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ORIGINAL ARTICLE

Outpatient crystalluria: prevalence, crystal types, and associations with comorbidities and urinary tract infections at a provincial hospital

Samira Natoubi[1*], Rim Jamal[2], Nezha Baghdad[3]

[1]Department of Nursing, Higher Institute of the Nursing Professions and Technical Health of Casablanca, Laboratory of Health, Care and Sustainable Development, Casablanca, Morocco
[2]Department of Applied Biology, Faculty of Science and Technology, University Hassan I, Settat, Morocco
[3]Medical Laboratory, Provincial Hassan II Hospital, Delegation of the Health Ministry, Settat, Morocco

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ABSTRACT

Background and Objectives: Crystalluria refers to the occurrence of crystals in urine resulting from urinary supersaturation, which disrupts the balance between factors that promote and those that inhibit crystal formation in urine. This study aimed to assess the prevalence of crystalluria, identify crystal types, determine associated comorbidities, and assess links with bacterial urinary tract infections in outpatients at Hassan II Hospital in Settat.

Materials and Methods: A retrospective study was conducted from January 2022 to May 2023 at Hassan II Hospital. Urine samples from patients suspected of urinary tract infections, who underwent cytobacteriological urine examinations, were analyzed.

Results: Among 1,025 urine samples, 22.04% showed crystalluria. The mean age of patients was 51.3 with a standard deviation of 18.1 years. The most common crystal types were calcium oxalate (46.4%), uric acid (23.5%), urates (15.1%) and struvite (9.3%). Comorbidities including, diabetes, kidney failure, prostatitis, and nephrotic syndrome was associated with urinary crystal formation. The prevalence of urinary tract infections in patients with urinary crystals was 10.6%. Struvite crystals were specifically associated with bacterial infections, especially with *Proteus mirabilis*, *Escherichia coli*, *Citrobacter freundii*, *Citrobacter koseri*, and *Enterobacter cloacae.*

Conclusion: Monitoring urinary crystals is essential for preventing the formation of kidney calculi and crystal-associated infections, especially in high-risk individuals.

Keywords: Crystalluria; Comorbidity; Urinary tract infections; Bacterial infections; Kidney calculi

INTRODUCTION

Crystalluria is characterized by the formation of crystals in the urine. The composition and features of spontaneous crystalluria are clinically significant for identifying and monitoring biological abnormalities linked to renal diseases (1, 2). The most common types of crystals in human urine include calcium oxalates, calcium phosphates, uric acid, urates, and magnesium ammonium phosphate (struvite) (3). Various modulating molecules, identified as receptors, promoters, and inhibitors control the process of crys-

*Corresponding author: Samira Natoubi, Ph.D, Department of Nursing, Higher Institute of the Nursing Professions and Technical Health of Casablanca, Laboratory of Health, Care and Sustainable Development, Casablanca, Morocco. Tel: +212667438357 Fax: +212 523403422 Email: samiranatoubi@yahoo.fr

tal formation and development (4). Metabolic-origin crystals result from an imbalance between promoters and inhibitors of crystallization. Promoters are substances excreted by the kidneys, with concentrations that exceed the urine's capacity to maintain them in soluble form, with calcium, oxalate, urate, and phosphate ions as primary promoters. In contrast, inhibitors, which either pass through the glomeruli or are produced locally by tubular cells, can prevent or delay the formation and adhesion of crystals to the tubular epithelium. Disruption of this balance may result from an excessive concentration of promoters, a deficiency in inhibitors, or alterations in the molecular structure of inhibitors (3, 5). Crystalluria can also result from excessive urinary supersaturation of one or more substances excreted by the kidneys (5). This phenomenon provides clinicians with valuable insights into urinary imbalances related to crystallogenic disorders. While crystalluria itself is not inherently pathological, certain types of crystals, may indicate an underlying condition (3). Additionally, although crystal formation in urine occurs before renal stone development, it does not necessarily lead to nephrolithiasis. When kidney stones form, they can cause various complications including acute kidney injury, obstructive uropathy, hydronephrosis, renal colic, pyonephrosis, and urosepsis (2).

The assessment of crystalluria should follow a standardized protocol, which involves collecting and delivering an appropriate urine sample to the laboratory, utilizing a microscope with polarized light, accurately determining urine pH, and conducting a thorough examination of the crystals. This examination includes their identification, quantification, and size measurement. In cases of atypical crystals, infrared spectroscopy may also be required (3, 6).

