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The Significance of Stone Analysis, Metabolic Evaluation and Their Effect on Metaphylaxis: The Results from Tekirdağ Province

Taş Analizi, Metabolik Değerlendirmenin Önemi ve Metafilaksi Üzerine Etkileri: Tekirdağ İlinden Sonuçlar

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ABSTRACT

Aim: The aim of this study is to present the results of stone analysis and metabolic evaluation in Tekirdağ province, determine the demographic and personal characteristics and relationships of patients with these, and reveal their effects on metaphylaxis.

Materials and Methods: The data of 312 patients with urinary system stone disease (USD), who applied to our clinic between August 2018 and January 2021, were analyzed. Stone analysis was performed on these patients using the spectroscopic method. The metabolic evaluation was performed in 24-hour urine and plasma simultaneously on 156 patients with high risk. Age, gender, body mass index, stone localization, stone density (HU), volumes, and 24-hour urine and serum plasma of the patients were evaluated.

Results: The USD was found predominantly in males, in multiple locations in the urinary system, frequently as a single stone, with sterile urine culture. The most frequently detected stone type was calcium oxalate; the least common type of stone was xanthine. The highest mean HU was in calcium oxalate stones, and the lowest was in uric acid + ammonium urate stones. As the calcium content increased, the HU of the stone increased. Hypercalciuria was the most common abnormality in urine, while hyperuricemia was the most common and hypercalcemia the least common abnormality in plasma. Potassium citrate was used most frequently for metaphylaxis. The rate of potassium citrate metaphylaxis in appropriate patients was 43.3%, and the recurrence rate in these patients was 20%.

Conclusion: Metabolic evaluation and stone analysis provide valuable data about USD patients. Urologists should evaluate and apply them more frequently, as these data may minimize stone-related interventions via metaphylaxis.

Keywords: Stone analysis, metabolic evaluation, metaphylaxis

ÖZ

Amaç: Bu çalışmanın amacı, Tekirdağ ilindeki üriner sistem taş hastalığı (ÜSTH) hastalarının taş analizi ve metabolik değerlendirme sonuçlarını sunmak, hastaların demografik ve kişisel özelliklerini ve bunlarla ilişkilerini belirlemek ve metafilaksi üzerindeki etkilerini ortaya koymaktır.

Gereç ve Yöntem: Ağustos 2018 ile Ocak 2021 tarihleri arasında kliniğimize başvuran ÜSTH olan 312 hastanın verileri analiz edildi. Bu hastalarda spektroskopik yöntem kullanılarak taş analizi yapıldı. Taş açısından yüksek riskli 156 hastada metabolik değerlendirme, eş zamanlı olarak 24 saatlik idrar ile analizi ve serumda yapıldı. Hastaların yaşı, cinsiyeti, vücut kitle indeksi, taş lokalizasyonu, yoğunlukları (HU), hacimleri ve 24 saatlik idrar ve serum parametreleri değerlendirildi.

Bulgular: ÜSTH çoğunlukla erkeklerde, üriner sistemde birden fazla yerde, sıklıkla tek, steril idrar kültürüyle bulundu; en sık tespit edilen taş cinsi kalsiyum oksalattı; en az görülen taş türü ise ksantindi. En yüksek ortalama HU kalsiyum oksalat taşlarında, en düşük ortalama HU ise ürik asit + amonyum ürat taşlarındaydı. Kalsiyum içeriği arttıkça taşın dansitesinin de arttığı tespit edildi. Hiperkalsiüri idrarda en sık görülen metabolik

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parametreydi; plazmada ise en sık hiperürisemi ve en az hiperkalsemi gözlenmiştir. Metafilaksi için en sık potasyum sitrat kullanılmıştır. Uygun hastalarda potasyum sitrat metafilaksisi oranı %43,3, bu hastalarda taş nüksü oranı ise %20'dir.

Sonuç: Metabolik değerlendirme ve taş analizi, ÜSTH hastaları hakkında değerli veriler sağlar. Ürologlar bunları daha sık değerlendirmeli ve uygulamalıdır. Çünkü bu veriler metafilaksi yoluyla taşla ilişkili ek girişimleri en aza indirebilir.

