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Changes in stone composition according to age and gender of patients: a multivariate epidemiological approach

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Abstract Urinary stone incidence and composition have changed markedly over the past half-century in industrialized countries, in parallel with profound changes in living standards and dietary habits, with a dramatic increase in the incidence of calcium oxalate stones. However, studies evaluating the influence of age and gender on the distribution of the various types of urinary calculi are scarce. We report the results of a study based on 27,980 calculi (from 19,442 males and 8,538 females) analyzed by infrared spectroscopy between 1976 and 2001. The relationships between age and sex and stone composition were investigated using a multivariate approach, based on correspondence factor analysis (CFA). We found a male predominance for calcium oxalate and uric acid, a female preponderance for calcium phosphate and struvite stones, and an increasing prevalence of uric acid stones with age in both genders. CFA was able to reconstruct in blind the age curve from stone composition. The first two axes of the multidimensional classification, which correspond to age, included 86.9% of the total variance, indicating that age was the main factor involved in stone type. Superimposition of age classes and stone components showed a strong relationship between age and whewellite, weddellite, brushite, carbapatite, octacalcium phosphate and uric acid, while other substances (whitlockite, amorphous carbonated calcium phosphate, struvite, proteins, mucopolysaccharides, triglycerides or ammonium urate) appeared weakly related to age. In addition, CFA suggests the role of common lithogenic factors between weddellite, carbapatite and brushite, which clustered in the same area, whereas the various crystalline forms of phosphate stones segregated into two different clusters, suggesting distinct pathogenic factors. In conclusion, this study provides a picture of the present epidemiology of urinary stones in France. CFA helped to confirm: (1) an etiopathogenic distinction between weddellite and whewellite, (2) etiopathogenic associations between chemical compounds, which were only suspected on a clinical basis, and (3) suggested yet unrecognized associations, especially with respect to the heterogeneous group of phosphate stones.

Keywords Urolithiasis · Correspondence factor analysis · Age · Sex · Epidemiology · Infrared spectroscopy

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Introduction

Nephrolithiasis is a cosmopolitan disease, occurring in both industrialized and developing countries and mainly affecting adults aged 20–60 years. All recent studies from the United States, Europe and Japan conclude that the prevalence of nephrolithiasis has been relentlessly increasing for about half a century, in parallel with the progressive increase in animal protein intake, which itself reflects the gradual rise in living standards [3, 32, 37, 38, 39]. Accordingly, stone composition has changed from predominantly urate and phosphate to calcium oxalate (CaOx), now the main component of 60–80% of stones [3, 11, 12, 28]. The number of women affected by nephrolithiasis rose in the past decades but the male:female ratio still remains close to 2 in most industrialized countries [3, 37, 28, 39]. Presently, CaOx and uric acid (UA) stones are more frequent in males than in females, whereas calcium phosphate (CaP) and struvite stones are more prevalent in females [18, 34]. However, only few reports to date have considered the relationship between stone composition and patient's age.

In 1980, Robertson et al. [34] reported that in Great Britain the peak of calcium urolithiasis frequency was observed at between 40 and 50 years, while the corresponding peak for UA stones was observed beyond 60 years. In Japan, Koide et al. [25] reported a frequency peak at 30–40 years for weddellite (Wd) stones compared to 40–50 years for whewellite (Wh) stones. In 1995, we reported our experience based on 10,617 calculi analysed by infrared spectroscopy between 1981 and 1993 [11]. We pointed out the increasing frequency of UA stones with patient's age and their predominance in males, with a frequency peak in the age range 60–70 years in both genders, and a sex ratio of 4.6.

In the present study, we examine the relationship between stone composition and patient age in the extended series of consecutive calculi analyzed in our laboratory over the past 25 years. The main characteristics of this study are: (1) the large number of stones included (about 28,000), (2) the results of stone analysis, which are expressed according to the relative contribution of each compound to the whole series of calculi, and (3) the methodology based on a multivariate approach, correspondence factor analysis (CFA), derived from the χ^2 metrics.

