

Evaluation of the composition of urinary tract stones in children from the Inner Western Anatolian Region in Turkey

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Cite this article as: Girişgen İ, Yüksel S, Karcılı K, Becerir T. Evaluation of the composition of urinary tract stones in children from the Inner Western Anatolian Region in Turkey. Turk J Urol 2020; 46(2): 152-8.

ABSTRACT

Objective: Pediatric urolithiasis is a globally growing problem. The composition and frequency of urinary tract stones vary not only among different countries, but across various regions in a country. Hence, we aimed to identify the types and frequencies of urinary tract stones in children from our region (Inner Western Anatolian part of Turkey), and to compare our findings with the results from other regions in our country.

Material and methods: In this retrospective analysis of 53 pediatric urolithiasis cases that were treated in our hospital between 2009 and 2019, the demographic data, clinical course, radiological and metabolic findings, the recurrence rate, and the composition of the stones were evaluated.

Results: The mean age of the patients was 5.9 ± 4.6 (0.5–18) years, and there were 30 (56.6%) girls and 23 (43.4%) boys. An analysis of the composition of the stones revealed that the majority (85%) consisted of calcium oxalate. The highest risk of recurrence and the need for multiple shockwave lithotripsy (SWL) sessions or surgical intervention appeared to be related with the presence of whewellite stones, which are the most challenging stones in childhood.

Conclusion: According to the study results, the urinary stone types vary across different regions in our country, and the frequency of uric acid stones decreased going westward, while the frequency of oxalate stones increased. We conclude that this difference in the frequency of the type of urinary stones might reflect the regional dietary habits. Regional frequency and etiology studies for the types of urolithiasis may facilitate the approach to the treatment of urolithiasis.

Keywords: Children; nephrolithiasis; oxalate; stone analysis; uric acid.

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Submitted:

26.08.2019

Accepted:

06.12.2019

Available Online Date:

06.01.2020

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www.turkishjournalofurology.com

Introduction

The incidence and the composition of urinary tract stones in childhood greatly vary among different countries and regions of the world. This difference is mostly related to nutritional habits, socioeconomic factors, climate, and ethnic and genetic characteristics, in addition to the geographical factors.^[1,2] A recent increase in pediatric urolithiasis cases and changes in the stone composition in children can be due to differences in nutrition patterns, such as high protein diets or an increased consumption of salty fast foods, the global rise in obesity, and sedentary lifestyles.^[3] Pediatric urolithiasis, which has a multifactorial etiology, is a very common disease in Western countries, Asia, the Far East and Middle East, and it is an epidemic in Turkey as well.^[4-6]

When the etiology of urolithiasis is related to metabolic factors in children, the recurrence risk is high.^[5] The success of the treatment, the avoidance of recurrence, and the prevention of renal damage highly depend on the delineation of the specific etiology of stone formation.^[5] The most common etiological factors of urolithiasis in Turkey were reported to be metabolic (20%–30%) and anatomic.^[2,7-9] As pediatric urolithiasis, which is caused by metabolic abnormalities, usually results in recurrence, the metabolic aspects of stone formation in children need extensive research.^[10] The qualitative analysis of the urinary tract stones and parts is also highly relevant considering appropriate treatment regimens.^[3]

In this study, we retrospectively analyzed the demographic data; clinical, radiological, and metabolic findings; and the recurrence rate with

respect to the composition of the stones in children who presented with urolithiasis at our hospital, which serves the Inner Western Anatolian region of Turkey. We also compared the type and frequency of the stones with the results of other studies from different parts of our country and discussed various etiological factors.

Material and methods

The medical records of 400 children admitted to the Department of Pediatric Nephrology in our hospital with a diagnosis of urolithiasis (2009–2019) were reevaluated retrospectively. Only 53 children that had a documented stone analysis were enrolled in the current study. The medical files were scanned for demographics, that is, gender and age at the time of diagnosis, body mass index, clinical presentation (i.e., abdominal pain, hematuria) results of laboratory investigations and radiological findings, previous medical and surgical history, family history regarding urinary tract stones, and disease-specific data, such as dimensions and localizations of stones, any signs of recurrence, concomitant urinary tract infection and abnormalities, metabolic abnormalities, and any attempts of medical treatment. It was also recorded whether the stone was spontaneously passed, treated by shockwave lithotripsy (SWL), or surgically removed.

