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ORIGINAL ARTICLE

Composition of urinary calculi: Lessons from a French epidemiologic retrospective study

Composition des calculs urinaires : données épidémiologiques d'une population française

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Epidemiology;
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Summary
Introduction. — Urolithiasis is a common urological disease whose incidence increases in developed countries. We studied relations between composition of urinary calculi, age and gender.
Material. — An epidemiologic study was conducted in a French population of patients encountered analysis of urinary calculi between 2013 and 2017. This retrospective cohort study was performed from urinary calculi samples analysed in a clinical biochemistry laboratory of University Hospital of Lyon in France. A total of 5782 samples were included. Data, according to stone composition, presence of a papillary umbilication and a Randall's plaque, age and gender, were investigated. Statistical analyses used the Chi^2 test (R software).
Results. — The overall male to female sex ratio was equal to 1.76. The average and the median of age were 52.1 and 53.0 years, respectively. Whewellite was the most frequent main component in our population (44.4%). Carbapatite, weddellite and uric acid represented the main component in 14.0%, 13.4% and 13.0% of samples, respectively. Differences between genders were shown. Whewellite and uric acid were more frequent in men ($P < 0.001$), while carbapatite and struvite were predominant in women ($P < 0.001$).

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Conclusions. — Our study provided recent data on the composition of urinary calculi in a French population and the relations between composition of urinary calculi and age and gender.
Level of evidence.— 3.

MOTS CLÉS
Analyse morpho-constitutionnelle ;
Lithiase urinaire ;
Calculs urinaires ;
Épidémiologie ;
France

Résumé
Introduction. — La lithiase urinaire est une pathologie urologique fréquente dont l'incidence ne cesse d'augmenter dans les pays industrialisés. Nous avons étudié les relations entre la composition du calcul urinaire, l'âge et le sexe au sein d'une population française.
Matériel. — Une étude épidémiologique rétrospective a été menée de 2013 à 2017 en France. Cette étude a inclus 5782 échantillons de calculs urinaires analysés au sein du laboratoire de biochimie des Hospices Civils de Lyon. Les données recueillies ont concerné le composant majoritaire des calculs urinaires, la présence d'une ombilication papillaire et d'une plaque de Randall, l'âge et le sexe. Les analyses statistiques ont été réalisées en utilisant le test du Chi^2 (logiciel R).
Résultats. — Le sexe-ratio H/F de la population étudiée était égal à 1,76. L'âge moyen était de 52,1 ans et l'âge médian de 53,0 ans. La whewellite a été identifiée comme le composant majoritaire le plus fréquent (44,4 %), suivie par la carbapatite (14,0 %), la weddellite (13,4 %) et l'acide urique (13,0 %). Des différences significatives, concernant le composant majoritaire des calculs urinaires, ont été montrées en fonction de l'âge et du sexe. La whewellite et l'acide urique étaient plus fréquents chez les hommes ($p < 0{,}001$) alors que la carbapatite et la struvite ont été majoritairement retrouvées chez les femmes ($p < 0{,}001$).
Conclusion. — Notre étude apporte des données récentes concernant la composition des calculs urinaires au sein d'une population française et sur la relation entre composition des calculs urinaires, âge et sexe.
Niveau de preuve.— 3.

Introduction

Urolithiasis is a common urological disease characterized by the presence of one or many calculi in kidney and/or urinary tract. Its incidence increases in developed countries [1]. Frequency and nature of urolithiasis depend on geographical area, age and gender [2,3]. In developed countries, the prevalence ranged from 3% to 15% for adults in Europe (3% for women in Iceland, 15% for a rural population in Greece) [1,2]. The male to female sex ratio decreased over decades but was reported to be maintained over 1 in developed countries: 1.3 in United States in the beginning of the 21th century [4], 2.3 in France in 2004 [5], 2 in Italy in 2011 [6]. Stone composition differs according to stone location and also to geographical area. For example, while calcium oxalate is the predominant component in developed countries, ammonium urate is endemic in developing countries [2,7,8].