Materials and methods

From 1976 to 2001, 27,980 calculi were analyzed by infrared spectroscopy at the Laboratoire Cristal. They came from patients aged from 3 months to 99 years, of whom 19,442 were males and 8,538 were females. Each stone was analyzed according to our previously published protocol [10]. In short, morphological examination of both surface and section was followed by sequential Fourier transform infrared spectroscopic analysis (FTIR) from the core to the surface of the stone. Finally, a global powder of the sample was analyzed in order to quantify the relative proportions of the various components. Only the qualitative and quantitative composition obtained from the whole stone powder constituted the study material in this report.

Data on stone composition were restricted to the 18 most frequent natural components among a total of 90 components identified in urinary calculi. The other 72 components, including drugs, were grouped into one class.

Frequencies were compared using the χ^2-test. Correspondence factor analysis (CFA) [5, 20] was used to analyze associations between the chemical type of the stones, age and gender.

Results

Whole series

Stone distribution according to the patient's age for both genders is given in Table 1. The overall male:female (M:F) ratio was 2.28. The M:F ratio was the highest in young children, whereas it was the lowest in teenagers and young adults, as well as in very old subjects. A sex ratio ≥2 was consistently observed in the age groups between 30 and 79 years with a maximum in the age group 50–59 years. The highest number of calculi was observed in the age groups 40–49 and 30–39 years in males and females, respectively.

Table 2 gives the relative proportions of the various stone components in the whole series of 27,980 stones. CaOx was by far the most prominent component in both genders (64.2% in males, 54.8% in females). The monohydrate form (whewellite, Wh) was 1.9 times more abundant than the dihydrate form (weddellite, Wd) in males and 2.8 times more in females. Wd was significantly more prevalent in males than in females ($P < 0.0001$). CaP, as carbapatite, was the second more abundant chemical component in stones and the third as crystalline species after Wh and Wd. It was twice as abundant in females as in males ($P < 0.0001$). The third component was UA in its anhydrous form (UA0), which accounted for nearly 7% of stones and was more prevalent in males than in females (7.8% vs 4.9%, $P < 0.0001$). Cystine (Cys) calculi represented 0–9.6% of stones depending on the age and sex of the patients; their frequency peak being observed in the second decade in both genders. All other components, including struvite, were under the threshold of 5%.

Stone composition in males according to age

In male patients, CaOx was the main component in every age class from 10 up to 80 years (Fig. 1). Before

Table 1 Distribution of urinary calculi according to age and gender of the patients. [a] Not significant, [b] $P < 0.05$, [c] $P < 0.01$, [d] $P < 10^{-5}$ vs males

Age (years)	Number	%	Males	%	Females	%	Sex ratio M:F
0–9	602	2.2	436	2.2	166	1.9[a]	2.63
10–19	597	2.1	304	1.6	293	3.4[d]	1.04
20–29	3,221	11.5	1,967	10.1	1,254	14.7[d]	1.57
30–39	6,062	21.7	4,139	21.3	1,923	22.5[b]	2.15
40–49	6,378	22.8	4,636	23.8	1,742	20.4[d]	2.66
50–59	4,953	17.7	3,644	18.7	1,309	15.3[d]	2.78
60–69	3,690	13.2	2,633	13.5	1,057	12.4[c]	2.49
70–79	1,940	6.9	1,340	6.9	600	7.0[a]	2.23
80–89	467	1.7	300	1.5	167	2.0[b]	1.80
≥90	70	0.3	43	0.2	27	0.3[a]	1.59
Total	27,980	100.0	19,442	100.0	8,538	100.0	2.28

Table 2 Relative proportion of stone components (%) ($n = 27{,}980$). ACCP = amorphous carbonated calcium phosphate. [a] Not significant, [b] $P < 0.01$, [c] $P < 0.0001$, [d] $P < 10^{-5}$ vs males