The clinical diagnosis of a urinary stone was confirmed by radiological studies such as direct X-ray and urinary ultrasound (US). When the size of the stone was <3 millimeters in diameter, the stone was labeled as microcalculi, while macrocalculi were used to describe a stone with a diameter that was ≥ 3 millimeters.^[11,12] When there were concurrent urinary tract infections, a voiding cystourethrogram was performed to investigate the potential presence of vesicoureteral reflux (VUR). After a diagnosis of urolithiasis was made, it was monitored by periodic US examinations. Spontaneous remission was defined as the permanent disappearance of calculus in those periodic US examinations. The localization of the stones was classified into two categories: upper urinary tract (i.e., kidney or ureter) and lower urinary tract (i.e., bladder or urethra).

The composition of the urinary tract stones was analyzed using the X-ray diffraction (XRD) method in the laboratory of the

General Directorate of Mineral Research and Exploration. The samples sent for analysis were obtained via spontaneous passage, SWL, or surgical procedures such as percutaneous nephrolithotomy and ureterorenoscopy. The composition and type of stones were determined from powdered samples in nickel-containing filters in Cu X-ray tube devices at 2–40°C.

The metabolic evaluation of the patients consisted of measuring serum electrolyte levels (calcium, phosphorus, uric acid), hormone levels (vitamin D, parathyroid hormone), and renal function tests (urea and creatinine levels, the glomerular filtration rates using the Schwartz formula), and the levels of calcium oxalate, citrate, cystine, magnesium, and uric acid during 24 hours or by spot urine analysis. To define the metabolic abnormalities, either the absolute urine concentration of metabolic variables in the 24-hour urine or the mineral-to-creatinine ratio in spot urine was analyzed and compared with reference values.^[5,13]

Statistical Analysis

Continuous variables were given as mean and/or standard deviation, while the number and percentage were used for categorical variables. The differences between categorical variables were analyzed by chi-squared analysis (*p*-values were listed in the text). All statistical analyses were performed using the Statistical Package for the Social Sciences 25.0 (IBM SPSS Statistics 24; Armonk, NY, USA) software.

Compliance with ethical standards

Ethical standard: The study was conducted in accordance with the Declaration of Helsinki and its amendments (approved by Pamukkale University School of Medicine ethics committee with the registration number of 60116787-020/35545 and date of 05/22/2019).

Results

Clinical features

We evaluated data regarding the stone composition from 53 children with urolithiasis. The mean age of the patients was 5.9 ± 4.6 (0.5–18) years, and there were 30 (56.6%) girls and 23 (43.4%) boys; the female-to-male ratio was 1.3. The body mass index >95th percentile was found in 4 of the patients.

We observed a positive family history of kidney stones in 56% of the children. In children without a positive family history, the ratio of stones refractory to the treatment was significantly higher than that of children with a positive family history (82% vs. 33%; $p=0.016$). In addition, we observed that children without a positive family history required more than one SWL session or surgery when compared to children with a positive family history, but this was not statistically significant (54% and 37.5%, respectively; $p=0.29$).

Main Points:

- The urinary stone types vary across different regions.
- The frequency of uric acid stones decreased going westward, while the frequency of oxalate stones increased.
- The frequency of the type of urinary stones might reflect the regional dietary habits.
- Whewellite type oxalate stones also carry a recurrence risk along with multiple shockwave lithotripsy sessions and surgical intervention, which are the most challenging stones in childhood.

Presenting symptoms of the patients were found to be abdominal pain (34%), macroscopic hematuria (9.4%), urinary tract infection (15.2%), dysuria (7.5%), vomiting (9.4%), anuria (1.9%), and spontaneous passage of stones (9.4%), while remaining patients (13.2%) had non-specific symptoms. Congenital abnormalities, such as VUR and ureteropelvic junction obstruction were present in 8 (15%) patients. The urinalysis at the time of initial presentation revealed microscopic hematuria in 16 patients (30.2%). Urinary tract infections were found in 15.2% of the patients along with 28 patients (52.8%) who had a previous history of recurrent urinary tract infections.

Stone localization

Stone sizes ranged from 3 mm to 25 mm according to US imaging classification. Macrocalculi and microcalculi were present in 48 (90.5%) and 5 (9.5%) of the cases, respectively. While the upper urinary tract stones were present in 41 patients (78%), 12 patients (22%) had lower urinary tract stones.

