1051	39.5**e	306	32.1b	1359	37.6e
IIb + Ia	1433	44.4**	380	38.7	1813	43.1
IIa	773	44.6**	161	37.6	934	43.2
IIb	400	39.1a	86	25.4	486	38.4
IIa + IVa1	959	48.5 **,b	286	40.8	1245	46.5c
IIb + IVa1	213	39.1	99	40.4	312	39.5
Ia + IIa + IVa1	682	46.4**	326	36.8	1008	42.8
Calcium phosphates						
IVa1 (w/o struvite)	110	47.8**,a	125	38.0	235	42.0
IVa2	26	70.3a	53	84.1e	79	79.0e
IVb	221	48.3***	335	35.2a	556	39.4b
IVd	229	73.6e	73	68.9e	302	72.4e
Struvite (magnesium ammonium phosphate hexahydrate)						
IVc	29	53.7	17	32.7	46	43.4
Uric acids						
IIIa	186	45.7	39	50.7a	225	46.5
IIIb	840	53.2**,e	230	47.2b	1070	51.8e
Cystine						
Va	312	90.7	233	84.7e	545	88.1e
Vb	20	100	7	100b	27	100e

[1]Complete description of the stone types is given in Daudon et al. [9, 10]

*$p < 0.05$; **$p < 0.01$; ***$p < 0.00001$ vs females

[a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.001$; [d]$p < 0.0001$; [e]$p < 0.00001$ vs mean stone recurrence for a given gender or for total

often inducing end-stage renal failure when undiagnosed [24–27]. Unexpectedly, there was a strong difference in the onset of the disease according to gender, males being prone to develop stones earlier than females. Perhaps a bias exists due to the small number of cases. Coming next were cystine stones which, despite the fact that they result from a congenital defect in tubular transport, in contrast to dihydroxyadenine stones, are known to make their appearance in the second or third decade of life [28, 29]. Indeed, the data here suggest that some cystine stone formers do not present their first stone until the seventh decade of life. The next earliest component was octacalcium phosphate, an instable form of apatite able to convert to it in some months. The next component was whitlockite, an infrequently found form of calcium magnesium phosphate, which, in our experience, is essentially a marker of infection [30].

Ammonium hydrogen urate stones were found significantly earlier in men than in women. A possible explanation is related to stones induced by urea-splitting bacteria. Such stones contain ammonium salts such as struvite and/or ammonium urate. They are especially frequent in very young boys (at the time where uricosuria is still elevated) and more later in life for women.

COD, found as the first stone at the mean age of 40 years, is a rather calcium-dependent form of calcium oxalate stone, mainly observed in hypercalciuric states [12, 13, 31]. Four forms of phosphate stone, including amorphous carbonated calcium phosphate, carbapatite, brushite and struvite, also appeared at an average first age in the forties. Interestingly, the average age of onset of the most common form of stone, COM, was later than all of these, at 48 years of age. Of note, in Japan, Koide et al. reported in the eighties that patients who form COD stones are different from those who form

