The Relationship Between Urinary Stone Disease and Nutrition Type in Infants

Kyaw Zin Latt[1], Yelda Turkmenoglu[1], Alper Kacar[2], Ahmet Irdem[3] and Hasan Dursun[4,*]

[1]Department of Pediatrics; [2]Department of Pediatric Emergency; [3]Department of Pediatric Cardiology; [4]Department of Pediatric Nephrology, Health Science University, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey

Abstract: The relationship between urinary stone disease and nutrition in infants is not well known. This study investigates the relationship between breast milk, formula and supplementary foods, vitamin D usage, and family stone history with urinary system stones in children aged 3-24 months. The study included 100 infants aged 3-24 months of age with urinary tract stones and 40 healthy infants with similar age and gender as the control group. Sixty of the patients were boys, and 40 were girls; the control group consisted of 26 boys and 16 girls. There was no significant difference in only breastfeeding, breastfeeding plus formula, and formula feeding in the patients and controls. Positive family history of urolithiasis was significantly higher in the patients compared to the controls (p=0.04). While breastfeeding duration time was negatively correlated with spot urine calcium to creatinine ratio in children exclusively breastfed infants. No direct effect of nutrition type and vitamin D usage on stone formation was found in infants. It has been shown that stone formation in this age group is associated with a family history of stones. In this study, the duration of breastfeeding is negatively correlated with the spot urinary calcium to creatinine ratio.

Keywords: Breastfeeding, formula, infant, urinary system stone, supplementary food, Vitamin D, family history.

INTRODUCTION

Urinary system stone disease, which is common in pediatric practice as well as adulthood, is an important cause of morbidity. The prevalence of urinary stone disease ranges from 1-5% to 5-15% [1-4]. In two separate studies conducted with school-age (6-18 years) children in Turkey, urinary system stone disease frequency was 0.8% and 1.3% [5, 6]. This disease, which is so common, can occur because of metabolic, anatomical, infectious, environmental, and nutritional factors [7, 8]. Some other factors, climate, diet, genetic and socioeconomic also affect the incidence [1, 9, 10].

Some substances taken in excess amount in the diet can cause stone formation. For example, high vitamin C intake in the diet may be a risk factor for calcium oxalate stones [10]. Excessive animal protein intake causes urinary uric acid, calcium, and oxalate excretion, increasing the susceptibility to stone formation [7, 11]. A diet rich in sodium or calcium can trigger hypercalciuria. In addition, diet may work as a morbidity-reducing factor in urinary system stone disease practice, as it can be modified and corrected [7, 11-13]. For these reasons, the diet and its contents are at least as important as the factors that contribute to stone formation.

In the first two years of age, nutrition varies according to months. Normally, only breast milk is recommended for the first 6 months, complementary foods are started after the sixth month, and a similar diet with adults is recommended after 12 months. The most appropriate diet for normal newborns is breastfeeding by their own mother. Today, babies are recommended to be fed exclusively with breast milk for the first 6 months after birth. In the absence of breast milk, situations in which breastfeeding is inconvenient (such as active tuberculosis in the mother, HIV infection, human lymphocytic 1-2 virus infection, herpes simplex virus infection in the mother's breast) or insufficient breast milk or the presence of some metabolic diseases [14-16]. It is recommended to give complementary foods for babies fed with breast milk from the sixth month. There are few studies in the literature showing that breast milk reduces the formation of stones in infants [17].

We hypothesized that breastfeeding/formula, age at supplementary food, vitamin D usage, and family stone history would be associated with stone disease. Based on this, our first aim in this study is to investigate whether diet contributes to stone formation in patients with urinary system stone disease between 3-24 months of age by comparing it with healthy controls. Our second aim was to examine the effect of breast milk nutrition with other foods and emphasize the importance of breast milk in the 3-24 months of age in urinary stone disease. It was also aimed to investigate the effects of Vitamin D use and family history of urinary system stones in this age group.

