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Study of crystalluria in goitrous patients

Souad Rabi[1], Malika Echajia[1], Constant Tcheka[1-2], Najat Elhadiri[3], and Mohamed Mbarki[1]

[1]Department of chemistry and environment,
Sultan Moulay Slimane University, Faculty of Science and Technology,
Transdisciplinary Team of Analytical Science for Sustainable Development, PB 523, Béni Mellal, Morocco

[2]Department of Inorganic Chemistry,
University of Yaoundé 1, Faculty of Science, Laboratory of Physical and Theoretical Chemistry,
P.O. Box 812, Yaoundé, Cameroon

[3]Department of chemistry,
Cadi Ayyad University, Faculty of Science Semlalia, Laboratory of reactivity of materials and process optimization,
PB 2390, Marrakech, Morocco

ABSTRACT: The present work reports a comparative study of spontaneous crystalluria for non- and goitrous patients with the aim to determine its correlation with parathyroid gland activity and goiter etiology. The crystalluria was accessed based on optical polarized light microscopy (OPLM). Goiter presents high woman predominance with an average age of 35.6 years. The frequency of majority constituents in crystalluria is age dependent and amorphous complex carbonated phosphates (ACCP) and uric acid (UA) are the frequent chemical species. The observed hyperphosphaturia can be explained by the estrogen's activity on parathyroid cells proliferation. The presence of oxalo-calcic crystalluria confirms hyperparathyroidism as one of the hypercalciuric kidney stone etiology. Clinical goiter diagnostic and treatment could be followed and confirmed by a simple fluctuations follow-up of crystalluria composition according to phosphate and calcium species.

KEYWORDS: Crystalluria, hyperphosphaturia, hypercalciuria, goiter etiology, hyperparathyroidism, kidney stone, OPLM.

1 INTRODUCTION

Goiter is known for a long time as a thyroid disease. Iodine deficiency of human organism is the most frequent reason of the most widespread goiter type commonly called endemic goiter. It has been shown that the mountainous regions undergo a phenomenon of iodine displacement toward of lowest altitude soils. Hence the mountainous populations present a higher frequency of endemic goiter than the one registered for the coasts peoples. Several recent papers have reported low iodine content in ground waters, especially in high altitude regions (Watts et al. 2010, Li et al. 2008, Gbadebo et al. 2010). World health organization (WHO) recommends remedying this problem, iodine addition in the salt (Delange, 2003). This disease is also more widespread in woman than man. Two hormones, parathormone (PTH) and thyrocalcitonine (TCT) play important roles in calcium homeostasis and blood phosphor. The medicines whose TCT is the active principle are in fact, used like hypocalcemic and hypophosphatemic by increasing excretion of calcium and phosphate by urine. Hence the risk of urinary oversaturation in calcium salts, notably in calcic-phosphates lead us to achieve a crystalluria study for a set of hospitalized goiter patients. There is a need of studies on the frequency and the chemical profile of crystalluria in patients presenting endocrinological pathology, such diabetes and goiter. In this present, the question is if the goitrous patient urines are so saturated in calcium salts, like calcium phosphates, that crystalluria frequency of these calcium salts could be relatively more important than in the case of non goitrous patients urines. So, clinician could derive profit of the suspected goitrous patient's

Corresponding Author: Souad Rabi

crystalluria study results to solve goiter diagnosis, then to propose a therapeutic treatment and propose prevention measures.

2 MATERIALS AND METHODS

Crystalluria study has been achieved on a set of 185 goitrous patients having been hospitalized, during the period of October 2012 to June 2013, at the endocrinology center of regional hospital in Beni Mellal city, as relevant service for such pathology in Tadla Azilal region. Comparatively, crystalluria study has been also achieved on a set of 169 non goitrous adult persons (age >15 years). Pocket pH - Meter ad 110 pH has been used for the measure of urinary pH while the observation of crystalluria has been done by using an Olympus BX41 optical polarized light microscope (OPLM). Crystalluria is considered positive when the Malassez cell grid contains at least a crystal of the concerned chemical species. Crystals have been identified thanks to their morphological characteristics, polarized light behaviors and urine pH. 180 of the 185 goitrous patients are women. Only two women among the 180 are considered young (age ≤ 15 years) while all patients of the non goitrous set have an age more than 15 years. Three range ages have been chosen for the two sets: the least age group (15 < age ≤ 28 years), the mean age group (28 < age ≤ 40 years), and the adult category (40 years < age). Table I expresses the two patient's distribution sets according to age and gender. For a convenience the results of the 87 non goitrous women and 180 goitrous women have been compared. The average age of non goitrous women was of 42.6 years while the one of the goitrous is of 35.6 years.