Constituants	Total no. (%)	Males (%)	Females (%)
Whewellite (Wh)	12,313 (43.7)	8,940 (46.0)	3,373 (39.5)[d]
Weddellite (Wd)	6,011 (21.5)	4,705 (24.2)	1,306 (15.3)[d]
Carbapatite (CA)	3,562 (12.7)	1,923 (9.9)	1,639 (19.2)[d]
Uric acid anhydrous (UA0)	1,932 (6.9)	1,515 (7.8)	417 (4.9)[d]
Proteins (PROT)	995 (3.6)	602 (3.1)	393 (4.6)[d]
Struvite (MAP)	614 (2.2)	272 (1.4)	342 (4.0)[d]
Uric acid dehydrate (UA2)	509 (1.8)	407 (2.1)	102 (1.2)[c]
Cystine (CYS)	375 (1.3)	213 (1.1)	162 (1.9)[c]
ACCP	359 (1.3)	154 (0.8)	205 (2.4)[d]
Brushite (Br)	300 (1.1)	232 (1.2)	68 (0.8)[b]
Ammonium urate (AmUr)	165 (0.6)	96 (0.5)	69 (0.8)[b]
Whitlockite (WK)	153 (0.6)	76 (0.4)	77 (0.9)[c]
Octocalcium phosphate (OCP)	101 (0.4)	58 (0.3)	43 (0.5)[b]
Mucopolysaccharides (MPS)	97 (0.3)	37 (0.2)	60 (0.7)[d]
Triglycerides (TRG)	70 (0.3)	19 (0.1)	51 (0.6)[d]
Sodium urate (NaUr)	29 (0.1)	20 (0.1)	9 (0.1)[a]
Miscellaneous	395 (1.6)	173 (0.9)	222 (2.6)[d]

the age of 10, CaPs, particularly carbapatite, were the most prevalent components. Among CaOxs, Wd was the preponderant crystalline species in young patients, especially in the age class 20–29 years; beyond this, its prevalence continuously decreased to only 4–5% in patients aged 80 years or more. In contrast, the proportion of Wh progressively rose from 10.5% in patients aged 0–9 years to 53.5% in the age class 50–59 years and then slowly decreased to reach 29.1% in patients aged 80 years or more. The prevalence of UA continuously increased with age. UA represented less than 2% of stones in patients under 30, and rose to 11.6% in the age class 50–59 years, 20.3% in the age class 60–69, 29.4% in the age class 70–79 and 40% in men aged ≥80 years. CaPs were the most abundant components of stones in children aged less than 10 years (46.2%). Thereafter, their proportion continuously declined to reach 9.3% in the age class 50–59 years; beyond this age, the proportion of CaPs increased slightly to reach about 12% in patients aged 60–90 years. Magnesium ammonium phosphate (MAP, or struvite), similarly to CaPs, was more frequent at the extremes of life (about 10%); its proportion was especially low (0.5%) in the age class 40–49 years. The frequency peak of ammonium urate stones was observed in the age class 0–9 years (5.3%). Thereafter, the proportion declined rapidly. A slight increase in the frequency of these stones was observed in the elderly (1.8% and 2.4% in the age classes 80–89 and ≥90 years, respectively).

Stone composition in females according to age

The relative proportion of stone components observed in female stone formers differed in several ways from that observed in males (Table 2, Fig. 2). CaOx was the most abundant component of stones in all age classes. With regard to the crystalline species, Wd was more abundant in female patients (25.5%) than in their male counterparts (16.6%) in the first two decades ($P < 0.001$). Thereafter, its prevalence continuously decreased to reach 4.8% in women aged more than 90 years. The proportion of Wh stones reached a plateau of about 45% between 40 and 70 years. Stones mainly composed of carbapatite were significantly more frequent in female than in male patients. They were predominant (31.5%) in the age class 20–29 years. Thereafter, their relative proportion decreased slightly and stabilized at about 18% in patients aged 50 years or more. As observed in male stone formers, the proportion

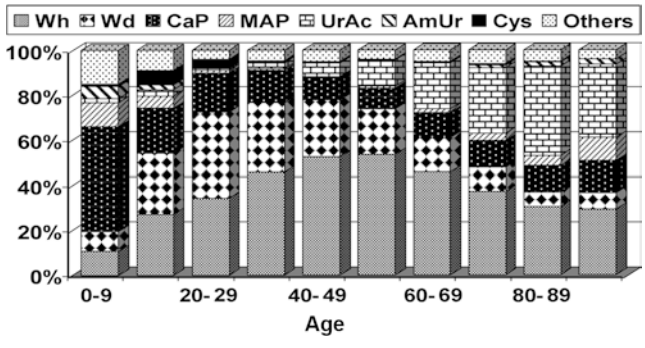

Fig. 1 Distribution of the main stone components in males according to age ($n = 19{,}442$ calculi)

