Metabolic evaluation in patients with recurrent calcium oxalate stones

Rekürren kalsiyum oksalat taş hastalarında metabolik değerlendirme

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Abstract

Objective: This study aimed to evaluate the metabolic changes in patients with recurrent calcium oxalate stones.

Materials and methods: We evaluated 143 patients with recurrent oxalate stones and measured serum calcium, phosphate, creatinine, urate, and parathormone. In addition, 24-h urinary output was monitored and collected for the measurement of total volume, pH, citrate, calcium, urate, oxalate, phosphorus, sodium, and magnesium.

Results: The mean age of the patients was 42.8±10.8 years, and 132 out of 143 patients (92.3%) had metabolic abnormalities. There were no metabolic abnormalities in only 11 (7.7%) patients. Thirty (20.1%) patients only had one metabolic abnormality, and 102 (71.3%) patients had multiple metabolic abnormalities. Hyperoxaluria was the major metabolic abnormality (64.4%), but we also detected low urinary volume, hypercalciuria, hypocitraturia, hypernatriuria, and hyperuricosuria in 66 (46.2%), 47 (32.8%), 47 (32.8%), 44 (30.8%), and 21 (14.7%) patients, respectively.

Conclusion: There were several metabolic abnormalities in patients with recurrent calcium oxalate stones, and the most important were hyperoxaluria, hypercalciuria, hypocitraturia, and low urinary volume. These metabolic abnormalities should be detected and corrected to prevent the recurrence of stones.

Key words: Metabolic changes; prevention; recurrence; urolithiasis.

Özet

Amaç: Bu çalışmada rekürren kalsiyum oksalat taş hastalarında metabolik değişikliklerin değerlendirilmesi amaçlanmıştır.

Gereç ve yöntem: Rekürren kalsiyum oksalat taşı olan 143 hasta değerlendirildi ve serumda kalsiyum, fosfat, kreatinin, ürat ve parathormon ölçüldü. Ayrıca 24 saatlik idrarda total hacim, pH, sitrat, kalsiyum, ürat, oksalat, fosfor, sodyum ve magnezyum bakıldı.

Bulgular: Hastaların ortalama yaşı 42.8±10.8 olarak saptandı. Çalışmaya alınan 143 hastanın 132'sinde (%92.3) metabolik bozukluk saptandı. Sadece 11 (%7.7) hastada metabolik bozukluk yoktu. Metabolik bozukluk saptanan hastaların 102'sinde (%71.3) mikst metabolik bozukluk varken 30'unda (%20.1) tek metabolik bozukluk belirlendi. Hiperoksalüri (%64.4) temel metabolik bozukluk olarak ortaya çıktı. Ancak düşük idrar hacmi 66 (%46.2), hiperkalsiuri 47 (%32.8), hipositratüri 47 (%32.8), hipernatriüri 44 (%30.8) ve hiperürikozüri 21 (%14.7) hastada belirlendi.

Sonuç: Rekürren kalsiyum oksalat taş hastalarında çeşitli metabolik bozukluklar vardır. Bu metabolik bozukluklardan en önemlileri hiperoksalüri, hiperkalisüri, hipositratüri ve düşük idrar hacmidir. Bu metabolik bozukluklar belirlenmeli ve taş rekürrenslerinin önlenmesi için düzeltilmelidir.

Anahtar sözcükler: Metabolik değişiklik; önlem; rekürrens; ürolitiyazis.

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Urolithiasis is a common disease throughout the world that affects the general population. Urolithiasis is characterized by a recurrence rate of approximately 50-60% within 10 years.[1] Several factors, such as age, gender, climate, metabolic abnormalities and heredity, are related to the development of urinary stones.[2] Insulin resistant states, history of hypertension, primary hyperparathyroidism, history of gout, chronic metabolic acidosis, and surgical menopause are also associated with increased risk of urinary stones.[3-5] Metabolic abnormalities are the most important factors because they can be modified to prevent the risk of urinary stones.

There are several types of urinary stones, and they are classified according to chemical composition. Calcium oxalate is the major component of the vast majority of stones. In patients with calcium oxalate stones, metabolic evaluation and intervention should be considered to prevent the recurrence of stones.

The purpose of this study was to determine the prevalence of metabolic changes and abnormalities in the blood and urine of patients with recurrent calcium oxalate stones.

Materials and methods

The present study prospectively examined 143 patients from December 2004 to April 2006. All patients had recurrent idiopathic calcium oxalate stones (i.e., calcium oxalate monohydrate or dihydrate stones), and the stones were either removed by operation or analyzed after spontaneous passage. The main criteria for inclusion were the presence of calcium oxalate stones and at least two episodes of urinary stones (i.e., endoscopic or surgical elimination of two or more urinary stones). Patients were excluded if they were younger than 16 and/or had any chronic diseases, chronic drug usage or other urinary disorders, such as proteinuria, urinary infection or obstruction.