Anahtar Kelimeler: Taş analizi, metabolik değerlendirme, metaflaksi

INTRODUCTION

Urinary system stone disease (USD) is the third most common medical issue in urology, following urinary tract infections and prostate pathologies[1]. It is a prevalent urological disorder with a variable incidence of 1% to 20% worldwide[2,3]. It is also a common disease in Türkiye, with a prevalence rate of 11.1%[4]. The treatment strategies for USD changed significantly with the technological developments in endourology. Extracorporeal shockwave lithotripsy, percutaneous nephrolithotomy, and retrograde intrarenal surgery are the most commonly used treatment methods, accompanied by a diverse range of available equipment due to technological developments[5]. On the other hand, USD is a chronic disease with high recurrence rates ranging between 21% and 59% within 5 years of the period[6]. Nearly half of the patients need multiple interventions. For this reason, preventing the stone recurrence is as vital as treating the existing stone.

To prevent the recurrence, determining the stone composition is important and essential[7]. Stone analysis can be performed by X-ray diffraction or infrared spectroscopy, whereas chemical analysis is ineffective[8,9]. After determining the type of stone, a metabolic evaluation using 24-hour urine and routine plasma biochemical parameters will help reveal the etiology of stone formation and identify any predisposing factors. Metabolic evaluation is strongly recommended in many guidelines for high-risk stone formers[9]. Unless these procedures are performed, USD treatment will be half-finished and incomplete. Metaphylaxis, and in appropriate patients based on the metabolic evaluation results, can prevent re-stone formation and reduce the need for re-operation, intervention, or stone-related hospitalization.

The first aim of our study was to document the single-center results of stone analysis and metabolic evaluations of patients who were treated for USD. The second aim was to determine the necessity of stone analysis and metabolic evaluation of patients for possible metaphylaxis.

MATERIALS AND METHODS

Approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (decision no: 2020.79.04.03, date: 30.04.2020). the patients who had surgery for USD between August 2018 and January 2021 were retrospectively included in the study. A written informed consent was obtained from participants (for the ones under the age of 18 years, a written informed consent was obtained from their parents/legal guardians/next of kin) to participate in the study. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

All patients were given written informed consent before the surgery. Although the study was designed retrospectively, the data used were obtained prospectively. The stone fragments were received during the surgeries, and the stone analysis was performed using infrared spectrometry (JASCO Ft/IR-4600 Fourier Transform Infrared Spectrometer, Japan). The patients for whom we could not obtain stone fragments were excluded from the study.

Stone types were classified into ten main types. According to these classifications, stones containing calcium, stones of a single type, and stones that combine more than one stone component were also noted as the subgroups. Patients' clinical and demographic properties, such as age, gender, body mass index, stone localization, stone density (HU), and stone volume, were noted. Non-contrast abdominopelvic tomography (NCCT) was used to evaluate the stone-related variables. Stone volumes were calculated with 3-dimensional diameters using the ellipsoid volume formula (axial diameter x coronal diameter x sagittal diameter x 0.167 x π) (mm^3)[10]. For multiple stones, the total stone volume was calculated by the addition of each stone's volume. The clinical and demographic properties of patients were compared according to the stone types.

A NCCT was performed at the end of the first month of the surgery, and stone-free status was evaluated. Fragments smaller than 3mm were considered significant for stone-free status. A metabolic evaluation was performed on patients, who were stone-free and who were categorized as a high-risk group according to the European Association of (EAU) guidelines[11].

None of the patients had a JJ stent during metabolic evaluation. The patients were asked to collect their 24-hour urine in special plastic containers. A container containing 10 mL of 6 mmoL of hydrochloric acid and a second clear container was used for the first and second 24-hour urine collection, respectively. There were no dietary restrictions for the patients when they collected the urine. Twenty-four-hour urine phosphorus, calcium, creatinine, magnesium, potassium, sodium, uric acid, cystine, and citrate were evaluated, and the serum parameters such as uric acid, sodium, citrate, potassium, parathormone, oxalate, magnesium, creatinine, chlorine, calcium, and phosphorus were tested at the same time. In addition, the results of stone analysis and metabolic evaluation also analyzed whether metaphylaxis was applied for pathological conditions or necessary situations.