Stones were located in the left kidney in 25 patients (47%), in the right kidney in 14 patients (26%), and bilateral stones were found in 13 patients (24%). Ultrasonographic findings showed accompanying hydronephrosis in 22.6% of the patients. Radiological techniques revealed radio-opaque urolithiasis in 37 patients (69.8%), while the stones were non-opaque in 16 patients (30.2%).

Metabolic abnormalities and stone composition

The biochemical analysis of the serum consisting of urea, creatinine, alkaline phosphatase, calcium, phosphorus, magnesium, parathyroid hormone, blood pH, and bicarbonate levels showed no abnormalities in any of the patients. The blood uric acid level in 1 patient with a hypoxanthine stone was lower than normal, with a value of 0.8 mg/dL.

Stone samples from the children were obtained through spontaneous passage (n=9), SWL (n=23), or surgery (n=21). Of the 46 patients with metabolic analysis, 45% showed 1 or more metabolic abnormalities. The most common metabolic abnormalities found were hypercalciuria (22%) and hyperuricosuria (22%). Hyperoxaluria and hypocitraturia were found in 12.5% and 13.3% of the subjects, respectively. Hyperuricemia was higher in boys than in girls, although the number was not statistically significant. Hypercalciuria was found in 25%, hyperoxaluria and hypocitraturia were found in 18%, and hyperuricosuria was found in 45% of the children with calcium oxalate stones.

The analysis of stone composition revealed that 85% (n=45) contained calcium oxalate (40 only calcium oxalate, 3 calcium oxalate+ammonium urate and 2 calcium oxalate+phosphate), 7.5% cystine, 3.8% struvite, 1.9% hypoxanthine, and 1.9% uric acid (Table 1). Out of 40 calcium oxalate stones, 10 were weddellite, 9 were whewellite, and 21 were weddellite+whewellite

Table 1. Stone analysis in patients

| | n | % |
|---|----|------|
| Calcium oxalate | 45 | 84.9 |
| Calcium oxalate dihydrate (weddellite) | 10 | |
| Calcium oxalate monohydrate (whewellite) | 9 | |
| Calcium oxalate dihydrate+calcium oxalate monohydrate (mix) | 21 | |
| Calcium oxalate monohydrate+calcium phosphate | 2 | |
| Calcium oxalate+ammonium urate | 3 | |
| Cystine | 4 | 7.5 |
| Struvite | 2 | 3.8 |
| Uric acid | 1 | 1.9 |
| Hypoxanthine | 1 | 1.9 |

Table 2. Comparison of stone composition in our study to that of other regions

| Region | Authors | No. of stone | CaOx (%) | CaP (%) | Cystine (%) | Struvite (%) | Uric acid (%) | Hypoxanthine (%) | Mix analyses |
|------------------|---------------------|--------------|----------|---------|-------------|--------------|---------------|------------------|--------------|
| Inner Western | Girisgen et al. | 53 | 85 | - | 7.4 | 3.7 | 1.9 | 1.9 | - |
| Aegean (Western) | Bak et al. [5] | 67 | 86 | - | 3 | 8 | 1.5 | - | - |
| Central Anatolia | Ozokutan et al. [7] | 40 | 80 | - | 5 | 12.5 | 2.5 | - | - |
| Central Anatolia | Dursun et al. [21] | 63 | 60 | 3 | 3 | 1.5 | 9.5 | 1.5 | 6.3 |
| Central Anatolia | Baştuğ et al. [19] | 56 | 64 | - | 12.5 | 7.1 | 16.1 | - | - |
| Marmara | Alpay et al. [23] | 10 | 80 | - | 10 | - | 10 | - | - |
| Eastern Anatolia | Tabel et al. [2] | 17 | 38 | 22 | 11 | 5.6 | 16 | - | 5.6 |
| Southeastern | Ece et al. [9] | 28 | 35 | 10.7 | - | 21 | 17 | - | 14.2 |
| Southeastern | Elmacı et al. [16] | 51 | 50.7 | 5.8 | 18.8 | 7.2 | 14.5 | 2.9 | - |
| Mediterranean | Güven et al. [24] | 9 | 55 | - | 22.5 | - | 22.5 | - | - |

