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Original Article

Survey of urinary crystals identified in residents of Ouagadougou, Burkina Faso: Implications for the diagnosis and management of renal dysfunctions

Jean Sakandé[1], Raogo Djiguemde[1,2], Abdoulaye Nikiéma[2], Elie Kabré[1], Mamadou Sawadogo[1]

[1]*Laboratory of Biochemistry, Health Sciences Training and Research Unit, University of Ouagadougou;* [2]*Laboratory of Bacteriology, Health Sciences Training and Research Unit, University of Ouagadougou*

**Corresponding author: Jean Sakandé, PhD, jsakande@gmail.com*

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ABSTRACT: The first step of renal lithiasis process is crystals formation. Because of this link, a prospective study on the profile of urinary crystals was conducted in Ouagadougou with the aim of describing profiles of these crystals in the context of a Sahelian tropical country. This study showed strong prevalence (78.69%) crystals within the population from 15 to 59 years old. Male subjects were the most concerned with 55.93 % prevalence. Among the crystals, we distinguished those who were without compulsory pathological interest with strong prevalence of the crystals of calcium oxalate (56.11%) and uric acid (20.55%). Crystals with immediate pathological interest were bilirubin (0.66%), the cystine (0.36%), leucine (0.06%) and tyrosine (0.06%). Prevalence of crystals derived from drugs were sulfamides (0.18%) and mycostatine (0.06%). Besides, 20.8% of the patients having urinary crystals had urinary tract infection. Bacteriological analysis of urines showed a presence of producing urease bacteria: Klebsiella (12.96%), Proteus (3.0%), Enterobacter (1.66%) and, Pseudomonas (1.66%). In conclusion, this work showed the interest to pay more attention on urinary crystals. Indeed this study brought to light crystals with compulsory pathological interest, in particular crystals of bilirubin, cystine, leucine, tyrosine, evidence of abnormalities of protein metabolism.

KEYWORDS: urine, crystals, lithiasis, urease producing bacteria, Ouagadougou

INTRODUCTION

Urolithiasis is a common condition that affects between 4 and 20% of the population, depending on the country (Hesse, 2005). In developing countries, like that was the case for industrialized countries since the end of the Second World War, the frequency of the urolithiasis disease seems to increase along with the increase of the standard of living (Fournier & Bataille, 1991). A recent study predicts up to 10% increase in the prevalence rate of urolithiasis before 2050 because of the global warming (Fakheri & Goldfarb, 2011). In Burkina Faso, little research on this subject has been conducted. A study on the lithiasis of the high urinary organs in the University hospital Yalgado Ouédraogo of Ouagadougou reported a hospital prevalence of 12.39% (Coulibaly, 2009). The first stage necessary for the lithiasis process is the formation of urinary crystals from substances which are in excessive concentration in urines because of a defect of diuresis, an excess of intakes (dietary, medicinal), an excess of production by the endogenous metabolism (primary hyperoxalluria) or of an excess of urinary excretion (cystenuria). The urine supersaturation can also result from an anomaly of the cycle of urinary pH which leads to a decrease of the solubility of the substance present in normal concentration in the urine. It is in particular the case of the uric acid, the calcic phosphates and the urates.

Generally, the crystalluria can be observed without any pathological context; however the presence of particular crystals (cysteine, struvite, urate of ammonium) has no direct to specific pathogenic processes (Daudon, 2005). Therefore, the analysis of urines performed routinely in Burkina Faso could bring useful information for the prevention of the lithiasis, the premature detection of a risk of lithiasis recurrence, the screening of congenital diseases (cystenuria), of metabolic anomalies (oxalluria) or the identification of risks of acute renal failure of medicinal origin (Daudon, 2005). However there is not enough interest in the urinary crystals isolated during a urinalysis in particular when the culture is negative. Indeed a survey performed with the clinicians in the Yalgado Ouédraogo University Hospital of Ouagadougou reported that only 8% have shown interest in crystals mentioned in the laboratory report (Sakande *et al*., 2008).

In this regard, we decided to pay interest in the description of these crystals in the context of a warm tropical country. This is to raise their use in the interpretation of the laboratory results.