Statistical Analysis

The statistical analysis of the variables was performed by SPSS 25.0 (IBM, Armonk, NY, USA) software. Frequency and percentage were used for categorical variables, while the mean and standard deviation were used for continuous variables. Normality tests were performed using the Kolmogorov-Smirnov and Shapiro-Wilk tests to compare the quantitative data of the groups. Parametric data were evaluated using the Student's t-test, and non-parametric data were assessed using the Mann-Whitney U test. The chi-square test was used to compare the data of age groups, and odds ratios were used to determine risk. The results were evaluated with a 95% confidence interval, with a p<0.05 value considered statistically significant.

Table 1. Patient demographics and stone parameters of the patients with stone analysis

Variable	Value
Age (mean ± SD)	52.0±15.9 (minimum: 3, maximum: 85)
Gender (n, %)	
Male	185 (59.3%)
Female	127 (40.7%)
BMI (kg/m²) (mean ± SD)	27.5±4.1 (minimum: 16.9, maximum: 44.1)
Stone location (n, %)	
Bladder	10 (3.2%)
Distal ureter	49 (15.7%)
Mid-ureter	26 (8.3%)
Proximal ureter	51 (16.3%)
Renal pelvis	53 (17.0%)
Middle calyx	8 (2.6%)
Lower calyx	18 (5.8%)
Upper calyx	7 (2.2%)
Multiple location	90 (28.8%)
Side (n, %)	
Right	139 (44.6%)
Left	162 (51.9%)
Bladder	11 (3.5%)
Stone number (n, %)	
Single	241 (77.2%)
Multiple	71 (22.8%)
HU (mean ± SD)	1012.2±315.1
Stone volume (mm³) (mean ± SD)	1605.0±3445.1
Preoperative urine culture (n, %)	
Negative	254 (81.4%)
Positive	58 (18.6%)

SD: Standard deviation, BMI: Body mass index, HU: Stone density

RESULTS

A total of 312 patients with stone analyses were included in the study. Metabolic evaluation was performed in 156 of these patients because they met the criteria for high risk USD. The clinical and demographic properties of the patients with stone analyses are given in Table 1.

Most patients in the study population had a pure stone composition, forming 81.1%, whereas 59 (18.9%) patients had the mixed type of stone composition. The most common stone type in the pure stone group was calcium oxalate (78.6%), whereas the combination of calcium oxalate and struvite (38.9%) was the most common stone type in the mixed stone composition group. The second most common stone compositions were uric acid (9.5%) and calcium oxalate + uric acid (18.6%) in pure and mixed stone composition groups. The compositions of both pure and mixed stones are given in (Figure 1).

Stone types were divided into two classes according to their content: those containing (n=249) and those not containing calcium (n=63). It was determined that the HU of stones containing calcium was statistically significantly higher (p=0.034), and their volumes were smaller (p=0.004) (Table 2).

Similarly, in the distribution to be made according to stone types between 600 and 1200 HU according to HU, 61.5% of stones with HU less than 600 contain calcium, while this rate increases to 91.50% in increasing HU levels and stones with HU greater than 1200. Conversely, the rate of stones without calcium decreases from 38.50% to 8.50% as HU increases (Figure 2).