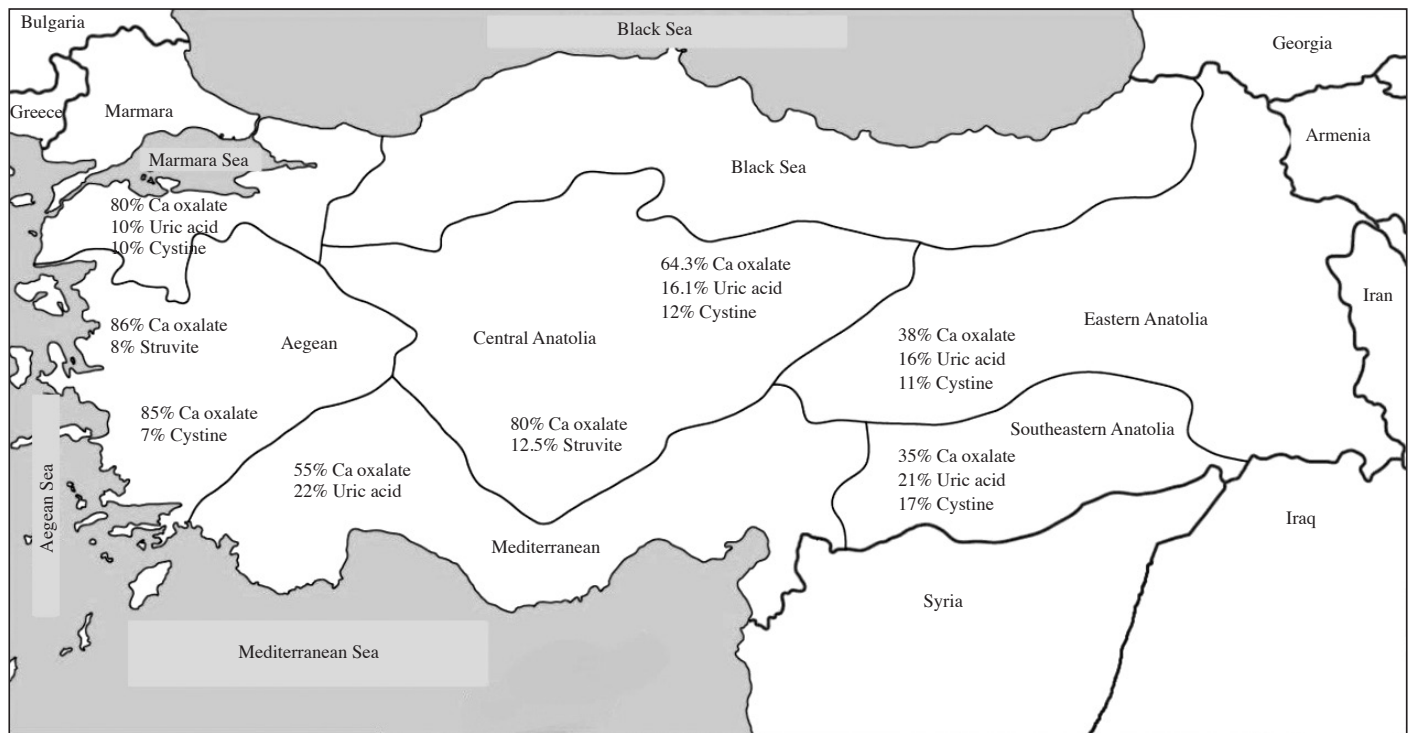


Figure 1. Comparative results of our study with other studies from different regions in Turkey

types (Table 1). In children with whewellite stones, the persistence of stones despite the treatment was higher than in children with weddellite stones (66% vs. 42.9%). Children with whewellite stones required more than one session of SWL or surgery than children with weddellite stones (75% vs. 33%). The gender comparison of patients with calcium oxalate stones revealed that weddellite stones were more common in girls, while whewellite stones were more common in boys; however, this difference was not statistically significant. The comparative results of the current study with other studies from different regions in Turkey are presented in Table 2 and Figure 1.

Urological and medical treatment

Medical treatment of the patients consisted of a low-salt diet along with potassium citrate in 13 patients, thiazides in 3, potassium citrate+thiazides in 7, thiopronin in 4, and pyridoxine in 1. Surgical removal of the stones was the choice of treatment in 39% of the children, while SWL was preferred in 43% of the children. The types of surgical treatment were percutaneous nephrolithotomy in 15 patients, ureterorenoscopy in 5 patients, and cystolithotomy in 1 patient.