MATERIALS AND METHODS

Subjects

The study was carried out in the laboratory of biochemistry of the Health Sciences Training and Research Unit of the University of Ouagadougou between May 2010 and May 2011. It was a prospective cross-sectional survey aimed at describing the urinary crystals in the context of a warm country. The study concerned 1603 patients received in four laboratories of the city of Ouagadougou for urinalysis. All the patients for which the crystals were found in urines and who gave their consent were included in the study. The variables of the study were: the age, the sex, the urinary pH, the type of urinary crystals and the isolated germs.

Materials

The material used for urinalysis and the identification of crystals includes polarized light microscope (Olympus CX31-P). Antibiotics and dipsticks for the determination of pH, urine specific gravity, blood, leukocytes and nitrites were supplied by Biomérieux Laboratory, France).

Urine collection

Fresh urines were collected in the laboratory using a midstream clean-catch technique. These urines were analyzed within two hours following the voiding.

Determination of the urinary parameters

The various urinary markers such as the pH, the specific gravity, the presence of blood, leukocytes and nitrites were searched for with test strips (Biomérieux Laboratory, France). According to the pH, urines were classified as following: Acidic urine: $4 \leq pH \leq 6.5$; Neutral urine: $7 \leq pH \leq 7.5$; Alkaline urine: $8 \leq pH \leq 9$. Cristalluria examination was performed by polarized microscopy in a Malassez cell according to the method recommended by Daudon (1987). Crystals were identified by two different technicians.

Urine culture

Urine culture was realized according to the standard method. The microorganisms were identified using Biomerieux's API 20E test kit. Antimicrobial susceptibility testing was performed using disk diffusion method.

Data collection and analysis

Data were collected using a standardized form. Data collected were recorded and analyzed using EPI-info Version 3.5.1 statistical software. Chi-squared test was used to determine statistical difference at significant level of 0.05.

RESULTS

Epidemiological characteristics

The study population was consisted of 1603 patients among whom 721 female (44.4%) and 892 male (55.6%) with a sex-ratio of 1:2. The age of the patients ranged from 0 to 67 years with a mean age of 34.47 years. Most of the patients (77.4%) were aged between 15 and 59 years.

Urinary pH

The urinary pH of the patients ranged from 4 to 9 (Table 1). Most of the urines (86%) were acidic.

Chemical nature of identified crystals according to the age

Results in Table 2 show that from 1603 urine samples, 1661 crystals were identified among which 1609 (96.87%) were common chemical species, 48 (2.89%) were metabolic species and 4 (0.24%) were medicinal species. The crystals of oxalate of calcium and uric acid with respectively 56.11% and 20.55% of all the isolated crystals were the main crystals without clinical significance. In total, 19 (1.15%) crystals with clinical significance were found (bilirubin, cysteine, leucine and tyrosine). As for the crystals due to medications, sulfonamide crystals (0.18%) mycostatin crystals (0.06%) were identified. According to the age the results have shown that the majority of crystals (78.69%) was found in the 15-59 age range. The crystals of leucine and tyrosine were only found in children from 0-14 years old.

Chemical nature of identified crystals according to the sex

Only crystals with pathological significance and those formed by drugs had a distribution significantly different according to the sex (Presented in Table 3). So cysteine, sulfonamides, leucine and tyrosine crystals were significantly more frequent in males whereas those of bilirubin and Mycostatin were more frequent in females.

Chemical nature of crystals according to the urinary pH

Results presented in Table 4 shows that oxalate calcium crystals were the most frequently identified in acidic urines (888 crystals or 53.46%) and in neutral urines, whereas Magnesium Ammonium phosphate crystals were more frequent in alkaline urines (47 crystals or 2.83%). Crystals with pathological significance like Bilirubin and Cystine crystals were more frequent in acidic urines.

Nature of crystals within patients with urinary tract infection

Mircroorganisms were isolated in 334 patients (20.8%) with urinary crystals. Magnesium Ammonium phosphate and Amorphous phosphate crystals were more frequent in patients with a urinary tract infection (Presented in Table 5).

Microorganisms isolated from urine culture

In total, 10 microorganisms were isolated (Presented in Table 6). The main urea-splitting bacterial genus were: Klebsiella (12.96%), *Proteus* (2.66%), *Enterobacter* (1.66%) and *Pseudomonas* (1.66%).