Recurrence rate of urinary calculi is elevated as it occurs in 40—50% of affected persons [9]. Stone recurrence depends on main component and also on the morphological characteristics of stones. Indeed, stone diseases due to inherited or acquired pathologies like stones containing 2,8-dihydroxyadenine or cystine showed higher recurrence rates than stone diseases resulting from dietary imbalance and/or chronic insufficient water intake [9]. Thus, it is important to determine the composition of urinary calculi and its morpho-constitutional type since the first episode of stone disease. The morpho-constitutional analysis is crucial in patient's care because composition and morphology of urinary calculi reflect the metabolic disorder causing urolithiasis. It provides information on clinical relevance for etiologic diagnosis and therapeutic strategy [10,11].

In this study, we aimed to describe a French population of patients encountered analysis of urinary calculi between 2013 and 2017 and to investigate data related to stone composition, age and gender.

Patients and method

This retrospective and descriptive study included all samples of urinary calculi analysed in the biochemistry laboratory of the University Hospital of Lyon in France from January 2013 to December 2017. Patient recruitment was from hospital structures and clinics. Exclusion criteria were: samples too small to obtain an infrared spectrum, artefact like real stones and other biological matrix like dried blood.

Urinary calculi were submitted to morpho-constitutional analysis. Briefly, they were described using a stereomicroscope and then they were crushed and diluted with potassium bromide. The powder was pressed into a pellet. Finally, the mid infrared spectra of each sample was acquired with a FTIR Tensor 27® (Bruker) between 4000 and 400 cm^{-1}. Thus, the composition of samples and the relative proportion of each component were determined by comparison with databases.

Statistical and epidemiologic analyses were performed on the following parameters: gender, age, main component, presence of a papillary umbilication and a Randall's plaque. The main component was defined as the component representing more than 50% if the sample contained two components, more or equal than 35% if the sample contained three components, etc. Statistical analyses used the Chi^2 test (R software).

This retrospective study was approved by the local IRB (*Comité d'Éthique des Hospices Civils de Lyon*, November 19th, 2018).

Results

Description of the cohort

A total of 5852 samples were analysed. Seventy samples were excluded from the study because they were not urinary calculi for 60 samples (dried blood, geological stones like quartz or granite) or too smaller for 10 samples. Therefore, this retrospective study was conducted on 5782 samples.

Papillary umbilication was observed in 5.9% of samples and a Randall's plaque was seen in 36% of samples with papillary umbilication. Therefore, a Randall's plaque was present in 2.1% of the overall samples and on 4.8% of samples containing whewellite as the main component.

Gender and age

The overall male to female sex ratio was equal to 1.76. The sex ratio remained above 1 whatever the age. The average and the median of age were 52.1 and 53.0 years, respectively. The younger patient was 2 days old and the older 97 years old. The distribution of samples combining age and gender is presented in Fig. 1. Distribution of urinary calculi according to patient's age showed that more than 50% of samples were removed or spontaneously expelled between 40 and 69 years for both men and women. A prevalence peak was observed for women between 50 and 59 years while the prevalence showed a plateau at ages 40 to 69 years for men. The prevalence peak of women between 50 and 59 years caused a slight break in the male to female sex ratio. Paediatric calculi represented 3.5% of the population.

Main components of urinary calculi

Distribution of main component for overall population and combining gender is presented in Table 1. The twelve following components, classified in order of decreasing frequency, were identified as main component in at least one sample: whewellite, weddellite, carbapatite, uric acid, brushite, struvite, cystine, ammonium urate, proteins, drugs, sodium urate and 2,8-dihydroxyadenine. Drug containing samples were composed of triamterene and metabolites for one, and atazanavir and metabolites for the other. The term ''weddellite/whewellite'' represents samples constituted with a core of whewellite covered with macrocrystals of weddellite. Among samples containing whewellite as main component, Ia morphology was much predominant representing more than 97% of samples. Ic or Ie morphology was found in 0.1% of cases. Among samples containing carbapatite as main component, IVa2 morphology, a morphology related to a specific diagnosis, was observed in 3% of calculi.

The proportion of samples constituted mostly by whewellite and uric acid was significantly higher in men than in women ($P < 0.001$). Inversely, carbapatite and struvite were significantly more often the main component of samples in women than in men ($P < 0.001$). The relative risk (RR) for a man with urolithiasis to present whewellite as main component compared to a woman with urolithiasis was 1.2. The RR for uric acid, carbapatite and struvite were 1.5, 0.4 and 0.4, respectively. For weddellite, brushite and cystine, no significant difference was observed between genders. For the other components, statistical analysis was not carried out because there were not enough samples.