Crystalluria may be linked to symptoms typically associated with urinary tract infections (UTIs), such as frequent urination, urgency, a burning during urination, and hematuria. Identifying these symptoms alongside crystalluria can assist in the early diagnosis and treatment of underlying urinary tract issues. The clinical context including the presence of nephrolithiasis, nephrocalcinosis, or renal failure is crucial for a comprehensive assessment (3).

While stone formation is always preceded by crystalluria, not all cases of crystalluria lead to stone formation. Some studies suggest that persistent crystalluria may serve as a potential marker for stone disease or impact kidney function. Therefore, crystalluria may reflect a predisposition to stone formation and serve as a clinically relevant indicator (7).

Crystalluria is considered one of the most reliable markers for predicting stone recurrence in patients prone to stone formation. It offers the opportunity to adjust dietary and drug management to prevent future occurrences. Additionally, certain bacteria such as *Proteus mirabilis* induce the formation of crystals within the invaded cells, which may contribute to their protection (7). The analysis of crystalluria is essential for managing patients with lithiasis-related conditions, such as urinary stones, kidney diseases, and certain metabolic disorders. It serves both an etiological purpose and allows for the monitoring of the effectiveness of dietary measures and treatments.

The study aimed to evaluate the prevalence of crystalluria, identify the types of crystals, determine associated comorbidities and assess their potential link to bacterial urinary tract infections in urine samples from outpatients at the laboratory clinic of Hassan II Provincial Hospital in Settat.

MATERIALS AND METHODS

Study design, population, and sample. From January 2022 to May 2023, we conducted a retrospective study, which was carried out at Hassan II Hospital in Settat, using a census sampling method. Urine specimens were collected from all outpatients clinically suspected of having a UTI and those who underwent a cytobacteriological urine examination during this period. In all urinary specimens, we looked for crystals in cytological analysis.

Experimental protocol. Following the microbiology laboratory's recommended procedure, each urine sample was collected in a sterile container from the first-morning midstream urine, as overnight urine is more concentrated. Urine samples were delivered to the laboratory within 2 hours, kept at room temperature, and processed promptly to prevent unintended compound precipitation. Before analysis, each sample was gently mixed to ensure proper homogenization (3).

A macroscopic examination was conducted to assess urine appearance and color, as these factors can

indicate pathological conditions. Normal urine appears light in color with a clear yellow appearance. The urine was then immediately inoculated onto Cysteine Lactose Electrolyte Deficiency (C.L.E.D) agar medium, and incubated at 37°C for 18 to 24 hours. Species isolation and identification were performed using standard bacteriological techniques, including colonial morphology, Gram staining, culture characteristics, and biochemical testing. Gram-negative colonies were identified using the commercial API 20E identification kit for Enterobacterales detection (Biomerieux, Marcy l' Etoile, France). Subsequently, a 10µL sample of urine was placed in a Malassez cell and examined under optical microscopy, following a benchmark technique (2, 8). Urine pH was measured using reagent strips, with a positive control included to ensure accuracy. The positive control consisted of a urine sample with a known pH value, verified using a calibrated pH meter, to confirm the reliability of the reagent strips. Regular quality control checks were performed in accordance with the manufacturer's guidelines (6). For crystal examination, a fresh midstream urine sample of typically, 10-15 mL was centrifuged at 1500-2000 rpm for about 5 minutes. The supernatant was carefully discarded, leaving a small amount of liquid to resuspend the sediment. A drop of the resuspended sediment was then placed on a slide, and examined under a light microscope.

Data collection. Data were collected from the registry, which included information on age, gender, comorbidities (such as diabetes, prostatitis, kidney failure, nephrotic syndrome and bladder tumors), as well as urine crystal types, urine pH and bacterial species associated with urine crystals. Patients lacking all necessary data for the study were excluded.

Statistical analysis. Data were collected from medical records, entered into Microsoft Excel, and then exported for analysis using JAMOVI version 2.3. Continuous variables were presented as mean ± standard deviation, while categorical data were reported as frequencies and proportions. To assess associations between categorical variables, the chi-square test (χ^2 test) was applied, and Fisher's exact test was used for comparisons of two independent proportions when sample sizes were small. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations. Before conducting the study, authorization for data collection was requested and approved by the administration of Hassan II Provincial Hospital (Ref. 388/2024). Patients anonymity and data confidentiality were rigorously maintained.

RESULTS

Among the 1,025 urine samples collected from outpatients, 22.04% (n=226) exhibited crystalluria. The mean age of these patients was 51.3, with a standard deviation of 18.1 years. Crystalluria was more commonly prevalent among women, who represented 56.2% (127/226) of the cases, compared to 43.8% (99/226) in men.