An informational form about the study design was given to all patients, and urine sample collected for 24-hour and blood sample were obtained for analysis. We also evaluated the medical history of each patient, including family history, recurrent urinary infections and oral fluid intake. In addition, we measured the serum levels of calcium, phosphorus, creatinine, urate and parathormone.

Twenty-four-hour urine samples were collected from the patients with normal dietary habits without acute stone disease for the measurement of pH and total volume. We also measured serum levels of citrate, calcium, urate, oxalate, phosphorus, sodium and magnesium. In addition, we also collected urine samples from patients who underwent urinary surgery (samples were not collected until at least six week after the surgery). Twenty-four-hour urine samples were collected in plastic boxes, which do not react chemically by standard methods, and were stored at 2-8ºC. Hydrochloric acid was used for the determination of oxalate, and boric acid was used for the determination of citrate.

The serum levels of metabolic parameters were measured by standard chemical procedures. Serum calcium (normal range 8.4-10.2 mg/dL), creatinine (normal range 0.5-1.4 mg/dL) and phosphorus (normal range 2.5-4.5 mg/dL) were measured by colorimetric assays; urate was determined by an enzymatic colorimetric assay (normal range 2.5-8 mg/dL for males and 1.5-6.0 mg/dL for females); and parathormone was measured by chemiluminescence methods (normal range 0.8-5.2 pmol/L). For 24-h samples, levels of calcium, phosphorus, sodium, and urate were measured with an Aeroset autoanalyzer with special kits (Abbot, Chicago, IL, USA). Oxalate was manually measured with Hitachi oxalate oxidase and peroxidase assays (Boehringer Mannheim, Laval, Quebec), and citrate was manually measured with a citrate lyase assay. Urinary pH was measured with Orion model 330 pH meter (MSUM Biochemistry, Moorhead, MN, USA). Hyperoxaluria was defined as a urinary oxalate level greater than 40 mg/day, and hypercalciuria was defined as a urinary calcium level greater than 300 mg/day. Hypernatriuria was defined as a urinary sodium level greater than 220 mmol/day, hyperuricosuria was defined as a urinary urate level greater than 750 mg/day and hypocitraturia was defined as a urinary citrate level less than 350 mg/day. Hypomagnesuria was defined as a urinary magnesium level less than 3 mg/day. Hypophosphaturia was defined as a urinary phosphorus level less than 0.9 g/day, and hyperphosphaturia was defined as a urinary phosphorus level more than 1.3 g/day. A urinary volume greater than 2,000 cc/day was considered to be normal.

Statistical analysis was performed using SPSS version 12.0 (SPSS Inc. Chicago, IL, USA). Results are presented as mean and median percentage and assessed statistically using *t* tests to compare between male and female. The frequency of metabolic abnormalities was compared using *t* and chi-square tests. $P<0.05$ was considered statistically significant.

Results

The present study consisted of significantly more males (91, 63.6%) than females (52, 36.4%). The mean age of the patients was 42.81±10.8 years, and the mean ages of the males and females were 41.2±9.4 years and 45.6±11.3 years, respectively.

Out of the 143 total patients, 76 (53.1%) had a family history of urolithiasis, and 20 (14.0%) patients had a history of recurrent urinary tract infection. Table 1 shows the gender, history of recurrent urinary tract infection and fluid intake of the patients.

Interestingly, 132 of the 143 patients had metabolic abnormalities, whereas there were no metabolic abnormalities in 11 (7.7%) patients. Thirty patients (20.1%) only had one metabolic abnormality, and 102 (71.32%) patients had multiple metabolic abnormalities. Table 2 shows the frequency of the metabolic changes that were diagnosed in the patients. In this study, hyperoxaluria was the most commonly observed metabolic abnormality. Indeed, hyperoxaluria was found in 92 (64.4%) of the patients [62 (43.4%) males and 30 (21.0%) females]. Slight hyperoxaluria (i.e., a urinary oxalate level between 40-100 mg/day) was found in 58 (40.5%) patients, and severe hyperoxaluria (i.e., urinary oxalate level >100 mg/day) was found in 34 (23.8%) patients. In addition, 66 (46.2%) patients had low urinary volume (urine amount <1 L/day). Other significant metabolic abnormalities were hypercalciuria, hypocitraturia and hypernatriuria. Hypercalciuria and hypocitraturia were each present in 47 (32.8%) patients, and hypernatriuria was found in 44 (30.8%) patients. Twenty-one (14.7%) patients had hyperuricosuria: 19 (13.3%) males and 2 (1.4%) females. Hypomagnesuria and primary hyperparathyroidism were found in 13 (9.1%) patients and 27 (18.9%) patients, respectively. Thirteen (9.1%) of the patients had a parathyroid adenoma, and this was more prevalent in females (12 females and 1 male). Secondary hyperparathyroidism was found in 2 (1.4%) patients.