The distribution of main component depending on age and gender showed an evolution for components (Fig. 2). Thus, some components increased with age. This is the case of whewellite which presented a maximum between 60 and 69 years in men and uric acid whose increase started from 40 years. Conversely, weddellite decreased with age. Carbapatite also decreased with age, mainly in men. In women, carbapatite remained the main component in more than 15% samples whatever the age. Struvite as main component showed two maxima at extreme ages (4.7% between 0 and 9 years and 4.0% after 80 years). Including all samples containing struvite even as minor component, it represented 4.6% of samples from adults with predominance in women (63%). In the paediatric population, carbapatite was the most frequent main component between 0 to 9 years in both genders (37.3% in male, 35.4% in female). From 10 to 17 years, whewellite and weddellite were the predominant main component, representing 63.8% of the samples. Brushite was more frequent in children than in adults (11.2% between 0 to 9 years and 9.2% between 10 to17 years). Cystine calculi were rare and presented a higher prevalence in children between 0 to 9 years with a value of 3.7%.

Discussion

This retrospective study including 5782 samples of urinary calculi presents a recent overview of epidemiological data of urinary calculi in the eastern center of France. This large scale study provides data from morpho-constitutional analysis of urinary calculi from 2013 to 2017 and updated results compared to precedent large scale studies conducted in France since 25 years [5] and in Germany since four decades [12].

Gender and age

Urinary lithiasis may occur at all ages in life, up to over 80 years. Indeed, patients over 80 years represented 6.5% of

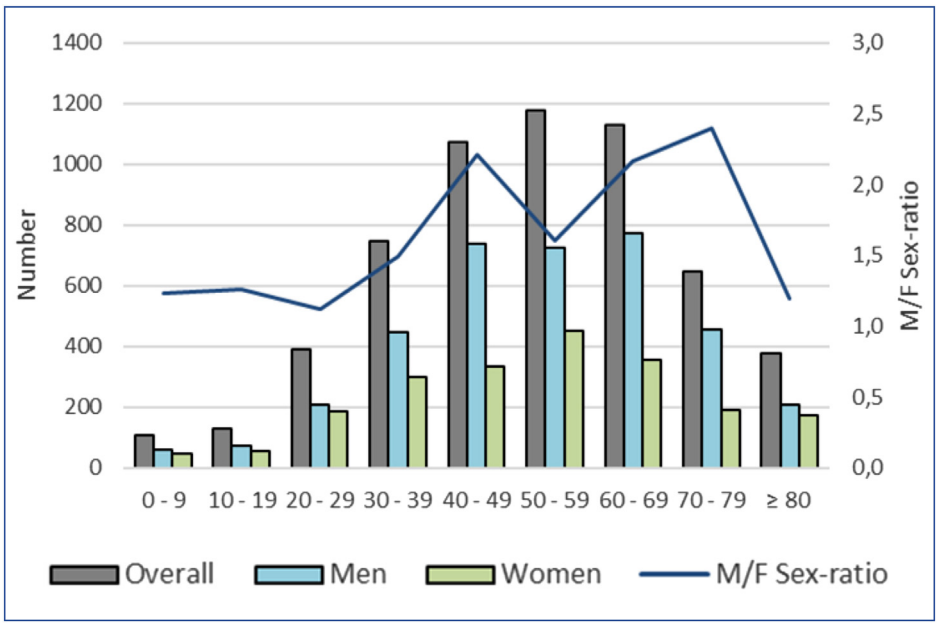

Figure 1. Distribution of samples combining age and gender. The male to female sex ratio is represented by the curve.

Table 1 Distribution of the main component according to the gender.