Table I: Distribution of the adult patients according to the gender and the age

Age group (years)	Men (number)		Women (number)		Total according gender	
	Non goitrous	Goitrous	Non goitrous	Goitrous	Non-goitrous	Goitrous
15< age ≤ 28	45	3	20	49	65	52
28 < age ≤ 40	14	2	27	71	41	73
40 < age	23	0	40	60	63	60
Total	82	5	87	180	169	185

3 RESULTS

OPLM crystal micrographs of the most frequent observed crystalluria (calcium oxalates, uric acids and calcium phosphates) are presented in Figure I. Table II illustrates crystalluria frequency of each one of the three age groups for the two sets. Table III gives this frequency distribution on the three age groups. In the non goitrous set, for each mixed crystalluria one chemical species is considered as majority constituent. Only two among all the 20 positive crystallurias (table II) were observed as mixed crystalluria. The frequency of crystalluria is similar as well in non goitrous as in goitrous patients (table II). The frequency evolution of each observed majority constituent of crystalluria is distributed in the three age groups presented in table IV for non goitrous and in table V for goitrous patients.

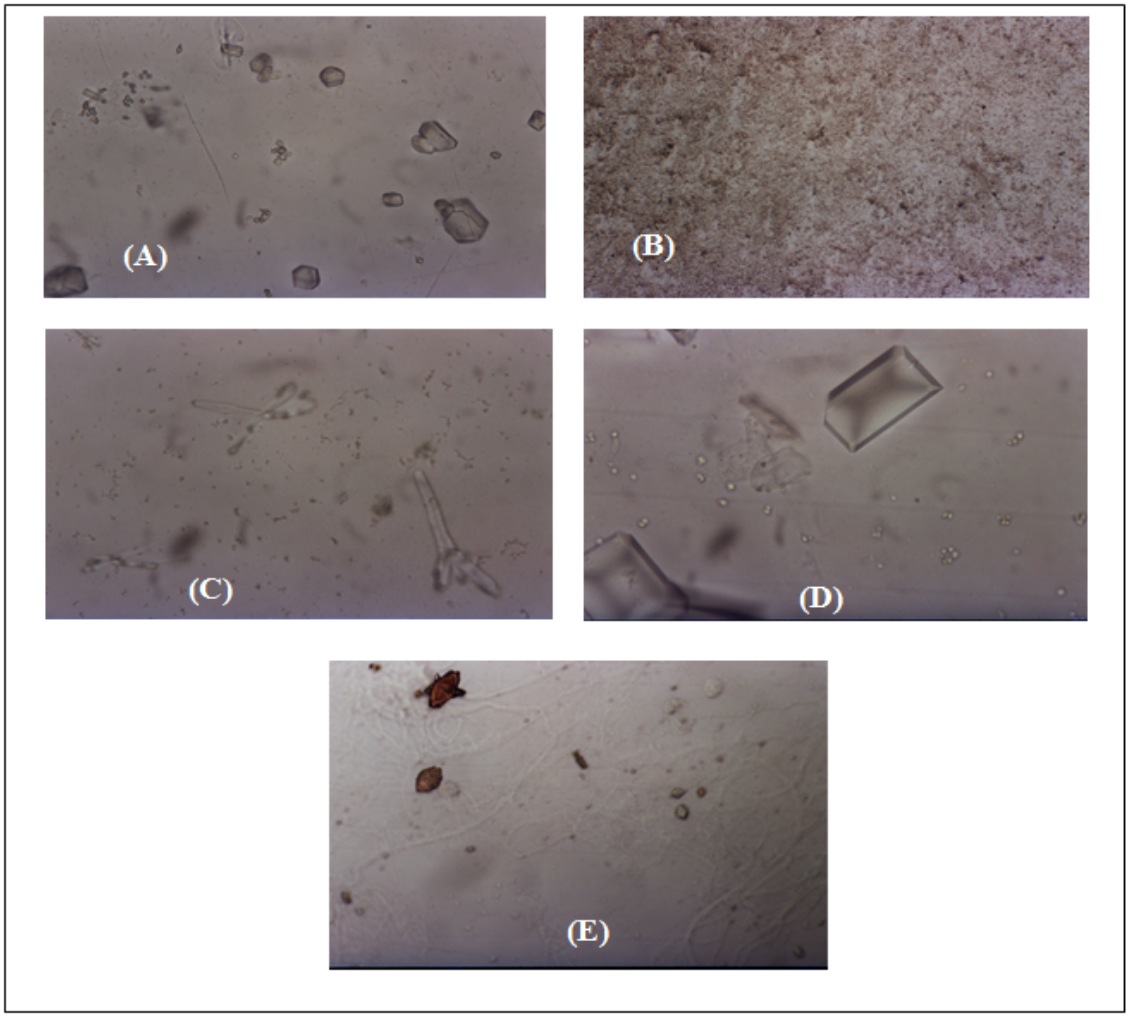

Figure I: OPLM crystal micrographs (x400) of: uric acid anhydrous and aggregate of calcium oxalate dihydrate (weddellite) and small calcium oxalate monohydrate (whewellite) crystals (A); amorphous complex urate (B); ammonium magnesium phosphate (struvite) crystals (needle shape) and amorphous carbonated complex phosphate (dark cloud shape) (C); two ammonium magnesium phosphate crystals (struvite coffin shape) (D); two uric acid dihydrate crystals (lemon shape) (E).