In 27 of patients (51.9%), stones were refractory to the treatment, while 48.1% of the patients were free of stones after treatment. We observed that there was a recurrence rate of 40% in the treated patients; however, re-treatment was successful in all of the patients.

Discussion

In this retrospective study conducted in a single center in the western part of Turkey, medical data of 53 children with an analysis of urinary tract stones were evaluated. The composition of the urinary tract stones derived from our study was compared with the data from various studies conducted in other regions in Turkey. We found that most of the patients in this study had calcium oxalate stones and observed that the stone composition varied with respect to the geographic region in Turkey. We thought that this variation is directly related to the regional dietary habits. We found that the stone recurrence and the need for multiple SWL sessions or surgical intervention were inversely related to a positive family history. In addition, we found that whewellite type oxalate stones also carried a recurrence risk along with multiple SWL sessions and surgical intervention.

As has been demonstrated in many studies, the risk of kidney stones is higher in boys in the first decade of life and girls in the second decade of life.^[2,14] Consistent with these studies, the male-to-female ratio in our study was 1.3, which revealed a mild predominance of boys. In our study, hyperuricemia was higher in boys than in girls although the number was not statistically significant. When the children with calcium oxalate stones were compared in terms of their gender, the weddellite type of stones was found to be more common in girls, whereas whewellite

types were more common in boys; however, no statistically significant difference was shown in this case.

The presence of a positive family history of urolithiasis has been strongly associated with both the risk of stone formation and the recurrence of the disorder.^[15,16] Contrary to the literature data on the subject, we observed that the urinary stones were refractory to treatment in the patients without a positive family history compared to those with a positive family history. In addition, we found that children without a positive family history required multiple SWL sessions or surgery compared to children with a positive family history.

Pediatric patients with urolithiasis most commonly complain on abdominal pain, which is the clinical manifestation in 40%–75% of these children.^[9,17] Consistently, the most common symptom during the admission was abdominal pain in 34% of the cases in our study. Clinical findings accompanying the abdominal pain in our patients were macroscopic hematuria, urinary tract infection, dysuria, vomiting, and anuria.

Reports from studies in our country showed that the rate of bladder stones decreased due to a better treatment of urinary tract infections and that the rates of upper urinary tract stones have increased in the last several years.^[1,5,18,19] Similarly, we found that the majority of the stones (78%) were located in the upper urinary tract and left kidney (47%). In our study, we did not observe any relationship between the metabolic disorders and the localization, bilaterality, size, or multiplicity of the stone.

Risk factors for urolithiasis include metabolic disturbances, urinary tract infections, and anatomical defects. The anatomical abnormalities, such as ureteropelvic junction obstruction and VUR can lead to stone formation.^[10,16,20] The incidence of anatomical defects in children with urinary tract stones as been reported as 5%–10%.^[1,2,21] We detected a rate of 15% for anatomical defects in our study, which is consistent with the literature. Studies from our country reported a 10%–36% incidence of urinary tract infections in children with urolithiasis.^[9,10,21] In 15.2% of the cases in our study, urinary tract infections were present, along with a history of recurrent urinary tract infections in 28 patients (52.8%). Despite these ratios, only two struvite stones were detected in our study.

It has been reported that the frequency of metabolic factors associated with pediatric urolithiasis is 33%–93%.^[16,20,22-24] In our study, metabolic disorders were observed in 24 patients (45%). Some studies from our country reported that the most common metabolic abnormalities were hypercalciuria and hypocitraturia.^[16,25,26] In our study, the most common metabolic abnormalities found were hypercalciuria (22%) and hyperuricosuria (22%).

Hyperoxaluria and hypocitraturia were found in 12.5% and 13.3% of subjects, respectively. The frequencies of hypocitraturia and hypercalciuria in our patients were lower when compared with some studies.^[19,21]