Distribution of urinary crystals by type and gender. The most commonly observed crystal type in both genders was calcium oxalate (n=105; 46.4%), accounting for 22.5% in females and 23.9% in males. Uric acid crystals were the second most common (n=53; 23.5%), representing 13.3% in females and 10.2% in males. Some crystals, such as magnesium ammonium-phosphate (struvite), were more prevalent in females (7.1%) compared to males (2.2%). Conversely, urates combined with uric acid crystals appeared only in males (0.9%). Certain crystals, like cystine and the combination of calcium oxalates with uric acid, were exclusively found in females, while drug-induced crystals were detected only in males (0.4%). Overall, females accounted for 56.2% of all crystalluria cases, while males represented 43.8%, indicating a slightly higher prevalence in females. Except for the presence of both "calcium oxalates and uric acid crystals", the p-values suggest that the crystal distribution between genders is not statistically significant (Table 1).

Distribution of urinary crystals by age. The analysis of crystal distribution across age groups reveals that calcium oxalate crystals are the most frequently observed, particularly in patients over 60 years old (n=43), followed by those aged 41 to 60 years (n=27). Uric acid crystals are also more common in older age groups, with 26 cases in the 41-60 age group and 20 cases in those over 60. Struvite crystals are notably prevalent among patients over 60 years old (13 cases). A p-value of 0.031 indicates a statistically significant association between patient age and the types of crystals observed (Table 2).

Table 1. Distribution of urinary crystals by gender

Crystal	Gender		Total (%)	p-value
	Female (%)	Male (%)		
Calcium oxalates	51 (22.5)	54 (23.9)	105 (46.4)	0.061
Uric acid	30 (13.3)	23 (10.2)	53 (23.5)	0.697
Urates	21 (9.3)	13 (5.8)	34 (15.1)	0.662
Carbonates	1 (0.4)	1 (0.4)	2 (0.8)	0.713
Cystine	1 (0.4)	0	1 (0.4)	0.376
Drug	0	1 (0.4)	1 (0.4)	0.256
Calcium oxalate + uric acid	6 (2.7)	0	6 (2.7)	0.028
Struvite	16 (7.1)	5 (2.2)	21 (9.3)	0.052
Urates + uric acid	0	2 (0.9)	2 (0.9)	0.108
Urates + Calcium oxalates	1 (0.4)	0	1 (0.4)	0.376
Total	127 (56.2)	99 (43.8)	226 (100)	

Table 2. Distribution of urinary crystals by age category

Crystals	Age				
	<20	21-40	41-60	>60	Total
Calcium oxalates	17	18	27	43	105
Uric acid	1	6	26	20	53
Urates	0	3	17	14	34
Carbonates	1	0	1	0	2
Cystine	0	0	1	0	1
Drug	0	0	0	1	1
Calcium oxalates +uric acid	0	0	2	4	6
Struvite	0	3	5	13	21
Urates + uric acid	0	0	0	2	2
Urates + Calcium oxalates	0	0	1	0	1
Total	19	30	80	97	226
p-value					0.031

pH variation in urinary crystals. Calcium oxalate crystals, the most commonly identified in this study, generally form in slightly acidic to neutral urine, with a median pH of 6.4 (6.0-7.0). Uric acid crystals, by contrast, form in more acidic urine, with a median pH of 4.9 (4.5-5.5). Urate crystals form at a slightly higher pH of 5.5 (5.1-6.5) still within the acidic range. Ammonium-magnesium phosphate crystals and carbonates develop in alkaline urine, with median pH values of 8.2 (7.2-8.5) and 7.5 (7.3-9) respectively. Cystine crystals appear in moderately acidic urine, with a pH of 5.4.

Associations between comorbidities and crystal formations. The bivariate analysis reveals significant associations between certain comorbidities and crystal formations. The prevalence of crystalluria in diabetic patients was 41.6% (94/226). Diabetic patients exhibited a high occurrence of uric acid crystals (n=36) and calcium oxalate crystals (n=22), with a statistically significant p-value of less than 0.01. Similarly, prostatitis was strongly associated with calcium oxalate crystals (n=17), while patients with kidney failure showed a notable presence of magnesium ammonium phosphate crystals (struvite). The p-values confirm that these associations are significant for most factors, especially diabetes and kidney failure. Conditions such as nephrotic syndrome and bladder tumors showed limited occurrences of specific crystals, reflecting a lower impact on crystalluria.

Additionally, p-values for patients without comorbidities suggest a statistically significant relationship between the absence of comorbidities and the occurrence of various types of crystals (Table 3).