	Total		Men		Women		*P* (Chi^2)
	n	Percentage	*n*	Percentage	*n*	Percentage	
Number of samples	5782		3685		2097		
Whewellite	2565	44.36	1732	47.00	833	39.72	< 0.001
Weddellite	775	13.40	512	13.89	264	12.59	NS
Weddellite/Whewellite	539	9.32	375	10.18	164	7.82	< 0.01
Uric acid	752	13.01	550	14.93	202	9.63	< 0.001
Sodium urate	4	0.07	1	0.03	3	0.14	NA
Ammonium urate	23	0.40	17	0.46	6	0.29	NA
Carbapatite	809	13.99	321	8.71	488	23.27	< 0.001
Struvite	95	1.64	39	1.06	56	2.67	< 0.001
Brushite	155	2.68	102	2.77	53	2.53	NS
Cystine	41	0.71	21	0.57	20	0.95	NS
2,8-dihydroxyadenine	1	0.02	0	0.00	1	0.05	NA
Proteins	17	0.29	12	0.33	5	0.24	NA
Drugs	5	0.09	3	0.08	2	0.10	NA

NS: not significant; NA: not applied. Results are expressed as number and percentage. Significant *P*-values of Chi^2 test between genders are presented.

our cohort. However, the incidence is greater between 40 and 60 years [1,6]. Average age found for the overall population in our study is in agreement with values reported recently in the south of France and in an Italian urban population: 50.7 and 52.9 years, respectively [6,8]. These values are a bit higher than mean age reported in the United States (48.1 years) and in China (50.0 years for men and 45.9 years for women) [4,13]. Concerning the age distribution according to gender, a plateau between 40 and 69 years was shown in our study for men. A similar plateau was raised by Knoll et al. in a German study at ages 30 to 69 years for men with calcium containing calculi [12]. In a French study, Daudon et al. reported a peak between 40 and 49 years for men in France and Wang et al. between 50 and 59 years in China [5,13]. The peak prevalence observed for women in our study between 50 and 59 years is shifted compared to Knoll et al. and Wang et al. who described a peak between 60 and 69 years [12,13]. Daudon et al. reported a lower range for age which was between 30 and 39 years [5]. We hypothesized that the differences about age distribution observed between our results and data from the French study were due to changes in diet, work and lifestyle since the end of the 20th century and the current decade. For differences between our study and foreign studies, environment risk