In patients with recurrent calcium oxalate stones, the single major metabolic abnormality was hyperoxaluria. Interestingly, 21 (14.7%) patients only had hyperoxaluria, and only 7 of these patients had severe hyperoxaluria. Only 4 (2.8%) patients had hypercalciuria as their only metabolic abnormality.

Table 1. The gender distribution, history of recurrent urinary tract infection, and fluid intake of the patients

		Number	%	Mean age
Gender	Male	91	63.6	41.2
	Female	52	36.4	45.6
Family history	Yes	76	53.1	40.4
	No	67	46.9	45.5
History of RUTI	Yes	20	14.0	43.9
	No	123	86.0	42.6
Fluid intake (daily)	Low (<1 L)	46	32.2	42.1
	Mild (1-2 L)	65	45.5	43.3
	High (>2 L)	32	22.4	42.9
Total		143	100.0	42.8

RUTI: Recurrent urinary tract infection.

Table 2. The frequency of metabolic abnormalities diagnosed in patients with recurrent calcium oxalate stones [n (%)]

	Male (n=91)	Female (n=52)	Total (n=143)
Hyperoxaluria	62 (43.4)	30 (21.0)	92 (64.4)
Low urinary volume	35 (24.4)	31 (21.7)	66 (46.2)
Hypercalciuria	28 (19.5)	19 (13.3)	47 (32.8)
Hypocitraturia	31 (21.7)	16 (11.2)	47 (32.8)
Hypernatriuria	31 (21.7)	13 (9.1)	44 (30.8)
Hypophosphaturia	24 (16.7)	14 (9.8)	38 (26.6)
Primer hyperparathyroidism	8 (5.6)	18 (12.6)	27 (18.9)
Hyperuricosuria	19 (13.3)	2 (1.4)	21 (14.7)
Hypomagnesuria	9 (6.3)	4 (2.8)	13 (9.1)
Parathyroid adenoma	1 (0.7)	12 (8.4)	13 (9.1)
Hyperphosphaturia	8 (5.6)	2 (1.4)	10 (7.0)
Secondary hyperparathyroidism	1 (0.7)	1 (0.7)	2 (1.4)
No abnormality	6 (4.2)	5 (3.5)	11 (7.7)

Discussion

Urolithiasis, which has several etiological factors, may occur as a result of metabolic changes and/or environmental nutritional factors. The most common stones are calcium stones, the majority of which consist of calcium oxalate.[6] Many previous studies have investigated metabolic abnormalities in several populations,[7-11] but further evaluations and metabolic investigations are required to prevent the recurrence of stones. Thus, the present study evaluated metabolic abnormalities in patients with recurrent calcium oxalate stones.

Urolithiasis is a disease that is known to predominantly affect males. In recent years, however, the incidence of urolithiasis in women has been increasing.

A study by Scales et al.[12] found that the male:female ratio of urolithiasis cases diminished from 1.7 to 1.3 during the last 20 years in the USA. Muslumanoglu et al.[13] updated the epidemiological data for urinary stone disease and reported that the male:female ratio was 1:1. In the present study, we found a male predominance (i.e., the male:female ratio was 1.75:1). Our results seem to be different from the literature, indicating the male predominance in patients with calcium oxalate stones.

In the present study, the interesting factors in the patients' medical histories were a genetic predisposition to urolithiasis and dietary fluid intake. Seventy-six (53.1%) patients had a genetic predisposition for stone formation and recurrence. Interestingly, 111 patients had an inadequate daily dietary fluid intake. In addition, 32.2% of patients had a history of fluid intake less than 1 L/day, and 45.5% of patients had a history of moderate daily (1-2 L/day) fluid intake. Metabolic abnormalities were detected in 132 out of 143 patients, which demonstrated that metabolic abnormalities are common in patients with recurrent calcium oxalate stones. In the present study of patients with recurrent calcium oxalate stones, 102 (71.3%) patients had multiple metabolic abnormalities. In a study by Amaro et al.[11] 62.2% of patients had multiple metabolic abnormalities; however, the patients did not have recurrent calcium oxalate stones. Therefore, it can be presumed that multiple metabolic abnormalities are more common in patients with recurrent calcium oxalate stones.

