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ORIGINAL ARTICLE

A new approach to urinary stone analysis acccording to the combination of the components: experience with 7,949 cases

F. Millán,[a,*] S. Gracia,[b] F.M. Sánchez-Martín,[a] O. Angerri,[a] F. Rousaud,[a] H. Villavicencio[a]

[a]Servicio de Urología, Fundació Puigvert, Barcelona, Spain
[b]Servicio de Bioquímica, Fundació Puigvert, Barcelona, Spain

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Abstract
Objective: To evaluate a new approach to urinary stone analysis based on the combination of their components.
Materials and methods: We analyzed a total of 7,949 stones and their main components and combinations of components and we classified them according to gender and age. We performed statistical analysis using the chi-square test.
Results: Calcium oxalate monohydrate (COM) was the most frequent component in both males (39%) and females (37.4%), followed by calcium oxalate dihydrate (COD) (28%) and uric acid (URI) (14.6%) in males and by phosphate (PHOS) (22.2%) and COD (19.6%) in females (p=0.0001). In young people, COD and PHOS were the most frequent components in males and females respectively (p=0.0001). In older patients, COM and URI (in that order) were the most frequent components in both genders (p=0.0001). COM is oxalate-dependent and is related to diets with a high oxalate content and low water intake. The progressive increase in URI with age is related mainly to overweight and metabolic syndrome. Regarding the combinations of components, the most frequent were COM (26.3%), COD+Apatite (APA) (15.5%), URI (10%) and COM+COD (7.5%) (p=0.0001).
Conclusions: This study reports not only the composition of stones but also the main combinations of components according to age and gender. The results prove that stone composition is related to the changes in dietary habits and life-style that occur over a lifetime, and the morphological structure of stones is indicative of the etiopathogenic mechanisms.

*Corresponding author.
E-mail: fmillan@fundacio-puigvert.es, fmillan@ono.com
(F. Millán).

PALABRAS CLAVE
Litiasis;
Análisis de la litiasis;
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Microscopía estereoscópica

Un nuevo enfoque en el análisis de la litiasis urinaria en función de la combinación de sus componentes: experiencia con 7.949 casos

Resumen

Objetivo: Evaluar un nuevo enfoque en el análisis de la litiasis urinaria en función de la combinación de sus componentes.
Material y métodos: Se analizaron un total de 7.949 litiasis y sus componentes principales y combinaciones, y se clasificaron en función del sexo y la edad. El análisis estadístico fue mediante el test de ji cuadrado.
Resultados: Oxalato cálcico monohidrato (OCM) fue el componente más frecuente en hombres (39%) y mujeres (37,4%), seguido de oxalato cálcico dihidrato (COD) (28%) y ácido úrico (URI) (14,6%) en hombres y de fosfato (PHOS) (22,2%) y COD (19,6%) en mujeres (p = 0,0001). En la gente joven COD y PHOS fueron los componentes más frecuentes en hombres y mujeres, respectivamente (p = 0,0001). En los pacientes mayores OCM y URI (por este orden) fueron los componentes más frecuentes en ambos sexos (p = 0,0001). OCM es oxalatodependiente y está relacionado con las dietas de alto contenido en oxalato y baja ingesta de agua. El aumento progresivo de URI con la edad se relaciona principalmente con el sobrepeso y el síndrome metabólico. Respecto a la combinación de componentes, las más frecuentes fueron OCM (26,3%), COD + Apatita (APA) (15,5%), URI (10%) y OCM + COD (7,5%) (p = 0,0001).
Conclusiones: Este estudio presenta no sólo la composición de las litiasis, sino también las principales combinaciones de componentes en función de la edad y el sexo. Los resultados muestran que la composición de la litiasis está relacionada con los cambios en los hábitos dietéticos y de estilo de vida que ocurren durante la vida, y la estructura morfológica de las litiasis es indicativa de los mecanismos etiopatogénicos.

Introduction

In recent decades the prevalence of urolithiasis in Europe and the United States has increased from 3.5 to 7% to 10-17%.[1-11] Moreover, as in other industrialized countries, the percentage of kidney stones and calcium oxalate[12] has increased, such that calcium oxalate stones are now more common in epidemiological studies. However, many stones have a mixed composition; according to Daudon, even 90%-95% have a mixed composition.[13] However, most studies published provided only the frequency of their main components, without providing information on the different combinations. We therefore believe that a study to analyze the different components and combinations of urinary calculi would help to identify possible etiopathogenic mechanisms of calculi. Thus, the purpose of this study was to identify the main components of urinary stones and their combinations in our population, which is representative of an industrialized country.