Table II: Frequency of crystalluria according to age group (non goitous: N = 87, goitrous: N = 180)

Category	15< age ≤ 28	28< age ≤ 40	40 < age	Total
Non goitrous	5 (1/20)	29,6 (8/27)	27,5 (11/40)	23 (20/87)
Goitrous	26.5 (13/49)	21.1 (15/71)	30 (18/60)	25.6 (46/180)

Table III: Distribution of crystalluria frequency according to age, in women (positive crystalluria in non goitrous: N = 20, positive crystalluria in goitrous: N = 46).

Category		Ages (years) 15< years ≤ 28	28< years ≤40	40 < years	Total
Non goitrous	(%)	5	40	55	100
	Number	(1)	(8)	(11)	(20)
Goitrous	(%)	28.3	32.6	39.1	100
	Number	(13)	(15)	(18)	(46)

Table IV: Distribution of crystalluria frequency of the major constituent according to age, in non goitrous women (N = 20).

Age group (years)	Crystalluria % (number)	Calcium oxalates		Uric acid and urates			Calcium phosphates	
		COM*	COD*	UA2*	UA0*	CAU*	ACCP*	AMP*
15< age ≤28	5 (1)	-	-	-	-	100 (1)	-	-
28< age ≤40	40 (8)	-	12.5 (1)	12.5 (1)	12.5 (1)	50 (4)	-	12.5 (1)
15< age ≤40	45 (9)	-	11.1 (1)	11.1 (1)	11.1 (1)	55.6 (5)	-	11.1 (1)
40 < age	55 (11)	(1)	27.3 (3)	27.3 (3)	-	27.3 (3)	9.1 (1)	-
Total of constituent	100 (20)	5 (1)	20 (4)	20 (4)	5 (1)	40 (8)	5 (1)	5 (1)
Total of chemical compound		25 (5)		65 (13)			10 (2)	

COM: calcium oxalate monohydrate; COD*: calcium oxalate dehydrate; UA2*: uric acid dehydrate; UA0*: uric acid anhydrous; CAU*: complex amorphous urates; ACCP*: amorphous carbonated complex phosphate; AMP*: ammonium magnesium phosphate (struvite).*

Tableau V: Distribution of constituent frequency of the major constituent according to age in goitrous women (N = 46).