*Address correspondence to this author at the Health Science University, Prof. Dr. Cemil Tascioglu City Hospital, Department of Paediatric Nephrology, Darülaceze Cad. No: 27, 34384, Sisli/İstanbul, Turkey; Tel/Fax: +90 212 3145555-6042; E-mail: dursunhs@yahoo.com, hasan.dursun@sbu.edu.tr

E-ISSN: 1929-4247/22

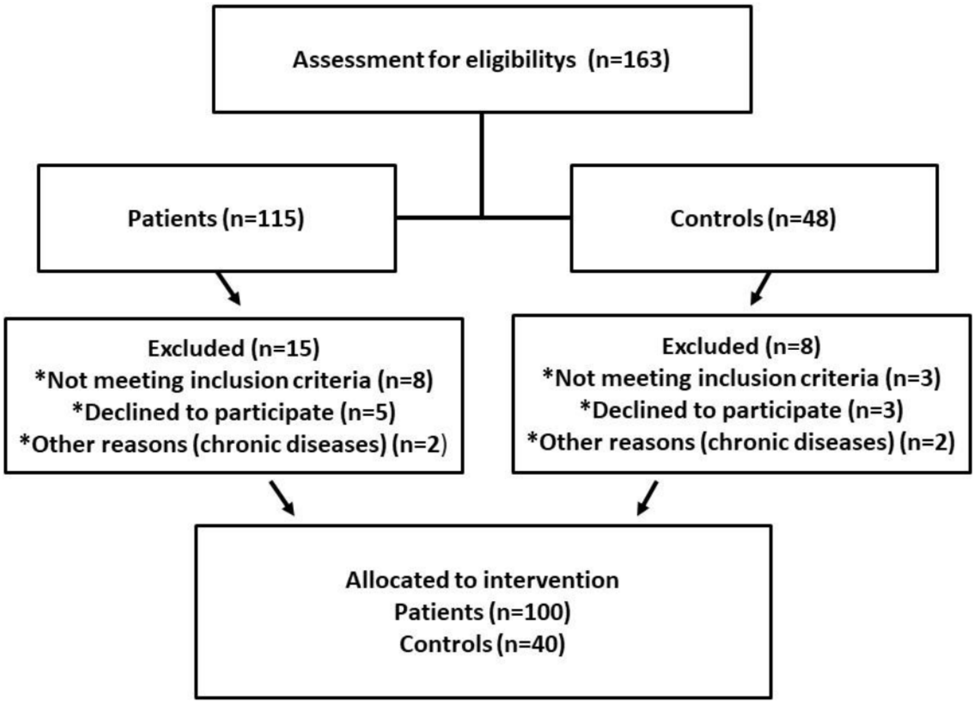

Figure 1: Flow diagram of the clinical trial of the patients and controls included in the study.

MATERIALS AND METHODS

Study Population

This retrospective study was conducted by the University of Health Sciences, Okmeydani Training and Research Hospital, Pediatric Nephrology, and Pediatrics outpatient clinics between January 2018 and October 2018. The study started with 163 children, including 115 patients and 48 controls. Fifteen children from the patient group and eight children from the control group were excluded from the study for various reasons. The study was continued with 140 children, including 100 patients and 40 controls (Figure **1**). Children who were completely healthy and applied to the Pediatrics outpatient clinic for vaccination or routine control were included in the study for the control group. Since the number of healthy children who underwent ultrasound was low, the number of patients in our study was higher than the number of controls.

Written consent was obtained from the parents before the study. The study was conducted in accordance with the Helsinki Declaration guidelines and was approved by the local ethics committee of Okmeydanı Training and Research Hospital (date/number: 17.04.2018/867).

The patient group consists of between 3-24 months of age, has urinary system stones, and does not have any other chronic disease. The control group consists of between 3-24 months old, not having urinary stones, with no other chronic disease. Patients with chronic disease and a history of chronic drug use, such as infants demonstrating anatomic abnormalities, neurogenic disorders, or urinary diversions, those who were born premature, and those receiving any diuretic agents, especially furosemide, were excluded from the study. In addition, children with stones detected in the first ultrasound but no stones in the second ultrasound were also excluded from the study.