Fig. 4 Recurrence of stones by morphology. Type Ia and type Ic stones are made of pure or nearly pure calcium oxalate monohydrate, which accounts for more than 95% of the stone mass. Type IVa1 and type IVa2 stones are made of nearly pure calcium orthophosphates (mainly carbapatite), which account for more than 90% of the stone mass. *Significantly different from mean of all stones, $p < 0.01$, with mean shown by horizontal line
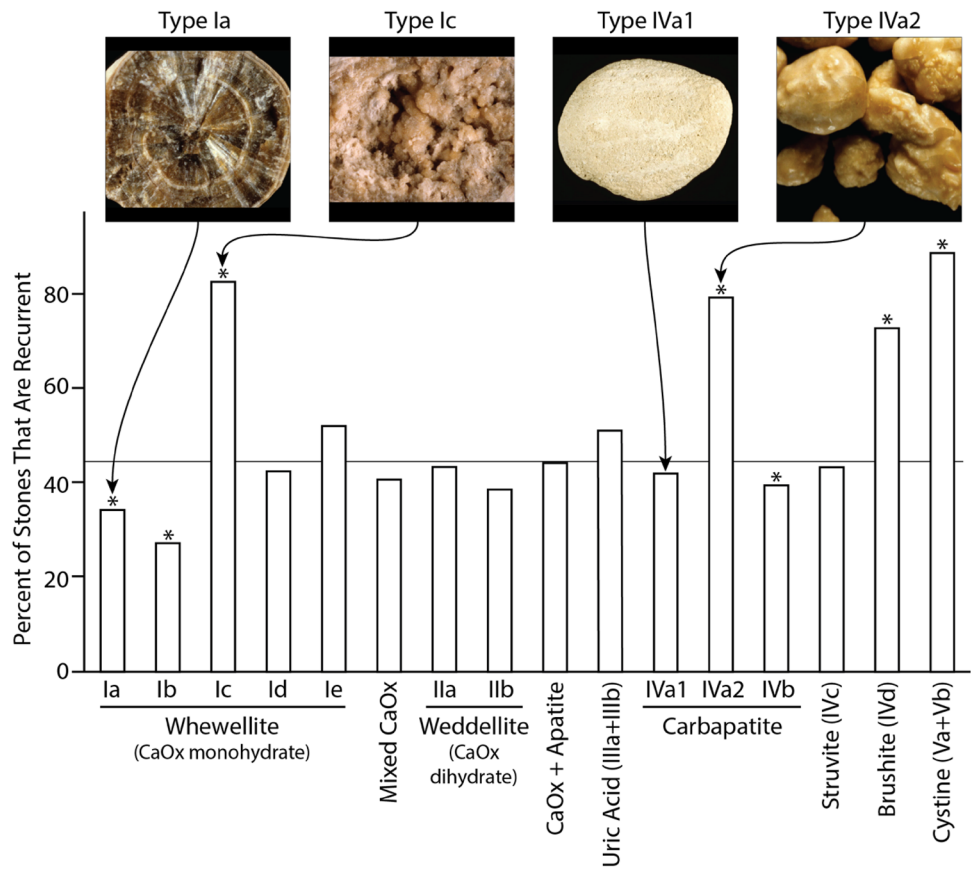
Table 5 Comparison between umbilicated stones or not

Morphological type	Males		Females		Total	
	First stone	Recurrence	First stone	Recurrence	First stone	Recurrence
Umbilicated stones with Randall's plaque						
Type Ia alone	1549	954 (38.1)***,b,xx	501	237 (32.1)x	2050	1191 (36.7)****
Mixed types I+II	869	650 (42.8)**,b,††	332	171 (34.0)	1201	821 (40.6)††
Mixed types II+I	360	328 (47.7) c,††††	108	57 (34.6)	468	385 (45.1)††††
Total	2778	1932 (41.0)**,d,xx	941	465 (33.1)xx	3719	2397 (39.2)*,xx
Stones without any umbilication nor Randall's plaque						
Type Ia alone	1551	781 (33.5)b	674	262 (28.0)xx	2225	1043 (31.9)xx
I+II	1332	825 (38.2)a,xx,†††	548	282 (34.0)x,††	1880	1107 (37.1)xx,††††
II+I	1433	1105 (43.5)a,††††	493	323 (39.6)††††	1926	1428 (42.6)††††
Total	4316	2711 (38.6)c,xx	1715	867 (33.6)xx	6031	3578 (37.2)xx

Stones of mixed types I+II include stones with various subtypes where COM was the main crystalline phase of calcium oxalate. By contrast, stones of mixed types II+I include stones with various subtypes where COD was the main crystalline phase of calcium oxalate. As shown in the table, the recurrence rate is not the same according to the main crystalline phase of calcium oxalate: when COD is the main crystalline phase, the stones are commonly more recurrent by comparison with type Ia stones used as a reference

*$p=0.02$; **$p<0.01$; ***$p<0.001$; ****$p<0.0001$ vs non-umbilicated stones

†$p<0.05$; ††$p<0.01$; †††$p<0.001$; ††††$p<0.0001$ vs type Ia stones for a given gender

a$p<0.05$; b$p<0.01$; c$p<0.001$; d$p<0.0001$ vs females

x$p<0.01$; xx$p<0.0001$ vs mean occurrence of stone recurrence for a given gender

COM stones and that COD stones were observed earlier than COM stones in Japanese patients [32]. Finally, the age of first occurrence of uric acid stones was much later, at about 60 years of age, probably related to the increased occurrence at older ages of overweight, metabolic syndrome, and type 2 diabetes [33, 34].