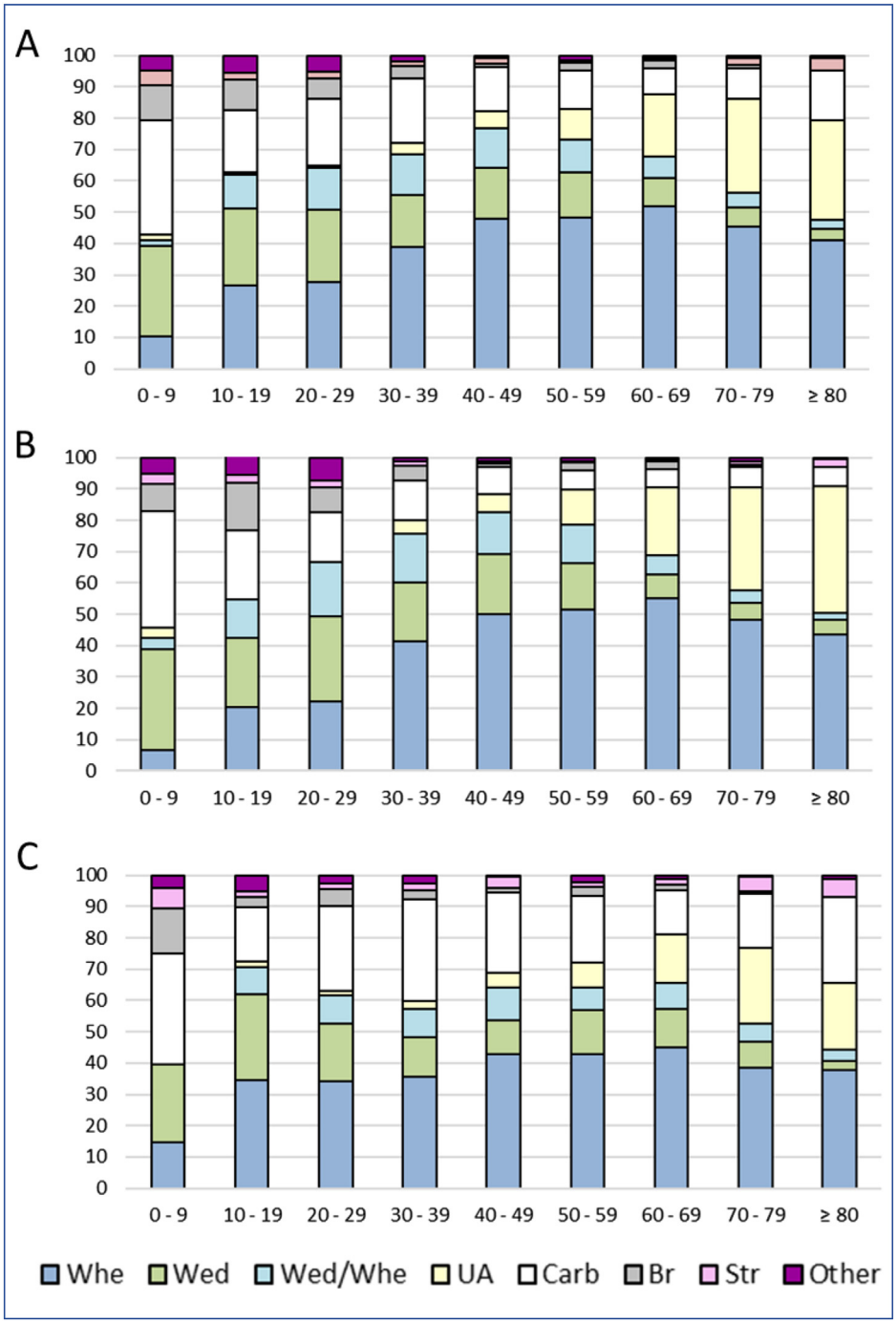

Figure 2. Distribution of main component depending on age and gender. A. Overall. B. Men. C. Women. Whe: whewellite; Wed: weddellite; UA: uric acid; Carb: carbapatite; Br: brushite; Str: struvite. The term ''Other'' includes cystine, ammonium urate, drugs, proteins and 2,8-dihydroxyadenine.

factors like diet, lifestyle and climates could be raised since they are known to be associated with stone prevalence [3].

Stone disease is known to be more frequent in men than women with a sex ratio of 1.5 to 2.5 across the world [1]. Despite the gap in prevalence between men and women tends to narrow [4], the male to female sex ratio (1.76 in our population) remained above 1. For the paediatric population, Luque Paz et al. reported a switch of the sex ratio after 12.5 years in a French study [14]. This observation was not confirmed in our study since sex ratio remained above 1. According to ages, a decrease of the sex ratio was observed between 50 and 59 years in our study. No significant difference ($P > 0.05$) was shown for the proportion of the main component between the age class 40—49 years and the age class 50—59 years. The hypothesis of the menopause as main factor leading to this decrease of the sex ratio may be suggested. Indeed, postmenopausal status was independently associated with a higher risk of a kidney stone in a study

conducted by Prochaska et al. The mechanism leading to this higher risk of kidney stones remains unclear [15].

Main components

As known since several decades, calcium oxalate remains the most frequent main component of urinary calculi in developed countries whatever the gender [5,13]. Calculi containing calcium oxalate as the main component represented 67% of cases. It is in agreement with other European studies reporting 65% and 74%, and with a recent Chinese study (67%) [5,13,16]. Among calcium oxalate calculi, the monohydrate form whewellite is by far the most prominent component in both genders. Renal Randall's plaques were demonstrated to play a role in calcium oxalate stone formation. Randall's plaques are small deposit made of calcium phosphate and located at the surface of the tip of papilla [17,18]. Its incidence was reported to be significantly higher in patients with calcium oxalate or calcium phosphate stones than in patients without a history of urolithiasis [17]. In our study, only 4.8% of samples containing whewellite as the main component exhibited a Randall's plaque. This prevalence is much lower than those reported using endoscopy. Indeed, in a population of 24 patients, Matlaga et al. observed a Randall's plaque in 91% of papillae [19]. Most of urological procedures used to remove urinary stones are based on fragmentation of stones leading to small fragments and sand. Thus, the Randall's plaque, if present, is lost during the urological procedure. That's why the prevalence of Randall's plaque reported from biological analysis is underestimated. The ways to evaluate with precision the presence of a Randall's plaque are i) analysis of the intact urinary stones; ii) looking for of a Randall's plaque in the papillae during ureteroscopy.