Materials and methods

Of our entire historical collection of nearly 60,000 urinary stones, we analyzed those obtained at our Lithiasis Unit from 1995 to 2005. The first step of the analysis was stereoscopic microscopy at 60x magnification. First we inspected the surface of the stone to discern whether it was complete or a fragment, and to determine whether it was a true or false stone. At the same time, we determined its possible papillary origin, its structure (morula, speculated, smooth or rough, polished or broken), its color, diversity and characteristics of the crystals (size, opacity, brightness, features and sharp angles) Secondly, to know the internal structure of the stone, we fragmented it with a scalpel blade, a small jeweler's hammer and a hard granite base. Special attention should be paid to the core, as it informs us on the stone's initial formation mechanism. At times there is a cavity in the core as a result of drying of proteins, organic material or clots. An internal examination of the stone also provides information on the fragments that act as nucleation elements and on its possible papillary origin. Finally, we analyzed the structure (organized or not, granular, porous, stratified, pseudostratified) and the color of the stones, which provide clues on their components and their age. All these observations allow differentiating several layers, whose morphological homogeneity is related to different factors involved in stone formation. Thus, these elements can help identify potential etiopathogenic mechanisms of calculi.

The second step of the analysis consisted of performing infrared photometry to identify and quantify the components of the stone in an objective manner. First we picked components of selected samples identified by microscopy; subsequently we analyzed representative samples to find out the proportions of the different components.

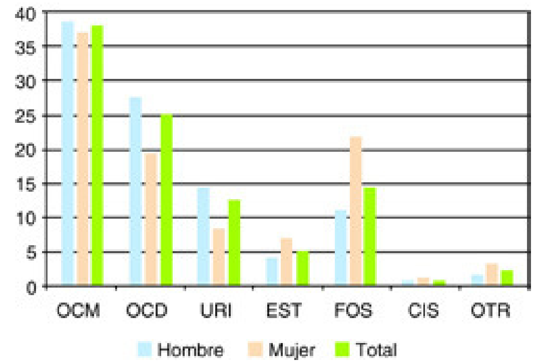

Figure 1 Principal component of calculi according to sex (%).

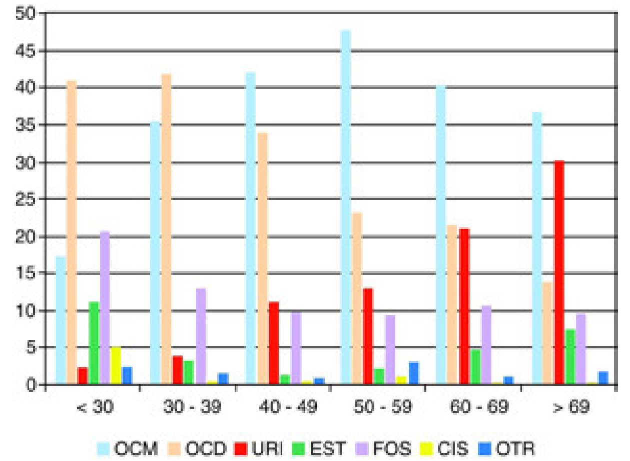

Figure 3 Principal component of calculi according to age in men (%).

As a result of the combination of the two methods, we classified the stones into 7 groups and 21 subgroups. The main groups were: COM (calcium oxalate monohydrate), COD (calcium oxalate dihydrate), URI (uric acid), PHOS (phosphate), STR (struvite), CYS (cystine) and OTH (Other). Since many of the stones were not pure, we also analyzed key combinations. All results were analyzed by gender and age percentiles (<30, 30-39, 40-49, 50-59, 60-69 and> 69 years). Statistical analysis was performed using the chi-square test and the results are given in percentages.

Results

7,949 urinary stones were obtained from 5,538 men (69.7%) and 2,411 women (30.3%).

The mean age of patients was 51.5 years (95% CI 51.2 to 51.9) and the most frequent age range was 50-59 years (20.8%), followed by 40 - 49 and 60-69 years (both 20.2%), 30-39 years (15.5%), > 69 years (12.8%) and <30 (10.5%).

The COM component was most common (38.5%), followed by COD (25.4%), PHOS (14.7%), URI (12.8%), STR (5.2%), OTH (2,3%) and CYS (1%) (fig. 1). By analyzing these data by gender, CMO continued to be the most frequent (39% men and 37.4% in women), the second most common was COD in males (28%) and PHOS in women (22, 2%) and the third, URI in men (14.6%) and COD in women (19.6%) (fig. 1). These differences were statistically significant (p=0.0001).