In order to standardize urinary calcium, uric acid, and oxalate excretion, all patients and controls included in the study were fed with age-appropriate foods. None of them was on a special diet program. Patients and controls received either breast milk or standard age-appropriate formula. Moreover, the amounts of protein and vitamin D in formulas were similar to breast milk. Both the patients and the controls were included in the study if their parents' consent was given for participation.

Imaging and Laboratory Evaluation

The presence of urinary system stones was demonstrated by ultrasonography in all children. For this purpose, urinary system ultrasonography was performed twice, with an interval of 3 months, on all patients by the only pediatric radiologist working in our hospital. An ultrasound was performed once to show no urinary tract stones in the controls. The finding in patients with stones detected in the first ultrasound but not found in the second ultrasound was interpreted as echogenic foci. If the stone image persisted in the second ultrasound, urinary system stone disease was accepted.

Urine samples were collected from all patients with a bag or catheter as the first urine in the morning. The test findings of the metabolic evaluation were noted based on serum- and urine-related risk factors basically depending on spot urine analysis. Family stone history, age, weight, height, hemogram and biochemistry values, examinations requested for solute analysis in spot urine of the patients, ultrasound findings, and nutritional characteristics (breastfeeding duration time, formula use, transition time to complementary foods) recorded on the registration forms.

Statistical Analysis

The packaged software SPSS 17.0 was used for statistically analyzing the data. The categorical measurements were summarized as numbers and percentages, while continuous measurements were summarised as averages and standard deviations (as median and minimum-maximum when needed). Distributions were checked for comparing continuous measurements between the groups; Student T-test was used for parameters exhibiting regular distribution, and Mann Whitney U test was used for parameters not showing normal distribution. The Chi-square test was used as statistical analysis when necessary. In addition, a Pearson correlation test was used for nutrition type and spot urine parameters. A $p < 0.05$ level was considered statistically significant.

RESULTS

The study included 100 children (60 boys and 40 girls) with urinary system stones under two years old and 40 controls (26 boys and 14 girls) who were similar in gender and age with these patients and who did not have urinary system stones. Some clinical

Table 1: Clinical and Spot Urine Findings of Infants with Nephrolithiasis

Parameters		n (%)
Symptoms	Unrest and abdominal pain	52 (52.0)
	Color change in urine and diaper	23 (23.0)
	Others	25 (25.0)
Stone size	< 3 mm	35 (35.0)
	3-5 mm	44 (44.0)
	5-10 mm	16 (16.0)
	>10 mm	5 (5.0)
Stone localization	Kidney lower pole	36 (36.0)
	Kidney middle pole	31 (31.0)
	Kidney upper pole	11 (11.0)
	Inside the parenchyma	8 (8.0)
	Upper end of ureter	7 (7.0)
	Lower end of ureter	3 (3.0)
	In the bladder	2 (2.0)
	In urethra	2 (2.0)
Treatment need	Only follow-up	47 (47.0)
	Medical treatment	51 (51.0)
	Surgical treatment	2 (2.0)
Final stone status	Remission	76 (76.0)
	Decreased number and size of stones	17 (17.0)
	Persistent stones or increased number and size of stones	7 (7.0)
*Metabolic risk factors (38/100)	Hypercalciuria	23 (23.0)
	Hypocitraturia	7 (7.0)
	Hyperoxaluria	5 (5.0)
	Hyperuricosuria	2 (2.0)
	Hypomagnesuria	1 (1.0)

*Based on reference values according to age (9).

characteristics and laboratory findings of the patients are given in Table **1**. According to these findings, 52% of the most common patients were admitted to the hospital with restlessness and abdominal pain symptoms, 23% had urine color change and diaper complaints.