After calcium oxalate, the next two most common main components were carbapatite and uric acid. For uric acid, although the occurrence depends on geographical area even for developed countries with large difference between United States, China or Germany, the prevalence is in accordance with data reported in Europe [12,16,20]. The prevalence of carbapatite in our population is a bit higher than values from Daudon et al. (12.3%) or Castiglione et al. (9.3%) [16,21]. Calculi composed with carbapatite are a heterogeneous group because they may be related to hypercalciuria and/or urinary tract infection [11]. As urinary tract infections are more common in women than in men and, moreover, as the male to female sex ratio in our study (1.76) was lower than other European studies (1.96 to 2.25), we could hypothesize that the higher prevalence of carbapatite containing calculi observed in our study may be linked to the higher percentage of women in the included population. For the others main components, data are correlated with the literature [5,12,16].

Relations between main component, age and gender

As already described in the literature, our study raised with a relation between the composition of calculi and gender, as well as age [5,16]. Whewellite was significantly more frequent in men than in women and remained the most frequent main component for adults aged over 30 years for both genders.

For weddellite, data from literature concerning a significant difference between genders present some discrepancies. Like our study, no significant difference was reported by Castiglione et al. in Belgium and by Menard et al. in the south of France [8,16]. In contrast, Daudon et al. observed a higher prevalence of weddellite in men than in women in a French population [5]. Some hypothesis may be suggested to explain the contradictory results: i) inclusion periods of the studies were different so the risk factors may have changed in connection with modifications in lifestyle; ii) dietary habits may differ between countries and regions within the same country. According to age, prevalence of weddellite as main component presented a peak between 0 to 9 years for men and between 10 to 19 years for women. This distribution is shifted to younger ages for men compared to Castiglione et al. and for women compared to Daudon et al. Then as already known, a decline in the prevalence of weddellite with ages was observed [5,16]. As the formation of weddellite is associated with hypercalciuria, this decline may be related to the decrease of the urinary excretion of calcium with age [5].

Concerning calculi composed of calcium phosphate, our results confirmed the markedly higher prevalence in women than in men in the adult's population, except for brushite [12,21]. For infection associated calculi, an increase appeared at the older age especially for women [12,16]. The female and elderly predominance may be in relation with the higher prevalence of urinary tract infections in women and over the age of 65 years [22]. For children under 10 years, calculi are mostly associated with an infectious cause [22,23]. Thus, carbapatite was reported to be the most frequent component in this paediatric population [14]. While our results confirmed the predominance of carbapatite in this population, the percentage of samples composed of struvite as a majority was much lower in our study (< 5%) than in a Dutch paediatric population (25%) [24]. In the latter study, struvite was considered for the statistical analysis even if it was not the main component. Taking into account this criteria, struvite was present in 10,2% of the paediatric samples in our study.

As is well known, uric acid calculi are more frequent in men than in women and the prevalence increases with ages in both genders [20]. A persistently low urinary pH is the main lithogenic factor of uric acid stones because it increases the formation of the insoluble form of uric acid. An inverse relationship between low urinary pH and insulin resistance has been demonstrated [25]. Mechanisms involved in this relationship appear not yet fully elucidated. Studies revealed that it could be linked with an insufficient ammonia production due to activation of the Insulin Receptor Substrate 2 (IRS-2) in proximal tubular cells by insulin resistance and/or a substrate competition by free fatty acids on the purine metabolism. Insulin resistance was also associated with low urinary levels of citrate, an inhibitor of crystallization [26,27]. Insulin resistance is a characteristic of metabolic syndrome and type 2 diabetes. Thus, uric acid urolithiasis was associated with type 2 diabetes with a higher percentage of uric acid stones in patients with than without type 2 diabetes [28]. As data from the World Health Organization and a French public agency indicated a

higher prevalence of diabetes in men than in women and an increase with ages, our results for uric acid, age and gender may be related to type 2 diabetes [29,30].

Conclusion

Our study provides recent data on epidemiology of urinary calculi in a French population. Our results agree with literature reporting a relation with the main component of urinary calculi and age and gender. A complementary study should be performed with the inclusion of clinical data like body mass index and data related to dietary habits.

Disclosure of interest

The authors declare that they have no competing interest.

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