We also studied the frequency of the main components in terms of age (fig. 2). COD was the most common stone in younger patients (34.9% in children under 30 years and 35.2% in 30-39 years), but subsequently the frequency gradually decreased. PHOS stones showed a similar decreasing pattern, with the lowest percentages in the older patients (rate fell from 23.7% in patients younger than 30 years to 10.9% in those over 69 years). By contrast, COM and URI showed a mixed and increasing pattern, respectively. COM calculi showed a progressive increase, reaching a peak at 50-59 years (46.5%), with a slight subsequent decrease. On the other hand, URI stones showed progressive and steady increase with age, occupying second place in elderly people (20% in patients aged 60-69 years and 28.2% in those over 69 years). The remaining stones had low percentages. Among them, STR stones presented a "U" pattern, with the highest percentages at extreme ages (11.6 and 8.1% respectively), while the highest percentage of CYS was found in young people.

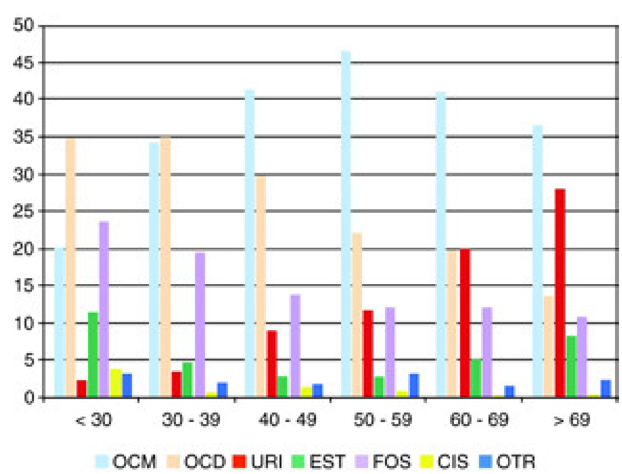

Figure 2 Principal component of calculi according to age (%).

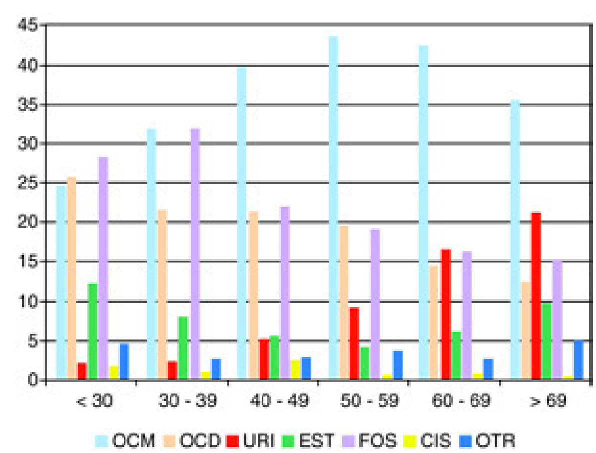

Figure 4 Principal component of calculi according to age in women (%).

Table 1 Mean age (years) according to stone components

	Total	Men	Women
COM	53.5	54.6	50.9
COD	47.1	47.6	45.7
URI	61.9	62.4	59.9
STR	49.2	51.7	45.7
PHOS	47.3	49	45.5
CYS	36.5	31.9	45
OTH	49.4	51.4	47
TOTAL	51.5	52.7	48.9

APA: apatite; CYS: cystine; EST: struvite; PHOS: phosphate; COD: calcium oxalate dihydrate; COM: calcium oxalate monohydrate; OTH: other; URI: uric acid.

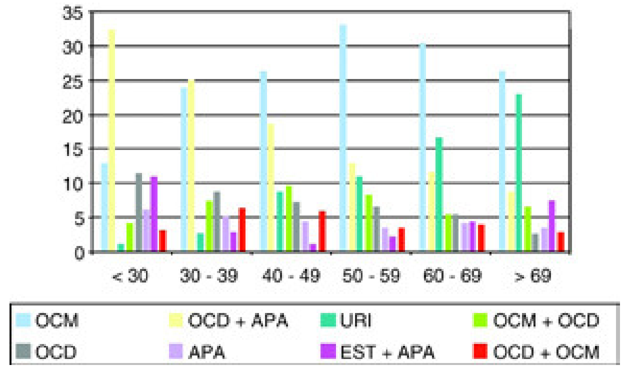

Figure 6 Component combinations according to age in men (%).