The demographic data, nutrition, supplementary food, vitamin D usage status, and family history of stones in patients and controls are shown in Table **2**. There was no difference in gender, age, weight, and height between the patients and controls (p>0.05). When the month of starting supplementary food in babies older than six months was evaluated, no significant difference was found between the patients and controls in terms of the month of supplemental feeding (p=0.250).

In general, when the whole patients and controls were examined, no statistically significant difference was found between the three groups in terms of those who were fed only breast milk, those fed with breast milk plus formula, and those fed only with formula (p=0.40, p=0.08, and p=0.72, respectively). It was

Table 2: Demographic Data, Nutrition, Supplementary Food, Vitamin D Usage Status, and Family History of Stone in all Participants

Parameters	Patients	Controls	p
Male/Female (n/n)	60/40	26/14	NS
Age (month) (Mean ± SD)	9.47 ± 5.67	8.36 ± 5.08	NS
Weight (kg) (Mean ± SD)	8.63 ± 2.27	8.14 ± 3.1.76	NS
Height (cm) (Mean ± SD)	70.70 ± 8.58	69.08 ± 6.61	NS
Time to start solid foods (months) (Mean ± SD)	5.8 ± 0.6	6.0 ± 0.8	NS
All patients (n=100) and controls (n=40)			
Only breastfeeding n (%)	45 (45)	16 (40)	NS
Breastfeed & formula n (%)	37 (37)	16(40)	NS
Only formula n (%)	18 (18)	8 (20)	NS
Negative family history of stones n (%)	51 (51)	28 (70)	0.04
Positive family history of stones n (%)	49 (49)	12 (30)	
Vitamin D usage (-) n (%)	11 (11)	3 (7.5)	NS
Vitamin D usage (+) n (%)	89 (89)	37 (92.5)	
Patients (n=37) and controls (n=19) younger than 6 months			
Only breastfeeding n (%)	21(56.8)	6 (31.6)	NS
Breastfeed & formula n (%)	8 (21.6)	9 (47.4)	
Only formula n (%)	8 (21.6)	4 (21.0)	
Vitamin D usage (-) n (%)	9 (24.3)	2 (10.5)	NS
Vitamin D usage (+) n (%)	28 (75.7)	17 (89.5)	
Negative family history of stones n (%)	20 (54.1)	11 (57.9)	NS
Positive family history of stones n (%)	17 (45.9)	8 (42.1)	
Patients (n=63) and controls (n=21) older than 6 months			
**Only breastfeeding n (%)	23 (36.5)	11 (52.4)	NS
**Breastfeed & formula n (%)	30 (49.2)	8 (40.0)	
**Only formula n (%)	10 (16.4)	2 (10.0)	
Vitamin D usage (-) n (%)	2 (3.2)	1 (4.8)	NS
Vitamin D usage (+) n (%)	61 (96.8)	20 (95.2)	
Negative family history of stones n (%)	31 (49.2)	17 (80.9)	0.01
Positive family history of stones n (%)	32 (50.8)	4 (19.1)	

SD: Standard deviation, **nutrition type before starting a solid food.

observed that a history of urinary stones was more common in the families of patients with urinary stones, and this was statistically significantly different from the controls (p=0.04). When the patients and the controls were compared according to their vitamin D use, it was observed that the rate of vitamin D use of the controls was not different than the patients (p>0.05; Table **2**).

The children in the patients and controls were divided into two groups as age <6 months and >6 months (Table **2**). A total of 56 children (37 patients and 19 controls) younger than six months were divided into breastfeeding, breastmilk plus formula, and formula only and compared in terms of feeding patterns within the groups. Nutritional characteristics of the patients and the controls were found to be similar (p=0.11). In the comparison made in terms of vitamin D use and family history in patients younger than six months, vitamin D use and family history of positive stones were found to be similar between the groups (p>0.05).