TABLE 1 Distribution of urine according to pH in a total population sample of 1603

Urinary pH	Frequencies (%)
Acidic	1379 (86)
Neutral	82 (5.6)
Alkaline	142 (8.9)

TABLE 2 Chemical nature of identified crystals and age distribution

Nature of crystals	Total Population n=1603 Frequency (%)	0-14 years n=203 Frequency (%)	15-59 years n = 1234 Frequency (%)	≥ 60 years n = 1570 Frequency (%)
Calcium Oxalate	932 (56.11)	86 (5.18)	782 (47.08)	64 (3.85)
Uric acid	341 (20.55)	59 (3.55)	252 (15.17)	30 (1.81)
Calcium phosphate	139 (8.37)	28 (1.69)	96 (5.78)	15 (0.90)
Magnesium Ammonium phosphate	73 (4.39)	10 (0.60)	44 (2.65)	19 (1.14)
Amorphous urates	76 (4.57)	10 (0.60)	61 (3.67)	5 (0.30)
Amorphous phosphate	41 (2.47)	5 (0.30)	33 (1.99)	3 (0.18)
Calcium carbonate	24 (1.44)	5 (0.30)	16 (0.96)	3 (0.18)
Ammonium urate	12 (0.72)	3 (0.18)	8 (0.48)	1 (0.06)
Bilirubin	11 (0.66)	3 (0.18)	8 (0.48)	0
Cystin	6 (0.36)	1 (0.06)	4 (0.24)	1 (0.06)
Sulfamides	3 (0.18)	1 (0.06)	2 (0.12)	0
Leucin	1 (0.06)	1 (0.06)	0	0
Tyrosin	1 (0.06)	1 (0.06)	0	0
Mycostatin	1 (0.06)	0	1 (0.06)	0
Total	1661	213 (12.82)	1307 (78.69)	141 (8.49)

TABLE 3 Distribution of crystals according to sex

Nature of crystals	Total Population (n=1603) Frequency (%)	Male n=892 Frequency (%)	Female n = 721 Frequency (%)	p
Calcium Oxalate	932 (56.11)	534 (32.15)	398 (23.96)	NS
Uric acid	341 (20.55)	202 (12.16)	139 (8.37)	NS
Calcium phosphate	139 (8.37)	73 (4.39)	66 (3.97)	NS
Magnesium Ammonium phosphate	73 (4.39)	38 (2.30)	35 (2.11)	NS
Amorphous urates	76 (4.57)	35 (2.11)	41(2.37)	NS
Amorphous phosphate	41 (2.47)	18 (1.08)	28 (1.69)	NS
Calcium carbonate	24 (1.44)	10 (0.60)	14 (0.84)	NS
Ammonium urate	12 (0.72)	6 (0.36)	6 (0.36)	NS
Bilirubine	11 (0.66)	5 (0.30)	6 (0.36)	0.03
Cystine	6 (0.36)	4 (0.24)	2 (0.12)	0.03
Sulfamides	3 (0.18)	2 (0.12)	1 (0.06)	0.02
Leucine	1 (0.06)	1 (0.06)	0	NS
Tyrosine	1 (0.06)	1 (0.06)	0	0.04
Mycostatin	1 (0.06)	0	1 (0.06)	0.04
Total	1661	929 (55.93)	732 (44.07)	NS