When we repeated the age analysis by gender, we found that the distribution in men (p=0.0001 [fig. 3]) was similar to that of the total series, but the distribution in women showed some differences (p=0.0001 [fig. 4]): thus, while COD was the most common stone in young men, PHOS was more frequent in women under 40 (28.4% in those under 30 years and 32% from 30 to 39 years) and the second most common in women aged 40-49 years. As in men, COM calculi were more common in women over 40 years, and the frequency of URI stones increased with age, but in both cases the percentages were lower. The mean ages for each type of stone are shown in table 1.

So far we have presented the results of the main groups of calculi. Figures 5-7 show the most common combinations. For this reason we use the term APA (apatite) instead of PHOS, since it is the most common phosphate stone. The first 3 groups (COM, COD + APA, URI) accounted for half of all combinations (51.8%) (fig. 5). Figure 6 and 7 show the combinations according to age in men and women, respectively. Data from these figures, whose differences were statistically significant (p=0.0001), are useful for predicting the most common combinations of stones depending on age and sex.

Discussion

The results of our study, with 7,949 cases, are quite comparable to other published studies, including larger study of 51,747 cases in France.[14] If our study is compared with the French study, it may be observed that the total number of percentages of PHOS (14.7 vs. 13.6%), URI (12.8 vs. 10.8%) and CYS/ OTH (3.3 vs. 2.6%) are similar, whereas in our study the percentage of COM / COD is lower (63.9 vs. 71.8%) and STR greater (5.2 vs. 1.3%). The reason for the foregoing differences may be the different origin of urinary stones in the French study samples were analyzed in several laboratories of general hospitals, whereas ours was performed in a single laboratory of a monographic urological hospital. For this reason, we received more complex cases, such as infectious staghorn calculi, and therefore the percentage of STR was higher. This is an important aspect that can lead to bias in the epidemiology of urinary stones: the more specialized a hospital is in calculi, the lower the percentage of oxalate stones it will have, because it will have a higher percentage of more complex and recurrent cases. Probably the percentage of oxalate calculi in the general population is higher than that published in epidemiological studies, because many of these patients only have one or two lithiasic episodes in their lifetime,[15] or they are not painful and lack complications, so many of these patients are not referred to a urologist. On the other hand, another factor that may have hindered calculi analysis in recent years is the small size of the fragments due to lithotripsy techniques. Therefore, in many cases it is not possible to find the initial nucleus or the stone layers.

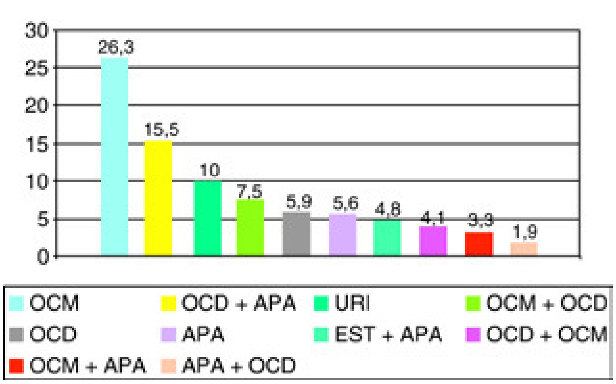

Figure 5 Component combinations (%).

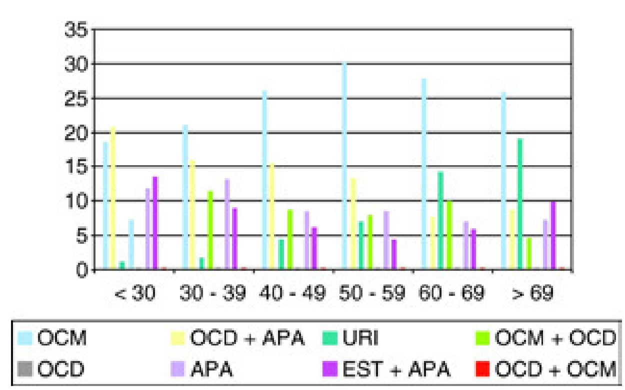

Figure 7 Component combinations according to age in women (%).

The male/female ratio in our study was 2.3:1. Scales et al.[16] found a lower and gradually decreasing ratio (from 1.7 to 1.3:1) from 1997 to 2002 in the United States. These authors suggested that factors associated with increased calculus risk in women were overweight and obesity. However, the male / female ratio published by Daudon[13] was similar to ours, with a slight increase in recent years. Additionally, he found a higher male / female ratio among relapsed patients compared with patients in their first lithiasic episode.