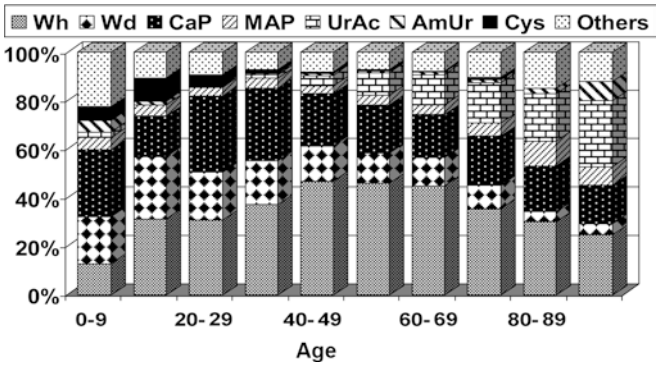

Fig. 2 Distribution of main stone components in females according to age ($n = 8{,}538$ calculi)

of UA rose continuously with age from 0% in the age class 10–19 years to 27.3% in patients aged 90 years or more. MAP was more prevalent in female than in male patients in all age classes. Its relative proportion ranged from 3.2% to 10.1% and was slightly higher at the extremes of life. The same was observed for ammonium urate stones, their proportion being 4.8% in the age class 0–9 years and 8% in the age class ≥90 years.

Correspondence factor analysis

Figure 3, which superimposes age classes and stone components, shows the succession of age classes based on stone composition as blindly reconstructed by CFA based on the whole series. The first two axes ϕ_1 and ϕ_2, corresponding to the age factor, embody 86.9% of the variance, meaning that age is by far the main determinant for stone composition at the epidemiological level. Only 13% of stones were dependent on other factors. The representative curve of patient's age is a horseshoe Guttman effect curve whose extreme values tend to draw nearer to one another. In male patients, age classes from 40 to 60 years were close to the barycentre (data not shown), indicating that stone disease in male patients is more frequent in these age classes. By contrast, in female patients (data not shown), age classes from 30 to 60 years were close to the barycentre, suggesting that the frequency peak of stone disease in these patients corresponds to slightly younger subjects than in males.

In the same figure, a number of compounds appear to be strongly related to patient's age, with differences according to the chemical nature of the components. Substances which best fit with the age curve are metabolic components, i.e. CaPs [except amorphous carbonated CaP (ACCP) and whitlockite (WK)], CaOx monohydrate (Wh) and dihydrate (Wd), Cys, and purines (except ammonium urate). In contrast, several components (MAP, ACCP, WK, proteins, triglycerides and mucopolysaccharides (MPS) are grouped as a dotted cloud close to the barycentre of the diagram and located inside the curve (close to the focal point of the "parabola curve"). This particular position suggests that these components are not related to the patient's age. All of these latter substances share the particularity of being present mainly or exclusively in calculi related to urinary tract infection.

As shown in Fig. 4, stone components may be grouped into four clusters according to their relative distances on the factorial map. The first cluster puts together Cys and dihydroxyadenine. The second, located in the area of young adults, gathers together Wd and the three CaP species octacalcium phosphate, brushite and carbapatite. The third cluster, which projects on the area of elderly patients, groups the anhydrous and dihydrate forms of UA together with sodium hydrogen urate. Interestingly, ammonium hydrogen urate and also sodium potassium urate (NKUr) are located very far from the other purines. Thus, they cannot be included in the cluster of purines. Finally, the fourth cluster, which is projected within the age curve, puts together MAP, ACCP, WK, MPS, proteins and triglycerides.

Discussion

This epidemiological study, based on the large number of calculi analyzed at our laboratory, describes the distribution of the main components of urinary stones as observed in France over the past 25 years. The main finding is a major influence of age on stone composition, despite differences according to gender, which has not