Medical preventive measures are very important in recurrent calcium stone patients. To decrease the recurrence of stones in these patients, their metabolic profiles should be carefully evaluated, and diet and medical preventive measures should be applied. The dietary intervention and preventive measures should aim to change patients' sedentary lifestyles and prevent diseases such as diabetes, obesity and hypertension. In addition, recurrent calcium stone patients should attempt to increase their fluid intake (mean urinary volume 2-2.5 L/day), restrict sodium and oxalate intake, maintain a normal calcium balance, and follow a diet that contains suitable levels of citrate and uric acid. Low urinary volume and low fluid intake are risk factors for urolithiasis, and increased fluid intake should be encouraged for all stone patients.[14] In the present study, we found that 66 (46.2%) patients had low urinary volume (less than 2,000 cc/day), but 14 (9.8%) of these patients had a urinary volume of more than 1,000 cc. In a study by Siener et al.[15] 57.9% of patients had low urinary volume (less than 2,000 cc/day). In our study, low urinary volume was confirmed to be a significant risk factor for urolithiasis.

Hyperoxaluria, which may result from an increased dietary intake of oxalate, endogenous production and/or excessive intestinal absorption, is the primary risk factor for the formation of calcium oxalate stones.[16] Interestingly, the rate of hyperoxaluria is not consistent between studies that have evaluated metabolic abnormalities. For example, Siener et al.[15] reported a 14% prevalence of hyperoxaluria, whereas Amaro et al.[11] found a 21% prevalence. In the present study, however, hyperoxaluria was most common metabolic abnormality with a prevalence of 64.4%. Because hyperoxaluria is a metabolic abnormality that can be reduced by dietary intervention, medical preventative measures should primarily contain dietary intervention for hyperoxaluria.

In the present study, hyperoxaluria was the major metabolic abnormality; however, other studies have found different results. In a study evaluating patients with recurrent calcium oxalate stones, Siener et al.[15] showed that the most common metabolic abnormality was low urinary volume (57.9%), and the second most common metabolic abnormality was hypocitraturia (57.0%). Conversely, Karabacak et al.[17] evaluated adult and pediatric patients with stones and found that the most common metabolic abnormality was hypercalciuria (50.5%), and the second most common metabolic abnormality was hyperoxaluria (31.9%). Furthermore, Yagisawa et al.[18] found that the most common metabolic abnormalities were hypercalciuria and low urinary volume. Taken together, the results of these studies show that there are several prevalent metabolic abnormalities in patients with recurrent calcium oxalate stones. Although there are different results in the literature, the most common metabolic abnormalities are hyperoxaluria, hypercalciuria and low urinary volume.

Other remarkable metabolic abnormalities in our study were hypercalciuria and hypocitraturia. Hypercalciuria causes an increase in urinary crystal-

lization and stone formation; however, restricting calcium is controversial, and some doctors do not believe that calcium restriction is necessary in patients with calcium oxalate stones.[19] In the present study, hypercalciuria was found in 47 (32.8%) patients. In contrast, a study by Amaro et al.[11] found a 74% prevalence of hyperoxaluria. Citrate is a natural inhibitor of stone formation, and its absence in urine causes an increase in the risk of stone formation. Numerous studies have shown that the prevalence of hypocitraturia is between 19% and 63%.[20,21] In the present study, the prevalence of hypocitraturia was 14%.

In recurrent stone patients, urinary sodium has hypocitraturic and calciuric effect.[22] In the present study, hypernatriuria was found in 39.8% of the patients. Therefore, urinary sodium should also be evaluated along with calcium, oxalate and citrate in patients with recurrent calcium oxalate stones.

Urate is an end product of protein metabolism, and hyperuricosuria is a potential risk factor for the formation of urinary stones. In a study by Brockis et al.[23] hyperuricosuria and hyperuricemia were the most common metabolic changes, and these conditions were more commonly observed in males. In a study by Amaro et al.[11] the prevalence of hyperuricosuria was 20.2%, and it was more common in males. Similarly, we also found hyperuricosuria in 19 (13.3%) male patients compared with only 2 (1.4%) female patients, which confirmed that hyperuricosuria is more common in male patients with recurrent calcium oxalate stones.

Hypomagnesuria, which has been considered to be a potential risk factor for the formation of calcium oxalate stones,[24] was detected in 9.1% of the patients. Magnesium supplementation has been shown to be effective in preventing stone recurrences.

Primary hyperparathyroidism and parathyroid adenoma were diagnosed in 18.9% and 9.1%, respectively, of patients with recurrent calcium oxalate stones. This result was different from the outcome of other studies that evaluated all stone patients;[11] thus, hyperparathyroidism and parathyroid adenoma should be considered in patients with recurrent calcium oxalate stones, especially in females.

In conclusion, several metabolic abnormalities are common in patients with recurrent calcium oxalate stones; and hyperoxaluria, hypercalciuria, hypocitraturia, and low urinary volume appear to be the most important abnormalities. Physicians should look for these metabolic abnormalities in patients with recurrent calcium oxalate stones, and measures should be implemented to prevent the recurrence of stones in these patients.

Conflict of interest

No conflict of interest was declared by the authors.

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