The most original aspect of this study, compared with those published previously, is that it provides a classification in accordance with the different combinations of their components. This is of interest because urinary stones typically have a heterogeneous composition, since according to different authors, 62%-95% of urinary stones have a mixed composition.[13,17] Consequently, based on the combination, this analysis provides more information than an analysis based only on the most important component. This study confirmed the frequent heterogeneity of urinary stones, as only 47.8% of the stones had a single component (COM 26.3%, URI 10%, COD 5.9% and APA 5.6%) (fig. 5).

The most important stone in both sexes was COM, alone (26.3%) or combined with COD (7.5%) or APA (3.3%) (fig. 5). COM presentation alone was more common in men older than 40 years (fig. 6) and in women over 30 years (fig. 7), with a gradual increase to a peak of 50-59 years and a gradual subsequent decrease in both sexes. While COM is oxalate-dependent, COD is calcium-dependent.[18,19] The high percentage of COM in both sexes in industrialized countries may be related to nutritional factors, such as diets high in oxalate and low water intake. The progressive increase in COM with age supports this theory based on nutrition and lifestyle. Moreover, the slight decrease in COM after 60 years does not refute this theory, since the cause of this decrease is not a change in the patient's habits, but an increase in the significance of URI stones. The combination of COM and COD was found in 11.6% of cases. The origin of these stones may be caused by intermittent hypercalciuria with hyperoxaluria, or a gradual conversion of COD to COM. Both COM and COD may be the main component (7.5 and 4.1% of all cases, respectively). The combination of COM and APA is very rare (3.3%) and can be found in Cacchi-Ricci syndrome and in cases of intermittent hyperoxaluria associated with non-urease producing infections.

The second most common type of stone was COD, combined with APA (15.5%), alone (5.9%) or combined with COM (4.1%) (fig. 5). COD was the most common type of urolithiasis in patients under 40 years due to the high prevalence in men, the peak incidence was in patients under 30 years, with a subsequent progressive decrease with age (figs 6 and 7). Since COD is calcium-dependent, the progressive decrease with age of COD-containing stones (more pronounced in women) can be considered a consequence of inadequate calcium intake (more evident in older women.) However, we found a higher percentage of calcium-dependents stones in older women in the years 1999-2001 compared with 1978-1984, attributed to an increased intake of calcium and vitamin D to prevent postmenopausal osteoporosis.[13] On the other hand, pure COD (5.9%) is the least frequent and is more frequent in combination with APA (15.5%) and COM (11.6%). APA promotes heterogeneous nucleation of COD stones and the combination with COM will depend on the level of associated hyperoxaluria or the conversion percentage of COD to COM (see above). However, the presence of primary hyperparathyroidism in patients with COD + PAC combination should be investigated.

The third most frequent group was that of phosphate stones (12.3%), APA (5.6%), STR + APA (4.8%), APA + COD (1.9%) (fig. 5). If considered together, phosphate stones were the most common in women younger than 30 years after this age, as in men, there was a progressive decrease with a rise in STR + APA in patients over 69 years (figs 5-7). Since the combination STR + APA is typical of urease-producing infection, the overall percentage is low compared to industrialized countries, and the risk increases in older people. APA alone is not very frequent (5.6%), and renal tubular acidosis should be suspected. As discussed earlier, APA in combination with COM is the most common (15.5%). Another type of phosphate stone is that of brushite, whose presence signifies that primary hyperparathyroidism or renal phosphate leak must be investigated.

The last group was URI (10%), which showed a progressive increase with age, with the highest incidence in males over 69 years (figs. 5-7). These results are consistent with a previous multivariate analysis which found that the two significant variables associated with the risk of URI stones were body mass index and age; in addition, the risk was higher in men than in women.[20]

To be more precise, the main risk factors were overweight and age in young people and in persons over 59 years, respectively. The relationship between overweight and URI stones is due to a dual mechanism. Firstly, urinary pH is inversely related to body weight,[21] as a result, the more obese a patient is, the more acidic his/her urine is, with the consequential increased risk of developing URI stones. Secondly, overweight is associated with insulin resistance and also with hyperuricemia (metabolic syndrome). On the other hand, the relationship between URI and age can be explained by the fact that ammoniagenesis is altered with age, so that urine is more acidic in the elderly. Some authors[13,22,23] have also established that diabetes is a risk factor for URI stones, mainly in women.[13]

Conclusions

This study shows that not only is it important to know the major component of urinary stones, but also the combination of their components. Furthermore, analysis based on age and sex composition proves that their composition is related to changes in dietary habits and lifestyle, and the morphological structure of the stones may explain the possible etiopathogenic mechanism.

Conflict of interest

The authors declare that they have no conflict of interest.

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