Evaluation and Comparison of Metabolic Disorders between Patients with Unilateral and Bilateral Staghorn Renal Stones

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Purpose: Metabolic disorders are common in patients with staghorn renal stones. Aim of this study was to evaluate and compare the metabolic disorders in patients with unilateral and bilateral staghorn stones.

Materials and Methods: In this cross sectional study, 78 patients who underwent percutaneous nephrolithotomy (PCNL) for staghorn renal stones were included. The urine volume, the level of calcium, oxalate, uric acid, phosphate, sodium, citrate, creatinine, and cystine from 24 hour urine collection as well as the serum levels of calcium, phosphorus, magnesium, creatinine, blood urea nitrogen (BUN), parathyroid hormone (PTH) and uric acid were recorded and compared among the two groups with unilateral and bilateral renal stones.

Results: 56 patients (71.8%) had unilateral and 22 (28.2%) had bilateral renal stones. At least one abnormal metabolic factor was found in 32 (57.1%) and 15 (68.2%) patients with unilateral and bilateral renal stones, respectively ($P = .044$). Cystine urine levels and serum levels of BUN were higher in cases with bilateral compared to unilateral renal stones (36.4% vs. 12.5%, $P = .025$ and 27.3% vs. 1.8%, $P = .002$, respectively).

Conclusion: Metabolic factors are strongly correlated with the formation of staghorn renal stones specially bilateral ones. In our study among different metabolic factors, cystine urine levels and serum levels of BUN were significantly higher in patients with bilateral renal stones. Proper metabolic assessments are recommended in patients with staghorn urolithiasis.

Keywords: metabolic diseases; risk factors; staghorn calculi; urinary calculi chemistry

INRTRODUCTION

Staghorn stones represent 10 to 20% of all nephrolithiasis cases. However, currently, in developed countries, this incidence has decreased con¬siderably due to early prevention and treatment of urinary tract infections (UTIs).[1] These stones are mainly composed of struvite followed by calcium or cysteine based materials. Despite several published papers focusing on the significant role of UTIs as the most important etiology of such conditions, it is also believed that other factors like metabolic diseases could finally lead to such morbidities.[2,3] Furthermore, the existence of metabolic disorders is highly expected to be accompanied by bilateral staghorn stones.[4]

The treatment of staghorn stones still remains controversial as the patients with sustained staghorns in their kidneys could end up in renal failure. Mostly, the therapeutic pathways consist of 3 steps as follows: complete extraction of the stone, looking for the underlying metabolic etiologies and final treatment with the maximum basic anatomy preservation for optimal renal functions.[4,5] Thus, it is assumed that proper treatment of patients with such renal stones must also include metabolic assessments in different aspects covering the possible recurrence.[6]

Considering the fact that metabolic disorders can play an important role in occurrence of staghorn stones and the critical role of diagnosis of these conditions in prevention of nephrolithiasis, we conducted this study to evaluate the metabolic disorders in patients with unilateral and bilateral renal stones.

MATERIALS AND METHODS

In this analytic cross-sectional study, 78 patients with staghorn stones who referred to our urology department from 2014 to 2016 were enrolled. All patients were candidates for unilateral or bilateral percutaneous nephrolithotomy (PCNL). The study protocol was approved by the ethical and scientific review committee of Isfahan University of Medical Sciences (ethics committee reference number: IR.IUMS.fm.REC.101947). Written consents were obtained and the patients were assured that all the data will remain completely confidential by the authors and results will be reported as overall statistics and not addressing to any specific individual.

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Table 1. Frequencies of metabolites in the urine and serum samples of subjects with staghorn urolithiasis.

Source	Variables		Unilateral stone Number (%)	Bilateral stone Number (%)	*P*-value
24 hour urine	Calcium	normal	52 (92.9)	21 (95/5)	0.99
		High	4 (7.1)	1 (4/5)	
	Oxalate	normal	47 (83.9)	18 (81/8)	0.99
		High	9 (16.1)	4 (18/2)	
	Uric acid	normal	50 (89.3)	18 (81/8)	0.46
		High	6 (10/7)	4 (18/2)	
	Phosphate	normal	56 (100)	22 (100)	1
		High	0 (0)	0 (0)	
	Sodium	normal	43 (76/8)	21 (95/5)	0.12
		High	12 (21/4)	1 (4/5)	
		Low	1 (1/8)	0 (0)	
	Citrate	Normal	42 (76/4)	20 (90/9)	0.072
		Higher than normal	3 (5/5)	2 (9/1)	
		Lower than normal	10 (18/2)	0 (0)	
	Creatinine	Normal	56 (100)	22 (100)	1
		Abnormal	0 (0)	0 (0)	
	Cystine	Normal	49 (87/5)	14 (63/6)	0.025
		High	7 (12/5)	8 (36/4)	
Serum	Calcium	Normal	55 (98/2)	20 (90/9)	0.19
		High	1 (1/8)	2 (9/1)	
	Phosphorus	Normal	54 (96/4)	21 (95/5)	0.99
		High	2 (3/6)	1 (4/5)	
	Magnesium	Normal	56 (100)	22 (100)	1
		High	0 (0)	0 (0)	
	Creatinine	Normal	51 (91/1)	16 (72/7)	0.07
		High	5 (8/9)	6 (27/3)	
	BUN	Normal	55 (98/2)	16 (72/7)	0.002
		High	1 (1/8)	6 (27/3)	
	Phosphorus	Normal	54 (96/4)	20 (90/9)	0.32
		Higher than normal	2 (3/6)	2 (9/1)	
	PTH	normal	50 (89/3)	17 (77/3)	0.28
		abnormal	6 (10/7)	5 (22/7)	