Distribution of bacterial isolates across different urinary crystal types in patients. In our study, the overall prevalence of UTIs among patients with urinary crystals was 10.6% (24 out of 226). Sterile urine samples showed a high occurrence of crystal formation, particularly for uric acid and calcium oxalate crystals. Conversely, struvite crystals were associated with bacterial infections, notably with *Proteus mirabilis, Escherichia coli, Citrobacter freundii, Citrobacter koseri,* and *Enterobacter cloacae.* Of all crystal types analyzed, only struvite crystals showed a significant relationship with bacterial presence (p-value<0.01). In contrast, uric acid, calcium oxalate, carbonate,

cystine, and urate crystals, were primarily found in sterile samples, with minimal bacterial involvement. *E. coli* was the most frequently detected bacterium in crystal-positive cases followed by *P. mirabilis*. Results are presented in Table 4.

DISCUSSION

Crystalluria, defined by the presence of crystals in urine, serves as a key indicator in understanding underlying metabolic disorders and potential risk factors for kidney stone formation. The available literature on the prevalence of urinary crystalluria remains very limited. In the present study, the prevalence of crystalluria is 22.04%, several studies have reported that crystalluria is detected in around 8% of analyzed urine samples (2, 8). These differences are likely due to variations in study populations, geographic regions, or risk factors such as diet and hydration practices.

Our finding indicates a higher prevalence of crystalluria among women (56.2%) compared to men (43.8%), this difference may be attributed to gender-specific risk factors. Women are more susceptible to urinary tract infections, which are associated with an increased risk of crystal formation due to alterations in urinary pH and concentration, promoting crystal precipitation. Additionally, hormonal differences and variations in hydration habits between

Table 3. Distribution of urinary crystals according to comorbidities

Comorbidity	U.ac	Carbonates	Cystine	Drug	CaOx	CaOx + U.ac	Struvite	Urates	Urates + U.ac	Urates + CaOx	Total
Prostatitis	1	0	0	0	17	0	1	3	0	0	22
Diabetes	36	0	0	0	22	4	9	21	2	0	94
Kidney failure	1	0	0	1	0	1	4	2	0	0	9
No comorbidities	10	2	1	0	62	0	6	8	0	1	90
Nephrotic syndrome	5	0	0	0	4	1	0	0	0	0	10
Bladder tumor	0	0	0	0	0	0	1	0	0	0	1
Total	53	2	1	1	105	6	21	34	2	1	226
p-value	<0.01	0.793	0.584	0.049	<0.01	0.074	0.008	0.009	0.667	0.584	

CaOx: Calcium oxalates; U.ac: Uric acid

Table 4. Prevalence of bacterial isolates among patients with urinary crystals

Crystals	Bacterial Isolate									
	C. freundii	*C. koseri*	*E. coli*	*E. cloacae*	*K. pneumoniae*	*P. mirabilis*	*S. aureus*	Sterile	Total	p-value
Uric acid	0	0	2	0	0	0	0	51	53	0.325
Carbonates	0	0	0	0	0	0	0	2	2	0.9
Cystine	0	0	0	0	0	0	0	1	1	0.9
Drug	0	0	1	0	0	0	0	0	1	0.055
CaOx	0	0	6	1	1	0	1	96	105	0.299
CaOx +uric ac	0	0	0	0	0	0	0	6	6	0.9
Struvite	1	1	4	1	0	3	0	11	21	<0.01
Urates	0	0	2	0	0	0	0	32	34	0.977
Urates + uric ac	0	0	0	0	0	0	0	2	2	0.9
Urates + CaOx	0	0	0	0	0	0	0	1	1	0.982
Total	1	1	15	2	1	3	1	202	226	

Sterile: No bacterial growth

genders may contribute to this disparity. Moreover, women are more affected than men due to the shorter distance between the female urethra and bladder, which facilitates the ascent of bacterial colonizers to the kidneys before being eliminated through micturition (9, 10). These results emphasize the importance of routine urinalysis in at-risk populations to detect crystalluria early, as it could be a precursor to more serious urological conditions, such as kidney stones (2).

The mean age of 51.3 years suggests that crystalluria may become more prevalent with age, likely due to cumulative metabolic changes, declining renal function, and the higher incidence of comorbidities in older populations. Our study found a statistically significant variation in the distribution of urinary crystals across different age groups ($p = 0.031$). Additionally, in more vulnerable individuals, particularly the elderly, diabetes mellitus predisposes them to fluid loss through osmotic diuresis, thereby heightening the risk of dehydration (11).

Our research revealed a predominance of calcium oxalate (46.4%) followed by uric acid (23.5%) and urates (15.1%). This sequence is consistent with findings from another study, with calcium oxalate (75.9%), uric acid (25.9%) and urates (7.9%) either alone or in combination. Calcium oxalate crystals were the most frequently observed (2, 8).