Stone recurrence

A stone recurrence rate around 50% is commonly accepted in the literature, both in children and adults [35, 36]. However, no data are reported regarding crystalline phases of the stones. Among the stone mineral types seen with the lowest percentages of recurrence (Table 3), three were phosphate stones composed of minerals that have been shown to be related to urinary tract infection (whitlockite, amorphous carbonated calcium phosphate, and struvite) [30]. These results seem reasonable because stones occurring due to infection are not likely to recur if the infection is successfully treated. Within the range of recurrence frequency of infection stones, however, are also stones composed of COM, for which the underlying cause for stone formation is generally a hyperoxaluria of moderate degree [12, 37, 38]. Thus, it is apparent that COM stones are less likely to be recurrent than are other calcium stones whose origins are also metabolic, but for which the endogenous biochemical abnormalities are more marked. It is also interesting to note that the percentage of recurrent COM stones is less than the mean percentage for all recurrent stones, for both men and women.

If we consider that physicians propose for preventing recurrence of all urinary stones adequate dietary advices or medical treatment according to the stone composition (calcium stone, uric acid stone, cystine stone, struvite stone…), it is unlikely that stone recurrence might be a consequence of an inappropriate medical care. Obviously, we cannot exclude that patients were not compliant with physician recommendations. However, there is no evidence that such default of compliance may depend on stone type. Thus, intrinsic characteristics of crystalline phases or of stone morphology appear highly suggestive for different courses of stone disease.

Among the four compositions that are least recurrent, struvite is obviously special. Although in women the percentage of recurrent stones composed of struvite was slightly less than the mean for all stones, struvite stones were considerably more recurrent in men. This difference may occur for a number of reasons. First, anatomical and disease conditions could make the formation of struvite stones more favorable in men, especially prostatic hypertrophy, which often causes incomplete emptying of the urinary bladder. However, in our experience, only one-third of bladder struvite stones associated with prostate hypertrophy were recurrent. Another reason for the higher incidence of recurrent

struvite stones in men could be that infection is less expected in men, and thus not recognized and promptly treated as often as it is in women. In any case, when one examines the epidemiologic changes in stones in France over the past 30 years, one can see that the frequency of infection stones has fallen dramatically for women—3.5-fold—while that for men has dropped by only 20% [39]. Of note, recent epidemiological data suggest that struvite stones could be more frequent in recent decades by comparison to previous reports, especially in men [40].

Ammonium urate was found to be slightly less recurrent by comparison to the whole series. It was a more recurrent component in women than in men. Although it is always found with hyperuricosuria, other factors are necessary to its formation and it can appear in the context of different pathologies (anorexia and laxative abuse, infection with urea-splitting organisms, poor animal protein diet and chronic diarrhea, etc. [41, 42]).

Among the more recurrent compositions, octacalcium phosphate and the two forms of uric acid are at levels just slightly above the average percentage for all stones. These stones include a species that is at least suspected of being calcium-dependent (octacalcium phosphate [30, 43]), and two species (uric acid, both anhydrous and dihydrate) that are frequently associated with metabolic syndrome and diabetes [33, 34, 44].

The three most recurrent species were found to be dihydroxyadenine, cystine and, surprisingly, brushite. The first two crystalline species are due to well-defined inherited disorders. In contrast, brushite in stones is not recognized as a marker of any genetically linked pathology; yet the rapid growth of brushite stones leads to recurrence rates similar to those of stones formed as the result of genetic disorders, with 75% of brushite stones coming from patients who have already had at least one stone episode. Moreover, patients with brushite stones very often have had repeated stone episodes and frequently are found to have multiple stones with each incidence and a higher number of urological procedures [18–20]. Brushite stones are also classed, along with those of cystine, as the stones most difficult to break [45]. These results suggest the need for more sophisticated studies of the metabolic disorders present in the patients who produce brushite stones. Indeed, the incidence of brushite stones has increased considerably over the past years, from 0.8% of all stones in 1980 to 2.2% today in France [46] and from 1.7 to 4.1% in the United States [47].