The inclusion criteria were as follows: patients with unilateral or bilateral staghorn renal stone (defined as any branched stone occupying more than one portion of the collecting system), availability of the necessary information in patients' admission files and the consent of the patient to enter the study. Furthermore, patients with spinal cord injury and urinary diversion were excluded from the study.

In order to collect the data and facilitate the statistical analysis, a compact questionnaire was designed, including all the variables in details. A 24 hour urine volume and the levels of calcium, oxalate, uric acid, phosphate, sodium, citrate, creatinine, and cystine from a 24 hour urine collection and also the serum levels of calcium, phosphorus, magnesium, creatinine, blood urea nitrogen (BUN), parathyroid hormone (PTH) and uric acid were recorded from the patients' files. According to the references of our laboratory, cystine > 250 mg, citrate < 450 mg in males and < 550 mg in females, sodium > 220 mEq, oxalate > 40 mg, uric acid > 800 mg and calcium > 200 mg from 24 hour urine collections and also serum levels of calcium > 10.2 mg/dL, phosphorus > 4.5mg/dL, magnesium > 2.2mg/dL, creatinine > 1.2 mg/dL in males and > 1.1 mg/dL in females, BUN > 20mg/dL, PTH > 65 pg/mL and uric acid > 7 mg/dL in males and > 6 mg/dL in females were considered abnormal.

Finally all the data were analyzed by the SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). The variables were initially evaluated for normality statistical tests and T-tests or non-parametric statistical tests (e.g. Man-Whitney or Chi-square tests) were applied whenever needed. The significance cut-off range was considered as *P* value < .05.

RESULTS

Of 78 patients, 56 (71.8%) and 22 (28.2%) cases had unilateral and bilateral renal stones, respectively. The mean age of patients with unilateral and bilateral stones were 48.4 ± 16.8 and 45.6 ± 12.3 years old, respectively revealing no significant difference ($P = .49$). Also, 51.8% of patients in the unilateral group and 40.9 % of bilateral group were under 50 years old ($P = 0.26$). 33 (58.9%) patients from unilateral and 16 (72.7%) from bilateral group were men ($P > .05$).

The mean size of stones in unilateral and bilateral stones was 3.53 ± 1.51 mm and 4.95 ± 0.21 millimeters, respectively which showed a significant difference between the two groups ($P < 0.001$).

Only one patient suffered from hyperparathyroidism (1.3%) and other co-morbidities relevant to staghorn stones formation like renal tubular acidosis (RTA) or gout were not reported by the patients.

High cystine, citrate, sodium, oxalate, uric acid and calcium levels from 24 hour urine collections were seen in 19.2%, 18%, 16.7%, 12.8% and 6.4% of patients, respectively. These metabolites were the most frequent urine components in our patients. Applying chi-square and fisher exact tests, only cystine levels from 24 hour urine collections were significantly higher in bilateral stones ($P = .025$). (**Table 1**) The *P* values refer to the comparison between the high levels of both groups.

High serum levels of creatinine, PTH, BUN, uric acid and phosphorus were seen in 14.1%, 14.1%, 9%, 1%, 3.8% and 3.8% of all patients, respectively. The serum level of BUN was also significantly higher in bilateral stones ($P = .002$). (**Table 1**)

According to the results, 24 (42.9 %) patients from unilateral and 7 (31.8%) from bilateral renal stone groups

Table 2. Frequencies of consisting materials of the stones in subjects with unilateral and bilateral staghorn urolithiasis.