Age group (years)	Crystalluria % (number)	Calcium Oxalates		Uric acid and Urates		Calcium Phosphates	
		COM	COD	UA2	CAU	ACCP	Brush*
15< age ≤28	28.3 (13)	7.7 (1)	15.4 (2)	23.1 (3)	30.8 (4)	23.1 (3)	-
28< age ≤40	32.6 (15)	6.7 (1)	20 (3)	26.7 (4)	26.7 (4)	20 (3)	-
15< age ≤40	60.9 (28)	7.1 (2)	17.9 (5)	25 (7)	28.6 (8)	21.4 (6)	-
40 < age	39.1 (18)	16.7 (3)	50 (9)	11.1 (2)	5.6 (1)	5.6 (1)	11.1 (2)
Total according to constituent	100 (46)	10.9 (5)	30.4 (14)	19.6 (9)	19.6 (9)	15.2 (7)	4.3 (2)
Total of chemical compound % (number)		41,3 (19)		39,2 (18)		19,5 (9)	

Brush : Brushite (calcium and hydrogen phosphate dihydrate)*

4 DISCUSSION

The average age of goitrous set (35.6 years) is relatively comparable to those reported by other authors (Mahmood et al. 2004, Paul et al. 2004). In fact Mahmood et al. have reported an average age of 29.4 years for a feminine predominance goitrous set while Paul et al have found for their same goitrous set, an average age of 33 years in the case of an advanced goiter and 37.5 years in the case of multinodular toxic goiter. In the present work the global goitrous women/men ratio is of 36/1 (table I). This ratio value confirms the fact that goiter is known like a high feminine predominance disease. In woman the estrogens can influence the thyroid and parathyroid glands development, especially in the case of papillary carcinoma that can appear before the menopause age (Kawabata et al. 2003, Arain et al. 2003, Golden et al. 2004). Moreover, pregnancy has been related to a high endemic goiter risk (Fadayev et al. 2003, Glinoer 2011, Kung et al. 2002). The phosphaturia seems probably to be correlatively accentuated by the parathyroidal hormone with evolution rate of cyclic monophosphate adenosine in urine (Zung et al. 1997, De Lellis et al. 2009). Almaden et al have suggested that the high phosphates content of urine well as the feminine sex promote the parathyroidal cells proliferation.