TABLE 4 Distribution of crystals according to urinary pH

Nature of crystals	Total Population (n=1603) Frequency (%)	Acidic pH n=1379 Frequency (%)	Neutral pH n = 82 Frequency (%)	Alkaline pH n = 142 Frequency (%)
Calcium Oxalate	932 (56.11)	888 (53.46)	19 (1.14)	25 (1.51)
Uric acid	341 (20.55)	317 (19.08)	9 (0.54)	15 (0.90)
Calcium phosphate	139 (8.37)	80 (4.82)	11 (0.66)	38 (2.30)
Magnesium Ammonium phosphate	73 (4.39)	15 (0.90)	11 (0.66)	47 (2.83)
Amorphous urates	76 (4.57)	55 (3.31)	10 (0.60)	11 (0.66)
Amorphous phosphate	41 (2.47)	24 (1.44)	9 (0.54)	8 (0.48)
Calcium carbonate	24 (1.44)	17 (1.02)	3 (0.18)	4 (0.24)
Ammonium urate	12 (0.72)	10 (0.60)	2 (0.12)	0
Bilirubin	11 (0.66)	10 (0.60)	1 (0.06)	0
Cystin	6 (0.36)	6 (0.36)	0	0
Sulfamides	3 (0.18)	3 (0.18)	0	0
Leucin	1 (0.06)	1 (0.06)	0	0
Tyrosin	1 (0.06)	1 (0.06)	0	0
Mycostatin	1 (0.06)	1 (0.06)	0	0
Total	1661	1428 (85.97)	85 (5.12)	148 (8.91)

TABLE 5 Nature of crystals in patients with urinary tract infection (UTI)

Nature of crystals	Total Population (n=1603) Frequency (%)	UTI (+) n=334 Frequency (%)	UTI (-) n = 1269 Frequency (%)	p
Calcium Oxalate	932 (56.11)	205 (0.59)	727 (0.43)	NS
Uric acid	341 (20.55)	61 (0.17)	280 (0.40)	NS
Calcium phosphate	139 (8.37)	36 (0.10)	103 (0.06)	NS
Magnesium Ammonium phosphate	73 (4.39)	31(0.09)	42 (0.02)	0.001
Amorphous urates	76 (4.57)	11 (0.036)	65 (0.005)	NS
Amorphous phosphate	41 (2.47)	2 (0.006)	39 (0.02)	0.004
Calcium carbonate	24 (1.44)	3 (0.008)	21 (0.01)	NS
Ammonium urate	12 (0.72)	1 (0.003)	11 (0.006)	NS
Bilirubin	11 (0.66)	0	11 (0.006)	NS
Cystin	6 (0.36)	1 (0.003)	5 (0.002)	NS
Sulfamides	3 (0.18)	0	3 (0.001)	NS
Leucin	1 (0.06)	1 (0.003)	0	NS
Tyrosin	1 (0.06)	1 (0.003)	0	NS
Mycostatin	1 (0.06)	1 (0.003)	0	NS
Total	1661	354 (21.32)	1307 (78.69)	NS

TABLE 6 Distribution of microorganisms isolated from patients with urinary tract infection (UTI)

Microorganisms	Frequency (%)
Klebsiella	12.96
Escherichia	33.22
Enterococcus	3.00
Proteus	2.66
Staphylococcus	34.88
Streptococcus	8.97
Enterobacter	1.66
Pseudomonas	1.66
Acinetobacter	0.66
Citrobacter	0.33

DISCUSSION

The study of the cristalluria from 1603 samples of urines allowed identifying 1661 crystals. The distribution of these crystals showed strong prevalence (78.69%) of cristalluria among the population aged from 15-59 years. Broadly, the male subjects were the most concerned with a prevalence of 55.93%. Higher male predisposition to cristalluria has been reported by other authors (Alaya et al., 2009; Oussama et al., 2000; da Silva et al., 2009). The majority of crystals (85.97%) were found in acidic urines.

The three main crystals isolated form acidic urines were calcium oxalate, uric acid and amorphous urates. Besides, all crystals with pathological significance in our study were found in acidic urines. This could be explained by the fact that the first factor significantly influencing the in vivo crystallization process is the urinary pH.

Some substances are soluble in the usual pH of urines (Calcium oxalate). Others on the contrary (Uric acid, Cystin) are dependent on the acidic pH which influence their degree of ionization. The pH also influence the solubility of most of drugs, which native forms or metabolites may crystallize in acidic urines as it is the case of sulfonamides (Daudon, 2005)

The majority of crystals (96.87%) were common chemical species crystals without any immediate pathological interest. Calcium oxalate and uric acid crystals with 56.11% and 20.55% respectively of all the isolated crystals were the main crystals without clinical significance. This is in agreement with the literature (Daudon *et al*., 2004). The presence of these crystals generally means that urines are very concentrated and supersaturated towards these crystals species. Even if the presence of these crystals is not linked to a lithiasis for the study subjects, it is reported in several studies the ascendancy calcium oxalate in kidney stones (Alaya *et al*., 2009; Jmal *et al*., 2006).