Material		Unilateral		Bilateral		*P*-value
		Count	Percent	Count	Percent	
Calcium phosphate	No	44	78/6	9	40/9	0.001
	yes	12	21/4	13	59/1	
Struvite	No	32	57/1	7	31/8	0.044
	Yes	24	42/9	15	68/2	
Cystine	No	50	89/3	16	72/7	0.09
	Yes	6	10/7	6	27/3	
Uric acid	No	27	48/2	13	59/1	0.39
	Yes	29	51/8	9	40/9	
Calcium oxalate	No	5	8/9	3	13/6	0.54
	Yes	51	91/1	19	86/4	

had no metabolic disorders. 32 (57.1%) patients with unilateral and 15 (68.2%) patients with bilateral renal stones reported at least one abnormal metabolic factor ($P = .044$). Calcium oxalate and uric acid were the most components in unilateral stones and calcium oxalate and struvite were the most in bilateral subjects. Applying Mann-Whitney test, we found that the proportion of calcium phosphate and cystine materials were statistically higher in patients with bilateral staghorn stones (**Table 2**).

DISCUSSION

To the best of our knowledge, there is no study that compares the metabolic state in unilateral and bilateral staghorn renal stones. Our finding showed the importance of metabolic evaluations in staghorn stones, particularly in bilateral ones.

The state of metabolic disorder in urolithiasis may be variable according to the ethnical and geographic differences. Some previously published papers reported metabolic alternations in 52.9% of men and 40.7% of women with staghorn calculus in western countries.[7] In a recent study done in US patients on 52 kidneys with complete staghorn calculi, 56% were metabolic and 44% were infection stones. Multiple urinary metabolic abnormalities were noted in all patients with metabolic stones who completed evaluation which the most common findings were increased urinary sodium, low urine volume, hypocitraturia and hypercalciuria while no patient had a corresponding serum abnormality.[8] Some studies showed greater correlation. In two Brazilian studies, metabolic disorders were present in nearly 70% and 95.5% of patients with staghorn calculi, respectively. In both studies hypercalciuria and hypocitraturia were the most common disorders.[4,5] Also in a Swedish study among 33 patients with staghorn stones, 24-hour urine composition was normal in only 3 patients. Furthermore, in 59 percent an increased calcium oxalate risk index was observed suggesting that calcium oxalate risk factors might contribute to the development of staghorn stones.[9] On the other hand some eastern studies revealed different results. In a study on Japanese patients with staghorn renal stones, it was shown that hypercalciuria and cystinuria was present in 37.8 % and 2.4% of the patients, respectively.[10] Another Japanese study on 58 patients showed that of 13 patients with infectious staghorn stones containing calcium oxalate in the nuclei, only 2 had metabolic disorders.[11] In a Thai study on 5445 urolithiasis patients complete staghorn stones were seen in 1.6% of cases and hyperuricemia was the most common metabolic disorder which was seen in 61.8% of patients with this calculus.[12] In our study the levels of metabolic factors had higher figures than normal ranges and were also found more in bilateral stone group significantly. The most common disorder was hyperuricemia which was seen in 13.1% followed by hypercalciuria (6.4%) but none of them had cystinuria. Also the levels of urine cystine and serum BUN were significantly higher in bilateral ones, while other factors were not statistically different.

In our study calcium oxalate was the main component followed by uric acid and struvite in unilateral and bilateral renal stones, respectively. This could be attributed to the increase of metabolic syndrome even among Iranian people,[13,14] which leads to the increase of urolithiasis specially calcium and uric acid stones.[15] Some previous studies and guidelines have shown that staghorn calculi are most frequently composed of struvite and/or calcium carbonate apatite.[16] Also they suggest that metabolic stones are uncommon in the composition of such stones. This is mainly because of the association between urolithiasis and urinary tract infection, although this relationship is complex and difficult to analyze.[17] Recently some other studies showed the changing composition of renal stones.[18,19] In one cohort study metabolic stones comprised a large proportion of complete staghorn calculi and calcium phosphate was the most common stone composition.[11]

One of the limitations of our study was that we did not evaluate the urinary cultures. Also the small sample size and the retrospective character of the study are considered major limitations of our study which was mainly based on the number of patients with staghorn renal stone referred to the pointed study center. For future studies we recommend considering multi-centric similar studies, evaluating other variables in even longer periods.

CONCLUSIONS

Metabolic factors are strongly involved in the formation of staghorn renal stones which is more significant in bilateral ones. In our study the most common disorder was hyperuricemia followed by hypercalciuria. Furthermore, among different metabolic factors, cystine urine levels and serum levels of BUN were significantly higher in patients with bilateral stones. Proper assessments are recommended regarding these conditions in patients with staghorn urolithiasis.

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CONFLICT ON INTEREST

The authors report no conflict of interest.

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