While the number of patients older than six months was 63, the number of controls over six months was 21 (Table **2**). No significant difference was found between the patients and controls older than six months in terms of the rate of those who started supplementary feeding (p=0.73). When the patients older than 6 months and the controls were compared in terms of eating habits, no significant difference was found between the two groups in terms of nutritional patterns. No significant difference was found between the patient and control groups in children over 6 months of age in terms of vitamin D use (p>0.05). While the rate of family history of stone was 50.8% in the patients older than 6 months, this rate was found to be 19.0% in the controls (p=0.01).

Our study found a metabolic cause in 45 of 100 (45%) children (Table **3**). For this purpose, we examined the patients' spot urine levels of some solutes such as calcium, uric acid, oxalate, cystine, citrate, and magnesium. We detected 11 patients had high spot urine calcium/creatinine, 8 patients had high

Table 3: Comparison of Patients' Blood and Urine Results with Normal Reference Values

Laboratory values	Patients (Mean ± SD)	Age (month)	Reference values
Hemoglobin (g/dL)	11.66 ± 0.86	3-24	9.5-13.5
Hematocrit (%)	34.63 ± 2.43	3-24	29-39
WBC counts (x10^3/mm^3)	10.11 ± 2.73	3-24	6.0-17.5
Platelets (x10^3/mm^3)	377.67 ± 79.22	3-24	150-350
Urea (mg/dL)	21.39 ± 7.41	3-24	10-40
Creatinine (mg/dL)	0.23 ± 0.05	3-24	0.3-0.7
Sodium (mmol/L)	137.51 ± 2.31	3-24	138-145
Potassium (mmol/L)	4.75 ± 0.46	3-24	4.1-5.3
Calcium (mg/dL)	10.34 ± 0.50	3-24	8.8-10.8
Phosphorus (mg/dL)	5.57 ± 0.57	3-24	4.5-6.7
Alkaline phosphatase (IU/L)	224.21 ± 65.79	3-24	82–383
Parathyroid hormone (pg/mL)	26.94 ± 24.98	3-24	9-52
25 (OH) Vitamin D3 (ng/mL)	33.72 ± 11.95	3-24	30-100
Spot uCa/uCr (mg/mg Cr)	0.41 ± 0.36	<6	<0.8
		7-12	<0.6
		12-36	<0.53
Spot uUA/uCr (mg/mg Cr)	1.46 ± 0.91	<12	<2.2
		12-36	<1.9
Spot uCystine/uCr (mg/mg Cr)	3.11 ± 6.62	<1	<0.18
		1-6	<0.11
		>6	<0.038
Spot uOxalate/uCr (mg/mg Cr)	0.55 ± 0.65	<6	<0.26-0.28
		7-24	<0.11-0.14
Spot uCitrat/uCr (mg/mg Cr)	20.43 ± 31.01	0-60	>0.42
		>60	>0.25
Spot uNa/uK	0.85 ± 1.47	For all ages	<2.5

SD. Standard deviation, WBC: White blood cell, uCa: Urine Calcium, uCr: Urine creatinine, uUA: Urine u0ric ascid, uCitrate: Urine citrate, uCystine: Urine cystine, uOxalate: Urine oxalate.

Table 4: Correlation between some Parameters in Infants with Nephrolithiasis (n=100)

Parameters		Duration of breast milk	Duration of Formula	Duration of additional food
PTH	r	0.095	0.088	0.286
	p	0.536	0.385	0.250
25 (OH) Vitamin D3	r	0.015	-0.014	-0.087
	p	0.922	0.893	0.732
Spot uCa/uCr	r	-0.392	-0.175	-0.286
	p	0.008	0.082	0.250
Spot uUA/uCr	r	-0.093	0.037	-0.285
	p	0.543	0.716	0.252
Spot uCitrat/uCr	r	-0.213	-0.088	-0.241
	p	0.159	0.385	0.335
Spot uCystine/uCr	r	-0.131	0.010	0.236
	p	0.392	0.918	0.347
Spot uOxalate/uCr	r	0.006	0.020	0.039
	p	0.968	0.841	0.879
Spot uMg/uCr	r	0.050	-0.091	-0.250
	p	0.712	0.367	0.317
Spot uNa/uK	r	0.456	-0.101	0.215
	p	0.005	0.365	0.407

r: Correlation Coefficient, PTH: Parathormone, uCa: Urine Calcium, uCr: Urine creatinine, uUA: Urine uric ascid, uCitrate: Urine citrate, uCystine: Urine cystine, uOxalate: Urine oxalate, uNa: Urine sodium, uK: Urine potassium.