If one compares the recurrence rate of stones between men and women, one can state that all stone types recur more frequently in men, with the exception of ammonium urate, uric acid dihydrate, brushite, and the stones of an obviously genetic origin (cystine and dihydroxyadenine) for which one observes no significant difference in recurrence rates between the sexes. These data suggest a role

for environmental factors, particularly nutritional differences, for those stone types that are more recurrent in men; conversely, endogenous metabolic disorders, congenital or acquired, for which stone occurrence is linked to the nature of the metabolic abnormality rather than to environmental factors, seem to be more important for those stone types for which recurrence does not differ between the sexes.

Relationship between stone recurrence and morphology

A unique aspect of the present study is the examination of relationships between stone recurrence and morphologies of stones, which can differ even within the same compositional class. For example, even though the overall recurrence rate of COM stones was relatively low, the recurrence rates of some morphologies of COM were significantly higher (Fig. 4). We are aware of the relatively small number of stones regarding some morphological types. However, despite this limitation, the significant differences between stones types for the same crystalline species may alert us on special risk factors related to such stone types. Thus, recognition of more recurrent morphologies of COM in a patient could be of benefit in diagnosis and treatment.

Among stones composed mainly of COD (type II), the sub-type IIb was found to be significantly less recurrent than were the sub-types IIa or IIa + IVa1, the latter of which was more recurrent than the mean for all stones, whether just for men or for the entire series. However, these recurrence rates among morphological forms of COD stones—in contrast to what was observed for COM—are relatively small, perhaps reflecting the overall influence of hypercalciuria in the formation of this mineral type [11–13].

Among stones composed mainly of carbapatite, the morphology of type IVa2 (stones with an irregular but shiny surface, with subsurface cracks visible beneath the translucent surface coat) correlated with a higher incidence of recurrence than for other carbapatite stones. In our experience, these stones are associated with all conditions of distal tubular acidosis, i.e., Sjögren syndrome, inherited renal tubular acidosis, medullary sponge kidney [48]. In contrast, carbapatite morphology IVb (heterogeneous surface composed of incomplete layers with varying texture and color, including bumpy/rough regions) was less recurrent, especially in women. This morphology is frequently associated with infection [9], so the difference in its recurrence between men and women could be related to a poorer detection and/ or a less effective medical surveillance for men in this context than for women.

At last, we found differences in the occurrence rate according to the presence or not of a RP. It was shown since more than twenty years that RP is now the main factor involved in initiating calcium oxalate stone formation [49–51]. Based on visual inspection of papillae thanks to ureteroscopy, it was reported that most calcium stone formers exhibit multiple papillary calcifications [52]. On the other hand, it was reported a higher occurrence of kidney stones related to the papillary coverage by Randall's plaque [53]. Thus, it would be expected that stones developed from RP should be especially at risk to recur. As shown in Table 5, the difference between stones developed from RP and similar stones developed without RP is not so high. However, when stone types are taken into account, calcium oxalate stones made of a combination of COM and COD (mixed types I + II and II + I) are significantly more recurrent than stones exclusively made of COM, suggesting that metabolic differences could exist between patients producing these different types of stones. Further studies are needed to confirm such hypothesis.

In conclusion, recurrence of urolithiasis is quite variable, being correlated with not only the crystalline composition of the stones, but also with morphological types and certain other structural characteristics. Among calcium oxalate stones, COD stones recur considerably more often than do stones composed of COM. Among calcium phosphate stones, octacalcium phosphate and, above all, brushite stones are more recurrent than other phosphate stone compositions. Brushite stones are especially notable in this regard, not only for their high degree of recurrence, but also because they tend to recur as multiple stones and because the underlying causes of brushite stone formation have not yet been clearly established. Our results also show that the morphology of the stones is important. Thus, it would seem appropriate for clinical work not to limit stone analysis to stone composition only, but also to take into consideration the morphology of the stone, as this can help in diagnosis and in pinpointing the factors that are causative for stone formation, so that better measures for prevention of stone recurrence can be prescribed for each patient.

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