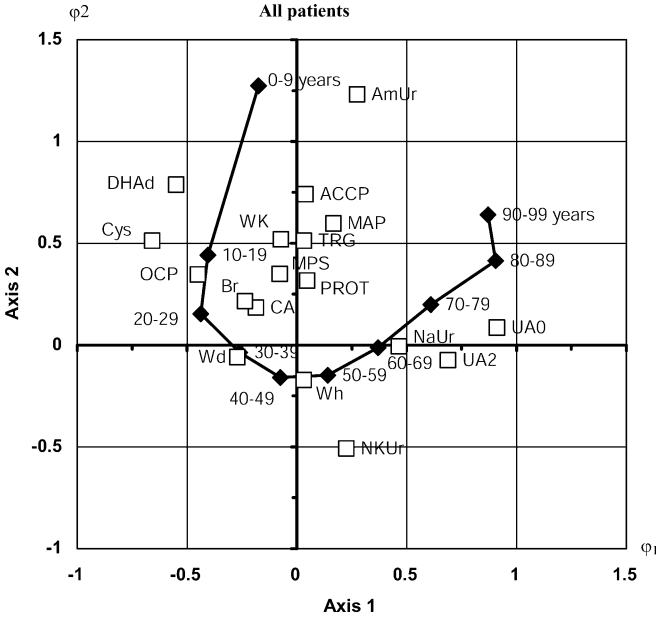

Fig. 3 Distribution of stone components by correspondence factor analysis in relation to patient' age (whole series)

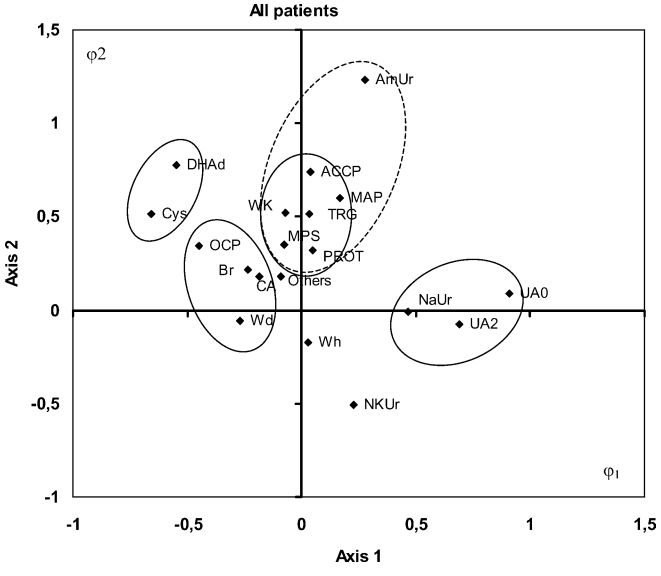

Fig. 4 Relationships between stone components by cluster analysis (both genders taken together)

yet been pointed out in a large series of stones analyzed during the past decades. In addition, multivariate analysis by CFA identified clusters of stone components superimposed on age classes, some of them not yet suspected. Such clustering indicates that these components share common etiopathogenic factor(s) and suggests that exploring possible pathophysiological links between the components would be of value.

A preponderance of male urinary stone disease, as well as the marked prevalence of CaOx as the major component in renal calculi, was observed in our series, as in all recent studies from other industrialized countries [26, 28]. However, no study to date has systematically analyzed the distribution of urinary stone components with respect to both age and gender. Our data, based on a large number of calculi, provide evidence that the composition of stones markedly differs according to the age of patients, as well as between males and females.

Among the crystalline forms of CaOx, Wd was found up to five times more frequently as the main component of stones in young adults than in older ones in both genders (Figs. 1, 2). However, the contribution of Wd as the main component of stones declined more rapidly in males (by about 5% every decade after the peak observed in the age class 20–29 years) than in females, in whom the mean rate of decline was 3% per decade between 50–80 years of age. Such a decline in the prevalence of Wd calculi with age may be related to the decrease in urinary calcium excretion with age [21, 27], as we observed that calculi mainly made of Wd electively form in hypercalciuric states [10, 13, 14], a finding confirmed by Asplin et al. [4] and Pierratos et al. [31]. As previously reported, the relationship between hypercalciuria and Wd is especially strong when Wd is the main component of the stone (86% of cases) [29]. The role of hypercalciuria as a major independent lithogenic factor was recently shown by Curhan et al. [9]. The especially slow rate of decline in the frequency of Wd stones in women aged 50–79 years may suggest that calcium and vitamin D supplements frequently prescribed to menopausal women in order to prevent or treat osteoporosis could result in hypercalciuria in at least some patients and thus contribute to Wd stone formation in menopausal women [8, 16].