A total of 156 high-risk patients for stone formation underwent metabolic evaluation. Eighty patients had hypercalciuria (>80

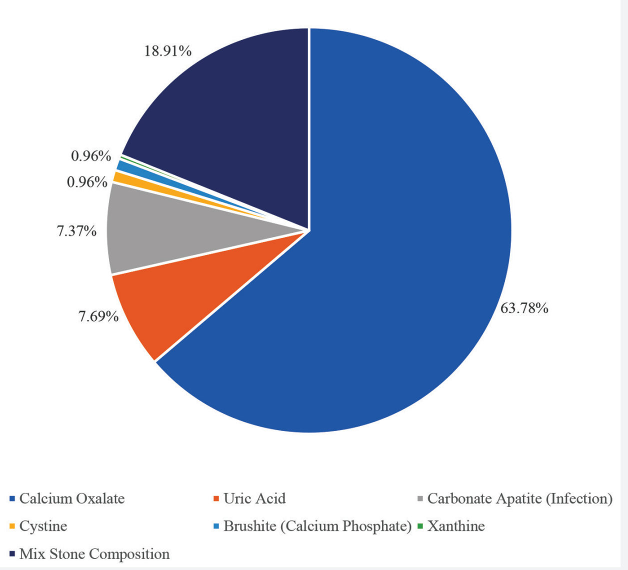

Figure 1. Stone types and their distributions (The percentages in the table are given according to the total of pure or mixed types

mg/day), 74 patients had hyperoxaluria (>40 mg/day), 79 patients had hyperuricosuria (>600 mg/day), 58 patients had hypocitraturia (<320 mg/day) (Figure 3).

When we analyze the metabolic evaluation results according to stone types, we see that calcium oxalate stones are the most common stones in patients with hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia (Table 3).

In calcium-containing stones, the hypercalciuria rate was found to be 52.5%, the hyperoxaluria rate was found to be 49.2%, the hyperuricosuria rate was found to be 50.9%, and the hypocitraturia rate was found to be 45.2%, while these rates were found to be 47%, 42.9%, 50%, and 40.7% for non-calcium stones, respectively. No statistically significant relationship was found between calcium-containing and non-calcium stones and elevated calcium, oxalate, uric acid, or decreased citrate in urine. (p=0.577, p=0.511, p=0.928 and p=0.678). It was concluded that hypercalciuria increased calcium stone formation by 1.24 times, hyperoxaluria by 1.29 times, and hyperuricosuria by 1.038 (Table 4).

Hypercalcemia rate was found to be 8.2%, hyperuricemia rate was found to be 36.1%, and hyperparathyroidism rate was found to be 19.7% in calcium-containing stones. These rates were 5.9%, 44.1%, and 20.6% for non-calcium stones, respectively. No statistically significant relationship was found in comparing calcium-containing and non-calcium stones with serum levels of calcium, uric acid, and parathyroid hormone (p=0.735; p=0.472; p=0.140). It was concluded that hypercalcemia increased calcium stone formation by 1.514 times (Table 4).

Based on metabolic evaluations, the metaphylaxis application rate was 43.3% for 135 patients and potassium citrate was mostly preferred for metaphylaxis. In hypocitraturia and hyperuricosuria in calcium oxalate stones and for specific uric acid stones, potassium citrate was used as metaphylaxis.

DISCUSSION

USD is one of the most common diseases worldwide. Prevalence rates vary widely, ranging from 2-20%. The recurrence rate can be as high as 50%[12]. In this disease, the most critical parameter

Table 2. Comparison of stones containing calcium with stones without calcium content

	Stones with calcium component (n=249)	Stones without calcium component (n=63)	p-value
Age (mean ± SD)	49.70±15.2	52.79±1.81	0.345
Gender (n, %)			
Male	153 (61.45%)	32 (50.79%)	0.125
Female	96 (38.55%)	31 (49.21%)	
Stone location (n, %)			
Bladder	6 (2.41%)	4 (6.35%)	
Distal ureter	44 (17.67%)	5 (7.94%)	
Mid-ureter	22 (8.84%)	4 (6.35%)	
Proximal ureter	45 (18.07%)	6 (9.52%)	
Renal pelvis	37 (14.86%)	16 (25.4%)	
Middle calyx	5 (2.01%)	3 (4.76%)	0.162
Lower calyx	14 (5.62%)	4 (6.35%)	
Upper calyx	6 (2.41%)	1 (1.59%)	
Multiple location	70 (28.11%)	20 (31.75%)	
Side (n, %)			
Right	116 (46.59%)	23 (36.51%)	
Left	127 (51.0%)	35 (55.56%)	0.073
Bladder	6 (2.41%)	5 (7.94%)	
Stone number (n, %)			
Single	191 (76.71%)	50 (79.4%)	0.654
Multiple	58 (23.29%)	13 (20.6%)	
BMI (kg/m^2) (mean ± SD)	27.55±4.05	27.8±4.8	0.897
HU (mean ± SD)	1020.2±305.0	822.2±306.8	0.034
Stone volume (mm^3) (mean ± SD)	1258.5±932.9	3000.9±4754.6	0.004
Preoperative urine culture (n, %)			
Negative	201 (80.72%)	53 (84.1%)	0.536
Positive	48 (19.28%)	10 (15.9%)	