The analysis of the urinary samples of our goitrous set showed that the quarter (25.6%) of the samples presents a positive crystalluria (table II). We observe that goiter doesn't make the crystalluria frequency increasing since this frequency increases with age as well in the non goitrous as in the goitrous (table III). This result confirms the fact that the crystalluria frequency increases with age but doesn't sufficiently explain the fact that the lithiasic patients would present a peak beyond the vicinity of the age of 40 years in the crystalluria frequency. In the present work, as well in the goitrous as in the non goitrous persons the majority of the observed crystalluria are so pure that the mixed crystalluria doesn't represent more than a fifth of all observed crystalluria. Urinary stone lithogenesis process constituted of only one chemical species releases around a first microscopic crystalline germ of the same chemical species. However, the fact that an urinary stone is constituted by different chemical species should not mean that it is due to the mixed crystalluria. It is for these considerations in the complex mechanisms of the lithogenesis that the registered homogeneity tendency of crystalluria can be reversed in the case of urinary stones. In this present work, the non goitrous women whose age is not more than 40 years, complex amorphous urates (CAU) is the majority constituent that dominates with a 55.6% frequency (table IV). This dominance is attenuated after this age since it is compensated fairly with anhydrous uric acid dehydrate (AU2: 27.3%) and calcium oxalate dihydrate (COD: 27.3%). In the goitrous women, the majority constituent that dominates (28.6%) before the age of 40 years (table V) is also the CAU and under the age of 28 years, each one of AU0 and ACCP comes in second position, with a 23.1% frequency. Contrarily to this last result, under the 28 years age in the non goitrous women, there is an absence of such phosphate and urate chemical species. Effectively, in this goitrous set, under the age of 40 years (table V) only a quarter of the crystalluria presents an oxalocalcic nature, COD (17.9%) and COM (7.1%) but remarkably, the ACCP as a phosphate chemical species is in the second position of frequency (21.4%) comparing to the non goitrous case (0%). This can be explained by the fact that in the goitrous women the crystalluria chemical nature tendency before the vicinity of menopause age should present an uric-phosphatic chemical character. In the table V, the uric character is expressed in terms of CAU, UA2 and UA0 while the phosphatic one is related to ACCP. Beyond the age of 40 years in the goitrous patients (table V), COD is majority consistent followed by COM in second position but in the case of the non goitrous (table IV), the dominance is equitably shared by the three chemical species CAU, COD, UA2. So, contrarily to the result in the non goitrous set the oxalo-calcic character, from COD and COM, of the crystalluria appears after the menopause age in the goitrous patients. We can observe from the two tables IV and V that, globally, COM crystals are more frequent in the urine of the goitrous than in those of the non goitrous patients. Elsewhere, a work carried out by our research team in the same Tadla Azilal geographical region has associated the relatively high frequency of calcium oxalate monohydrate (COM) urolithiasis to the food style habits of the populations (Oussama et al. 2000). These results show the "crystalluria-stone" correlation (Kaid-Omar et al. 1999) according to the chemical composition, and comes particularly from the transformation of calcium oxalate dihydrate (COD) to its monohydrate shape (COM) when passing from the crystalluria state to the urinary stone one. Moreover, the populations in the region have some non convenient food habits, particularly, excessive consuming of animal proteins and beet sugar (Mbarki et al. 2006). Such habits express all abnormal, metabolic, hereditary and congenital predispositions, of the organism to develop the urinary lithiasis. COD depends more of calcium rate than of the oxalate one and the ACCP depends on calcium and phosphate. So, the frequencies of oxalo-calcic and phosphatic crystalluria are important in the case of the goitrous set, in the present work, to menopause age, since they can be linked to the calciuric and phosphaturic Thyrocalcitonine (TCT) effect (Asch 1978). Effectively, it is known that the PTH leads to a phosphaturia by inhibition of sodium-phosphor co-transport (Blaine et al. 2011). A study at the molecular scale is susceptible to determine whether the genetic parameter plays a role in this trend in phosphate excretion in the urine of patients presenting goiter. Anterior researches (Tomer et al. 2009, Citterio et al. 2013) have reported he etiology of autoimmune thyroid disease and have they highlighted the impact of the environment on genes related to thyroid, parathyroid and hypothyroid disorders. Other studies have noted that the goiter is linked to other diseases such as cardiovascular disease (Patene 2012). So one can understand the fact that thyroid gland firstly plays a

role in the organism growth and that a part of calcium and phosphor, major constituent of bone are eliminated in urines. The phosphates metabolism should be controlled by proteins so-called phosphatonines (Schiavi et al. 2002). Between the puberty and the menopause ages one woman presents a risk of the homoeostasis mess of calcium and phosphor. These two elements are essential at the time of the fetus growth in the pregnant woman. In this work, two third (120/180) of the women are constituted by women whose age doesn't exceed 40 years. Globally, we observe that in the goitrous women (table V) the phosphatic character appears with a 19.5% frequency and the two more frequent characters are oxalo-calcic (41.3%) and uric-uratic (39.2%). In the non goitrous women (table IV) only the uric-uratic character dominates enough extensively (65%). Such a contrast could provide riche information on the goiter epidemiology. Comparable results have been unregistered, in an anterior work done by our team, on a set whose patients present diabetes as another endocrinological pathology (Mbarki et al. 2005).

5 CONCLUSION

As it has been reported by other authors, the present work confirms that goiter in the Tadla Azilal has a feminine predominance. The frequently homogeneous crystalluria of the goitrous woman presents, notably, an "uric-phosphatic" chemical character before menopause age. This uric-phosphatic character decreases after this age since the tendency becomes oxalo-calcic. The decrease of phosphaturia can be related to the reduction of phosphates needs owing to the disappearance of the woman's hormonal metabolisms, in particular with the presence of the fetus growth at the pregnant woman. Thus other crystalluria studies on goitrous can confirm if the evolution of the chemical constituent frequency can give a lot of information for both of the researcher and the clinician. So, clinical analyses for goiter diagnosis and treatment could be accompanied and confirmed thanks to following the fluctuations of the crystalluria composition, notably in calcium phosphate species. Goitrous crystalluria studies can contribute to understand the mechanisms and etiology of such an epidemiology and so, to support better the goitrous patients.

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