Of interest, the distribution of calcium-dependent stones according to age has changed over the past 25 years in our series. As shown in Fig. 5, the decrease with age in the proportion of Wd stones observed in the recent years was less marked compared to the beginning of the study period, especially in women after the age of 50 years, but it was also detectable in men. One may speculate that this change may parallel the increasing practice of prescribing both calcium and vitamin D supplements to prevent bone loss following natural hormonal alterations related to age in our country.

In any case, this observation suggests that measuring urinary calcium excretion prior to and then some months after the initiation of vitamin D and/or calcium

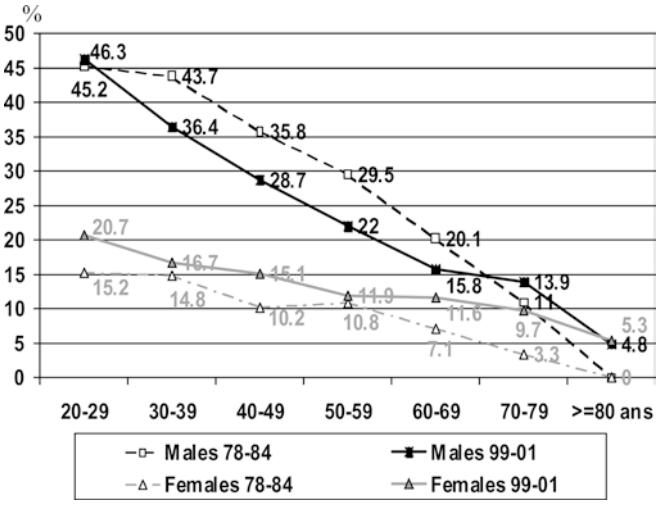

Fig. 5 Changes in the distribution of calcium-dependent calculi according to the age and gender of patients between the beginning and end of the study period

supplementation should be an advisable precaution in older patients, especially those having a history of stone formation or hypercalciuria.

In contrast Wh, which was found to be the commonest main component of calculi in both genders, is mainly associated with hyperoxaluric states [13, 14], but can also come from the crystalline conversion of Wd [6, 36] and may thus be initiated by transient hypercalciuria. In common forms of CaOx urolithiasis, elevated urinary oxalate concentration results chiefly from low urine volume, with post-prandial peaks of oxaluria initiating Wh crystal formation. The lithogenic role of insufficient daily diuresis has been established in recent studies [7]. The high prevalence of Wh stones in both genders in a wide age range is therefore a strong argument for recommending a high fluid intake to all calcium stone formers, either hypercalciuric or not [7].

Our data highlight a striking increase in the proportion of UA stones with age in both genders, especially beyond the age of 50, and a male predominance of UA nephrolithiasis. Overall, UA stones were about twice as frequent in males as in females in all age classes, but the rate of increase in prevalence with age was similar in both genders. Robertson et al. in the United Kingdom, have already reported a higher prevalence of UA stones in patients over 60 years [34]. In Japan, Ito et al. [22] reported, in a short series of patients, a marked male preponderance of UA nephrolithiasis (M:F ratio 11:1) and a peak of prevalence in subjects aged 50–60 years. In view of the well-established pH dependence of UA nephrolithiasis [30], the rising proportion of UA stones with age may be put in parallel with the progressive defect in urine ammoniagenesis that manifests with ageing [2], and which is considered the main factor of low urine pH in UA stone formers [24, 35].

Interestingly, a correlation between hyperuricemia, low urine pH, reduced ammoniagenesis and insulin resistance characteristic of metabolic syndrome has been

found recently in recurrent UA stone formers by Abate et al. [1]. The prevalence of metabolic syndrome increases with age in both genders, to exceed 40% in the population aged 60 years or more [17]. Thus, metabolic syndrome, the frequency of which is relentlessly rising in all western countries, could be a factor in acidic urine and UA nephrolithiasis in older patients. From a practical point of view, the search for the metabolic syndrome appears to be of good clinical practice in patients with UA nephrolithiasis, especially in those who are overweight and have hypertension.

The present study confirmed the markedly higher proportion of CaP stones in females than in males in all age classes, as reported by Robertson et al. [32, 34] and more recently by Gault et al. who found a higher urine pH in these patients than in patients with stones made principally of CaOx [19], thus suggesting a role for metabolic factors. An interesting finding in our study involves the significant differences found to be dependent on the crystalline phase. In particular, carbapatite (the most frequent form of CaPs), amorphous carbonated CaP and whitlockite all were found as the main component of stones twice as frequently in women as in men (Table 2). In contrast, brushite was significantly more prevalent in men, which suggests the role of different pathogenic mechanism(s) than in the other CaPs.