SD: Standard deviation, BMI: Body mass index, HU: Stone density to reduce the patient's recurrence is to make the patient stone-free. As crucial as stone surgery, it is to analyze the stone obtained from the person and to determine metabolic disorders that may cause stone formation. Determining preventable factors and including them in treatment protocols can guide the person to the relevant departments in terms of additional diseases, if any. In this respect, stone analysis and an appropriate metabolic evaluation are among the steps to take in this direction.

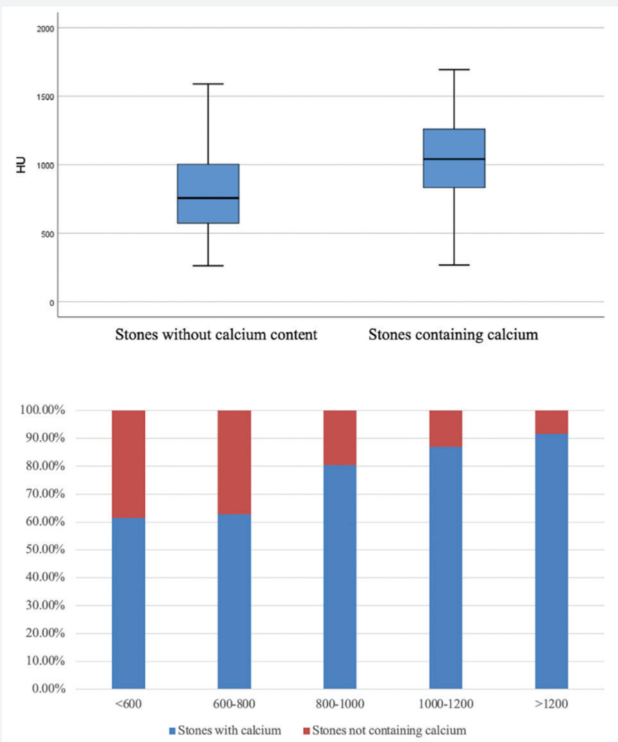

Figure 2. HU distribution of stones with/without calcium content

HU: Stone density

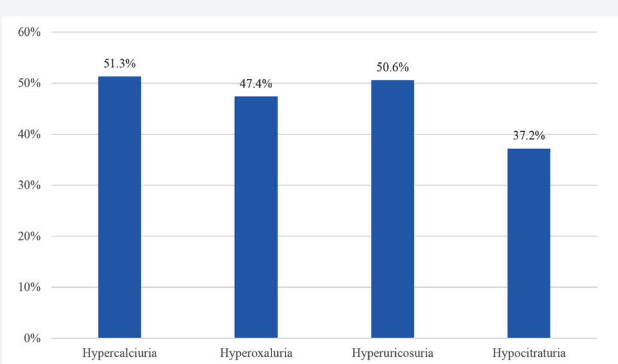

Figure 3. Metabolic analysis results of the patients

Our study found more male patients with USD than female patients, with a ratio of 1.45:1. In the literature, USD is a male-dominant disease, and the male/female ratio is 1.7-1.5-1.3:1[13,14]. In the stone analysis results in Tekirdağ province, the most frequently detected stone type was calcium oxalate, and the least frequent was xanthine stone. In a study by Güner and Şeker[15] based on 1304 stones in the Northern Marmara region, it was reported that calcium oxalate stones were the most common stone type at a rate of 64.34%, followed by uric acid stones at 6.8% and cystine stones at 2.1%, respectively. The study by Karabacak et al.[16] based on all of Türkiye emphasized that calcium oxalate content was more frequently encountered in the Marmara region than in other geographical regions. However, it is mentioned in the literature that genetic differences, bacterial colonization in the urinary system, environmental factors, and nutritional habits may cause differences in the distribution of stone types between cities and even within the same city[17].