An increase in the frequency of renal calcium oxalate and/or phosphate stones, which has been demonstrated in recent studies, is suggested to be mostly related to diet rich in protein, refined carbohydrates, sodium, and fat, and poor in potassium and citrates.^[11] Calcium oxalate stones are found in many urinary imbalances such as hypocitraturia, hyperoxaluria, hypercalciuria, and hyperuricosuria.^[21] In our study, hypercalciuria was found in 25%, hyperoxaluria and hypocitraturia were found in 18%, and hyperuricosuria was found in 45% of children with calcium oxalate stones. The most common urinary tract stone in patients who had stone composition analysis (85%) was the calcium oxalate stone. Although this is a similar rate to those observed in the Aegean (86%), central Anatolian (64%–80%), and Marmara (80%) regions, it is significantly higher than the rates observed in the southeastern (35%, 57%) and eastern Anatolian (38%) regions of our country. Although the struvite (21%) and uric acid stone (17%) ratios were high in the southeastern Anatolian region, the rate of uric acid stones was higher in the eastern Anatolian (16%) and central Anatolian (16.1%) regions compared to our region (Figure 1). Dietary habits are among the factors involved in stone formation. A person who mostly consumes animal proteins is more predisposed to excrete higher amounts of uric acid, calcium, and oxalate in his or her urine.^[16] Food culture varies from region to region in our country, while the vegetable- and olive oil-based dishes of Mediterranean cuisine are especially common in the Mediterranean and Aegean regions.^[27] Diet high in animal proteins, which might be responsible for the higher ratios of hyperuricosuria and uric acid stones, are generally present in the eastern and central Anatolia, and southeastern regions of Turkey. Some study results have suggested that poor economic conditions, in conjunction with urinary tract infections, might lead to a higher rate of struvite stones in the southeastern Anatolian region of Turkey.^[10,16] Although there is no agreement in the literature regarding the effectiveness of dietary recommendations for children with urinary tract stones, diet regulations may decrease the risk of urinary stone formation and its recurrence. A large meta-analysis evaluating the effects of dietary therapy on stone formation was published by the CLU Working Group.^[28] According to their recommendations, we advise children with oxalate stones to increase fluid intake, moderate dietary salt restriction (especially processed and salty fast-food), balance fruit/vegetables, and lower chocolate/cola intake.

There are few studies in the literature that have evaluated the relative recurrence risk of different urinary stone types.^[29] Some studies have suggested that cystine and uric acid stones are of-

ten more recurrent than other types of stones.^[29-31] For calcium oxalate, studies have indicated that weddellite stones are more likely to recur than whewellite stones.^[32] In our study, we found that the ratios of the whewellite and weddellite forms of calcium oxalate stone were 20% and 22%, respectively, while the ratio of the mixed type was 46%. Contrary to the studies in the literature, our study results showed that the recurrence of whewellite stones was more frequent and required multiple SWL sessions or surgery than the weddellite stones.

In the present study, medical treatment was given to 52.3% of patients. Patients with hypercalciuria were administered thiazides and a low-salt diet, and hypocitraturia in patients was treated with potassium citrate, while cystinuria and hyperoxaluria were treated with tiopronin and pyridoxine, respectively. Surgical removal of the stones was performed in 39% of the patients, and SWL was the choice of treatment in 43% of the patients. The percentage of patients requiring multiple SWL sessions or surgical intervention was 43. After the treatment of 53 patients, 27 (51.9%) still had the stones, while the remaining 48.1% were stone free. Although the recurrence occurred in 11 of the patients (40%), whose stones had disappeared before, they disappeared completely after another course of treatment.

The major limitations of our study are its retrospective design and the lack of metabolic evaluation in some of the study participants.

In conclusion, urolithiasis is an important health problem in childhood. Appropriate management of urinary tract stones is critical to avoid the development of kidney damage and chronic renal failure. As the medical treatment of urolithiasis is highly dependent on the nature of the stones, it should be determined to choose the optimal therapeutic approach. In contrast to the literature, the results of our study showed that the whewellite stones carried a risk for stone recurrence and the need for multiple SWL sessions or surgical intervention, which were inversely related to the family history. We observed that the urinary stone types vary across different regions of our country, and the frequency of uric acid stones decreased going westward, while the frequency of oxalate stones increased. We suggest that this variation is directly proportional to the regional dietary habits. Regional frequency and etiology studies for the types of urolithiasis may facilitate the urolithiasis treatment approach.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Pamukkale University (60116787-020/35545 and date of 05/22/2019)

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.Y., İ.G.; Design – S.Y., İ.G.; Supervision – S.Y., T.B.; Materials – K.K.; Data Collection and/or Processing – K.K., İ.G.; Analysis and/or Interpretation – İ.G., T.B.; Literature Search – İ.G., T.B.; Writing Manuscript – İ.G., T.B., K.K.; Critical Review – S.Y., İ.G.; Other – T.B., K.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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