Struvite stones, commonly named infection stones, were nearly three times more frequent in females than in males, in all age classes, although they were slightly more frequent at the extremes of age. In addition, we found that a number of calculi, mainly composed of carbapatite, also contained struvite in variable amounts, thus indicating past or current urinary tract infection by urea-splitting bacteria [29]. These findings suggest that infectious factors are also involved in the pathogenesis of CaP stones [32], which appear as an heterogeneous group. In our experience, CaP stones were often associated with either UTI or both UTI and metabolic disorders, the latter being predominant in men.

CFA contributed to the disclosure of unsuspected associations, and confirmed suspected ones, especially in the field of CaP stones. As shown in Fig. 4, CaP-containing stones segregated into two separate clusters. The first, located in the area of young adults, groups carbapatite, brushite, OCP and Wd. This unsuspected association strongly suggests that these four components share the same lithogenic factor in common. This may be hypercalciuria, because Wd is typically calcium-dependent [10, 13]. In fact, we observed that most patients with stones mainly composed of carbapatite and, even more, brushite, exhibited marked hypercalciuria in addition to elevated urinary pH [29]. The role of hypercalciuria is thus supported by the findings of CFA. From a clinical point of view, the treatment of hypercalciuria should be an important part of the therapeutic strategy in these patients, together with an alteration of the urine pH. The second cluster groups struvite, whitlockite, ACCP, proteins, MPS and triglycerides in an area projected close to the barycentre, distant from the age curve. This location suggests that these compounds are not (or weakly) dependent on age, but rather on urinary tract infection, mainly but not only with urea-splitting micro-organisms, as previously reported [29].

The segregation of Cys and 2,8-dihydroxyadenine in the same cluster located in the area of young subjects is in keeping with the usual onset of these inherited types of nephrolithiasis in the second decade of life [23].

The anhydrous and dihydrate forms of UA and sodium hydrogen urate monohydrate appear in the same cluster projected on the area of elderly patients, in keeping with epidemiological observations. However, of note, ammonium hydrogen urate appears in another region, alone between the ends of the age curve (Fig. 3), a location which suggests an intervention of both age-related and non-age-related pathogenic factors. The former could be a high urinary urate concentration as often found in the youngest patients, whereas the latter involves a high ammonium concentration in the urine. Increased urinary ammonium excretion may result from two different situations. In industrialized countries, the main causes are the local formation of ammonium by urea-splitting micro-organisms, or a chronic occult diarrhoea due to laxative abuse [15]. In developing countries, the main mechanism involves infectious diarrheic episodes in young children receiving a phosphate-poor diet [33]. Thus, CFA confirms the distinct pathogenic pattern of urate compounds, which was suspected on a clinical basis.

Finally, Wh stones constituted a single cluster by themselves, located on the age curve but distinct from the cluster including Wd stones. This finding, which was obtained in a blinded, non-oriented fashion by CFA, confirms the hypothesis that Wd and Wh stones result from distinct metabolic abnormalities, namely high urinary calcium concentration in the former and high urinary oxalate concentration in the latter. Thus, calcium-oxalate stones should no longer be taken as a unique category. Instead, monohydrate and dihydrate forms should be identified using morphology and FTIR or X-ray analysis, as they result from distinct pathogenic mechanisms.

In conclusion, our data provide a picture of the epidemiology of urinary stones in France. They point out the increasing contribution of UA stones with age in both genders, and the preponderance of phosphate stones in females. CFA strongly supports a prominent role for age in the etiopathogeny of stones in both genders. In addition, CFA revealed common metabolic factor(s) between Wd and certain phosphate stones, and helped to identify distinct metabolic and infectious pathogenic factors among the heterogeneous group of CaP stones. This provided confirmation of associations that were only suspected on a clinical basis. From a clinical point of view, prospective studies should evaluate the possible lithogenic risk of calcium and vitamin D supplements in menopausal women (and in older men), and the relative contribution of metabolic versus infectious factors in patients with CaP stones.

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