Many studies have attempted to reveal the relationship between stone type and density. While these studies have shown that the density of stones with high calcium content is higher than other components, their HU also varies across studies. In our study, the density of stones with calcium content was statistically significantly higher than those without calcium. According to the study by Ogawa et al.[18], the mean HU value of calcium stones was reported as 1151±308, cystine stones as 677±64, and struvite stones as 569±63. Again, in an article by Motley et al.[19], the mean HU value of calcium stones was determined as 440±262, the mean HU value of uric acid stones as 270±134, the mean HU value of struvite stones as 401±198, and the mean HU value of cystine stone patients as 248±0. However, it has been discussed that the very low HU values in this study may be due to the helical computed tomography (CT) used. The reason for the differences in HU measurements in these studies is the differences in the imaging methods used in the measurement and the variability in the measurement point of the stone. The use of radiological imaging methods in stone analysis is also one of the notable issues in the literature. The types of stones in patients were tried to be determined with direct radiographs[20], and new measurement methods were developed with the introduction of CT in the 1970s. This new method measured the mean attenuation level in preoperative helical CT imaging of the stones, and its ratio to the stone volume was used[21].

In the study conducted by Gudeloglu et al.[22], comparing pure stone types with combined stones, it was determined that the pure stone type rate was 53.7% in 24,768 patients. In Türkiye, it was emphasized that it was more common than combined stones and statistically significantly higher in women than men. In our study conducted in Tekirdağ, the pure stone rate was significantly higher (81.1%); no statistically significant difference was observed based on gender, but only a statistically significant difference was observed between urine cultures. In this direction, it can be concluded that our province does not reflect the whole country, Türkiye, for these parameters.

Table 3. Distribution of urine metabolic analysis according to stone types

Stone type (n, %)	Hyper-calciuria (n=80)	Hyper-oxaluria (n=74)	Hyper-uricosuria (n=70)	Hypo-citraturia (n=58)	Hyper-calcemia (n=12)	Hyper-uricemia (n=59)	Hyperparathyroidism (n=31) (n=31)
Calcium oxalate	54 (67.5%)	46 (62.2%)	49 (70.0%)	44 (75.9%)	9 (75.0%)	33 (55.9%)	19 (61.3%)
Uric acid	4 (0.5%)	7 (9.5%)	8 (11.4%)	5 (8.6%)	0 (0%)	6 (10.2%)	2 (6.5%)
Carbonate apatite (infection)	10 (12.5%)	3 (4.1%)	4 (5.7%)	2 (3.4%)	2 (16.7%)	4 (6.8%)	4 (12.9%)
Cystine	1 (1.25%)	1 (1.4%)	1 (1.4%)	3 (5.2%)	0 (0%)	2 (3.4%)	0 (0%)
Xanthine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Calcium oxalate + struvite	4 (5.0%)	5 (6.8%)	1 (1.4%)	0 (0%)	0 (0%)	3 (5.1%)	2 (6.5%)
Calcium oxalate + uric acid	1 (1.25%)	3 (4.1%)	1 (1.4%)	2 (3.4%)	1 (8.3%)	5 (8.5%)	1 (3.2%)
Calcium oxalate + carbonate apatite	5 (6.25%)	5 (6.8%)	4 (5.7%)	1 (1.7%)	0 (0%)	3 (5.1%)	2 (6.5%)
Brushite (calcium phosphate)	1 (1.25%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Uric acid + ammonium urate	0 (0%)	4 (5.4%)	1 (1.4%)	1 (1.7%)	0 (0%)	3 (5.1%)	1 (3.2%)