The presence of calcium oxalate crystals is often linked to dietary factors, particularly a high intake of calcium and oxalate-rich foods, as well as insufficient hydration. This high prevalence suggests the need for dietary interventions and the promotion of proper hydration to help prevent kidney stone formation. Notably a study reported that the immune system, particularly macrophage differentiation, plays a critical role in the development of calcium oxalate kidney stone (12).

Uric acid crystals are linked to medical conditions that result in increased uric acid production or altered metabolism, like gout, as well as to conditions that cause lower urine pH, including metabolic syndrome and diabetes mellitus (2).

Urate crystals in urine form when sodium or potassium urate precipitates in acidic conditions. These crystals are often associated with dehydration or dietary factors but may also arise from metabolic disorders. While usually harmless, high levels of urates can suggest underlying issues such as hyperuricemia or an increased risk of kidney stones (10).

The presence of magnesium ammonium-phosphate, or struvite crystals, in highly alkaline urine ($pH > 7$) is a strong indicator of a urinary tract infection caused by bacterial urease, which hydrolyzes urea, producing ammonia and carbon dioxide. This process increases urine alkalinity, which promotes the formation of phosphate salts (4). In the present study, struvite crystals were associated with bacterial infections, particularly *P. mirabilis*, *E. coli*, *C. freundii*, *C. koseri*, and *E. cloacae*. The most common bacteria implicated in crystalluria or stone formation is *P. mirabilis*. In addition, other studies have also associated *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Providencia stuartii*, *Serratia*, and *Morganella morganii* with the presence of these crystals (2, 13, 14). The presence of *Enterobacter* spp. and *Citrobacter* spp. has been reported in a study identifying bacterial isolates from urinary stone cultures (15).

In our study, we identified a single case of cystine crystals which are rarely found in urine, and are typically associated with the genetic disorder cystinuria (16, 17). As for drugs, certain medications (e.g. sulfamethoxazole, ceftriaxone) can also crystallize in urine due to prolonged, high-dose usage (2, 4).

Our study noted a high occurrence of uric acid crystals (n=36) and calcium oxalate crystals (n=22) among patients with diabetes, with a statistically significant p-value of less than 0.01. Diabetes can contribute to hyperuricemia due to insulin resistance, which reduces renal excretion of uric acid, leading to elevated uric acid levels in the blood and subsequently, in the urine (18). Uric acid crystals in the urine can contribute to kidney stone formation. Furthermore, diets high in meat, seafood, sugar, and beer are linked to an increased risk of hyperuricemia (19).

Regarding calcium oxalates, diabetic patients often have altered renal handling of calcium and oxalate due to changes in kidney function, oxidative stress, and increased production of oxalate precursors. Moreover, diabetic nephropathy can increase the risk of stone formation due to these metabolic and functional alterations (20). In our study, calcium oxalate crystals were predominant in patients with prostatitis compared to other types of crystals. Previous research indicated that calcium oxalate is the main component of prostate stones commonly detected in men with acute or chronic prostatitis, and it may contribute to the development of chron-

ic prostatitis. The presence of crystals in the urine of patients with prostatitis can be influenced by several factors related to the condition, particularly chronic prostate inflammation and urinary retention (21). Interestingly, our findings also revealed that a considerable number of crystalluria cases occurred in patients without any documented comorbidities. This may be attributed to the influence of modifiable lifestyle factors, such as insufficient hydration, dietary imbalances, and limited physical activity, which can lead to increased urinary concentration and favor crystal formation. In such individuals, crystalluria may develop independently of underlying diseases. Furthermore, some patients categorized as having "no comorbidities" might actually have undiagnosed or subclinical conditions not captured at the time of data collection. These factors may explain the higher observed prevalence in this group (2, 4).

CONCLUSION

In conclusion, our study reveals a notable prevalence of crystalluria among outpatients, highlighting the relationship between struvite crystals and bacterial urinary tract infections. These findings emphasize the importance for clinicians to consider crystalluria in the management of patients with urinary symptoms and associated comorbidities, particularly those susceptible to bacterial infections.

Effective prevention of crystalluria involves addressing underlying risk factors and promoting urinary tract health. Key strategies include maintaining adequate hydration, adhering to a balanced diet, and monitoring medications that may increase risk. Managing underlying conditions such as hypercalciuria or urinary tract infections, practicing good hygiene, and ensuring regular urination can further reduce the risk. For individuals with a history of crystalluria, regular check-ups are recommended to monitor urinary health.

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