Tunisian authors linked the high frequency of the calcium oxalate crystals with food rich in Sorghum (which is rich in oxalate). This hypothesis can be also retained for Burkina, the food of which consists essentially of Sorghum. Besides, the frequency of 20.55% of uric acid crystals can be associated with the food rich in red meat and giblets used in Ouagadougou. Along with the common crystals, 1.15% of all isolated crystals were crystals with clinical significance: bilirubin, cysteine, leucine and tyrosine crystals. Normally, the elimination of bilirubin is biliary and instestinal. Its presence in urines is pathological (Daudon, 1987b).

The presence in abundance in the urine of cysteine crystals constitutes a major risk of lithogenesis which should be reduced by appropriate therapeutic measures. Indeed, these cysteine crystals in urines can be the first stage of the screening of genetic diseases such as the cysteinuria-lysinuria, the deficit in adenine phospho-ribosyl transferase or xanthine oxidase (Werness *et al*., 1981). Leucine and tyrosine crystals were found only in children from 0-14 years old. The presence of tyrosine crystals signifies a family tyrosinemia or a serious hepatitis whereas the leucine crystals are found in case of leucinosis, or Hartnup disease (Daudon, 1987b).

Finally, 0.24% of the isolated crystals were originated from drugs and consisted of sulfonamide and mycostatin crystals. The mycostatin crystals found in a female subject could be justified by the use of this medicine in gynaecology. Usually, the identification of medicinal crystals must alert the clinician on the potential risk of renal complications and incite to modify the posology, to increase the diuresis of the patient or even to change the drug. Also a medicine cristalluria can explain a particular renal symptomatology like hematuria, acute renal insufficiency or lithiasis (Bertrand, 1999).

Concerning alkaline urines, the main crystals found were phosphates crystals, what is in accordance with the literature (Baledent, 2010). There was: Calcium phosphate (brushite) and Magnesium –Ammonium phosphates (struvite crystals). The presence of these crystals that must direct to a urinary tract infection with germs urea-splitting or ammoniogenesis bacteria, we thus realized the urine culture. The results showed that the Magnesium-ammonium phosphates and amorphous phosphates crystals were significantly more frequent in subjects with urinary tract infection ($p<0.005$). These findings are consistent with what have been reported in the literature (Meisnner *et al*., 2010). Several urease producing bacteria genus were identified. They were: Klebsiella (12.96%), Proteus (2.66%), Enterobacter (1.66%) and Pseudomonas (1.66%). The responsibility of these urea-splitting bacteria in the development of the majority of Struvite kidney stone is not any more disputed (Goldfarb, 2004; Bichler *et al*., 2002; Ma *et al*., 2010). Along with the urea-splitting bacteria, the genus Escherichia isolated in 33.22% of the cases.

Several authors demonstrated that the genus *Escherichia coli* experimentally cause the formation of crystals. Cohen *et al*. (1982) studied the behavior of urines sowed by collibacillus and incubated at 37 °C during several days, and concluded that Escherichia coli can favours the precipitation of calcium phosphate. Hedelin *et al*. (1988) observed that the preliminary incubation of urines with *E. coli* increased the precipitation of magnesium–ammonium phosphate crystals when they introduced secondarily urease into the reaction medium. This suggests that *E. coli* can contribute to destabilize the urine and to make it more sensitive to the effects of urea-splitting bacteria (Cohen *et al*., 1982; Mahmood & Zafar, 2008). The genus Staphylococcus isolated 34.88% of the cases in our study is also incriminated experimentally in the formation of crystals (Jan *et al*., 2008).

CONCLUSION

Crystals of different chemical species were found in urines of the patients regardless to their age and sometimes in the presence of urea-splitting bacteria. This situation calls up to a meticulous research for crystals in laboratories and to their consideration in the interpretation of the laboratory results by the clinicians. Indeed, this study allowed the identification of crystals with compulsory pathological interest, in particular bilirubin, cysteine, leucine and tyrosine crystals signs of anomalies proteins metabolism anomalies.

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