Table 4. Relationship between calcium-containing/non-calcium-containing stones and serum and urine metabolites

	Stones with calcium component and metabolic analysis (n=122)	Stones without calcium component and metabolic analysis (n=34)	p-value	Odds ratio
Hypercalciuria (n=80)	64 (52.5%)	16 (47.0%)	0.577	1.241 (95% CI: 0.580-2.658)
Hyperoxaluria (n=74)	59 (48.4%)	15 (44.1%)	0.511	1.290 (95% CI: 0.604-2.755)
Hyperuricosuria (n=70)	55 (45.1%)	15 (44.1%)	0.928	1.038 (95% CI: 0.462-2.330)
Hypocitraturia (n=58)	47 (38.5%)	11 (32.4%)	0.678	0.834 (95% CI: 0.353-1.969)
Hypercalcemia (n=12)	10 (8.2%)	2 (5.9%)	0.735	1.514 (95% CI: 0.316-7.257)
Hyperuricemia (n=59)	44 (36.1%)	15 (44.1%)	0.472	0.753 (95% CI: 0.348-1.631)
Hyperparathyroidism (n=31)	24 (19.7%)	7 (20.6%)	0.140	0.439 (95% CI: 0.153-1.253)

CI: Confidence interval

Stone analysis and subsequent metabolic evaluation in USD are strongly recommended in the literature, including European and American guidelines[11]. Unfortunately, very few urologists in our country use these methods. In a study conducted in Tekirdağ province in 2017 with 32 urologists, it was found that 65.5% of urologists did not perform metabolic evaluation in children and 34.5% in adults, 20.7% did not perform stone analysis, and 44.8% had stone analysis in 1-25% of their patients[6]. When the reasons for this were asked, it was concluded that almost half of the physicians did not have the opportunity to do this, and 17.2% did not have time for metabolic evaluation. As these results show, urologists do not give sufficient importance to other advanced evaluations as much as surgical treatment of the stone. Again, in a Türkiye-based study by Gudeloglu et al.[22], the number of stone analyses performed annually was only 1152 in 2006, while this number increased over the years and was recorded as 2698 in 2018. However, even these numbers are pretty low. There is no metabolic evaluation data in this study. Metabolic evaluation was performed in our center, and 24-hour urine analysis was performed on 50% of the patients included in our study. The most important reason for this low rate is that many of our patients did not comply with the patient selection criteria in the EAU guidelines. This guideline recommends metabolic evaluation only for patients at high risk for stone formation[9]. Another reason that reduces this rate is the presence of postoperative residual stones or double J stents in patients who undergo surgery. From the patient's perspective, the biggest reason for this low number is the difficulty in collecting two consecutive days of 24-hour urine, which is necessary for this measurement, according to patient feedback.

In the study of Kuo et al.[23], it was determined that hypercalciuria was positively correlated with the number of stones formed, which is thought to be related to Randall plaques in idiopathic calcium stone formers. In our study, hypercalciuria was detected in more than half of the stone formers, and the mean urine calcium level was calculated as 249.6 mg/day (upper limit 200 mg/day). Again, a statistically significant result was obtained: calcium oxalate-containing stones were formed in 80% of hypercalciuria patients. Hypercalciuria was detected in 25.7% of those who formed calcium oxalate stones, and this rate was reported as 30-60% in the literature[24,25]. Coe et al.[26] stated that one of the critical factors affecting calcium stone formation was hyperoxaluria. Our study determined the hyperoxaluria rate as 47.7%, and the mean urine oxalate level was 43.6 mg/day (upper limit 40 mg/day). 79.7% of those with hyperoxaluria had calcium stones, and 23.7% of those with calcium stones had hyperoxaluria. Again, this rate is reported as 26-67% in the literature[24,25]. In the studies conducted by Pak[27] and Levy et al.[28] in 1995, hypocitraturia was detected in up to 10% of those who formed calcium stones and was reported in 20-60% of all stone formers. In our study, the rate of hypocitraturia in patients who underwent metabolic evaluation was determined as 44.3%, and the average citrate level was 497.2 mg/day (upper limit 320 mg/day). Hypocitraturia was seen in 18.9% of those with calcium stones, and this rate was reported as 5-29% in the studies[22,23]. In the study by Huynh et al.[29], in non-Western countries, the rate of hyperoxaluria was reported as 36%, hypercalciuria as 29%, hyperuricosuria as 20%, and hypocitraturia as 1% in individuals with recurrent stone formation.

In the literature, USD is emphasized as one of the obvious symptoms of hyperparathyroidism. Bilezikian et al.[30] reported that this association was less than 20% in their study. In another study, half of the patients with primary hyperparathyroidism were asymptomatic, and 44% had kidney stones[31]. In other words, hyperparathyroidism is seen in 5% of patients with stones[32].

Potassium citrate dramatically reduces the recurrence of kidney stones, especially uric acid stones, by alkalinizing urine and enhancing citrate excretion. Urine alkalinization and increased citrate excretion inhibit uric acid stone formation by sustaining a higher urine pH, reducing uric acid crystallization[33]. Potassium citrate chelates calcium in the urine, inhibiting the development of calcium oxalate calculi. It is especially efficacious in individuals with hypocitraturia, a disorder marked by diminished citrate levels in the urine[34]. In the long-term 1-year follow-up of our patient population who received metaphylaxis, the stone recurrence rate was found to be 20%, and these patients were spared from morbidity thanks to the data obtained from stone analysis and metabolic evaluation. In a study by Ettinger et al.[35], when administered potassium-magnesium citrate, the treatment group exhibited an 85% decrease in stone recurrence over a three-year period compared to a placebo. In another study[36], potassium citrate treatment decreased the stone recurrence rate to 0% in patients who were stone-free after SWL, in contrast to a 28.5% recurrence rate in untreated individuals. These data show us the significance of metabolic evaluations to initiate metaphylaxis.

Although there are regional differences in the formation of different stone types, genetic and environmental factors also have important roles in these differences. There is indicative evidence for a susceptibility gene next to the VDR locus, which may be associated with idiopathic hypercalciuria and calcium nephrolithiasis[37]. Polymorphisms in the *CaSR* gene are linked to differences in urine calcium excretion and the production of stones, especially in normocitraturic individuals[38]. Other genes that control calcium and phosphate reabsorption, including CLDN14, which is linked to hypercalciuric individuals, have been found via genome-wide association studies. Calcium stones has been associated with genetic variations that impact the metabolism of calcium and vitamin D, such as those in the CYP24A1 locus, which alter the concentration of calcium in the blood and the excretion of calcium in the urine[39]. Additionally, research conducted in a Sardinian community discovered potential loci associated with uric acid stones on chromosomes 10q21-q22 and 20q13.1-13.3[40]. Serum uric acid levels and stone formation are impacted by certain genetic variants, and the insulin-like signaling system has been linked to uric acid metabolism[41].

Study Limitations

The main limitation of our study is the retrospective evaluation of the data and the inclusion of the population at only one province. In addition, despite being an endemic region for stones, the low number of stone analyses, especially metabolic evaluation, is another study limitation.

CONCLUSION

Metabolic evaluation and stone analysis should be more common in clinical practices and given the necessary importance by urologists. With these data obtained, patients' stone recurrences and re-intervention needs can be reduced and low morbidity can be achieved via metaphylaxis.

Ethics

Ethics Committee Approval: Approval was obtained from the Non-Interventional and Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (decision no: 2020.79.04.03, date: 30.04.2020).

Informed Consent: Although the study was designed retrospectively, the data used were obtained prospectively.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.F.Ş., M.A., Concept: M.F.Ş., C.M.Y., R.Ö., Design: M.F.Ş., C.M.Y., Data Collection or Processing: M.F.Ş., C.M.Y., Analysis or Interpretation: M.F.Ş., C.M.Y., M.A., Literature Search: M.F.Ş., R.Ö., Writing: M.F.Ş., C.M.Y., R.Ö., Ç.D., M.A.

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