spot urine uric acid/creatinine, 17 patients had low spot urine citrate/creatinine, 2 patients had high spot urine cystine/creatinine, 3 patients had high spot urine oxalate/creatinine, 2 patients had low spot urine magnesium/creatinine, and 4 patients had high spot urine sodium/potassium ratios. These findings were divided by spot urinary creatinine values. Obtained rates were compared with reference values for age [9]. Results above or below the reference values were considered pathological.

The relationship of patients under two years of age with urinary solute excretion according to nutritional status was examined (Table **4**). No correlation was found between the solutes excreted in urine and the feeding duration in the other feeding type groups. However, a negative correlation was found between breastfeeding time and spot urinary calcium/creatinine ratio in babies fed breast milk (r=-0.392, p=0.008) exclusively. Apart from that, a positive correlation was found between breastfeeding time and urinary sodium/potassium ratio (r=0.456, p=0.005).

DISCUSSION

We hypothesized that breastfeeding/formula/age at supplementary food and Vitamin D would be associated with urine stone disease in children first two years. Based on this, we aimed in this study is to investigate whether diet contributes to stone formation in patients with urinary system stone disease in children under the age of two by comparing with healthy controls. We have shown that a family history of renal stone disease is an important factor for urinary system stone disease, especially after 6 months, and the use of 400U/day vitamin D is not directly related to stone formation. Another important result is that breastfeeding is exclusively associated with lower urine calcium. However, we could not show the direct relationship of stone formation with diet in children under two years of age, with supplementary foods and the time to start supplementary foods.

Urinary system stones can be encountered at any age. One of the important causes of urinary stone disease in children is metabolic causes [18]. In our study conducted in different regions of the world, it has been observed that the stone can be seen at any age [19, 20]. In the study conducted by Shatha *et al*. with 204 patients, the mean age at the time of diagnosis was 41.9 ± 34.7 months (4 months-14 years) [4]. In a study conducted in our country, among pediatric stone diseases, the rate of stone disease in infancy was reported as 41% and 34%, respectively [7]. There are few studies in the literature on stone disease in infancy, and children with stones constitute 20% of all pediatric cases [7-9, 12, 21]. Approximately one-third of pediatric patients are asymptomatic and get diagnosed in ultrasonography performed for other reasons [5, 22]. In infants, the stone is mostly located in the kidneys and in older children in the ureter. It is stated that stone formation may also be associated with gender (source). Urinary system stones are more common in boys under 10 years of age and girls over 10 years [23, 24]. In this study, no significant difference was found between the patient and control groups in terms of gender, age, and height. 4 (4%) patients in the patient group and 1 (2.5%) child in the control group had growth retardation. In our study, patients were younger than 2 years old, and as reported in the literature, there was male dominance. In this study, 52% of the patients were admitted to the hospital with restlessness and abdominal pain symptoms. However, it was found that 23% had urine color changes and diaper complaints. When the size of the stones detected in the patients was examined, it was shown that 44% of the stones were 3-5 mm in diameter, and 35% were <3mm. When the localization was examined, it was located in the lower pole of the kidney with a maximum of 36%. In addition, the middle pole of the kidney with 31% was found to be the second most frequent localization site.

Considering epidemiological observations, it is certain that diet plays a role in urolithiasis [11, 25]. High animal protein intake contributes to the formation of hyperuricosuria, hyperoxaluria, hypocitraturia, and hypercalciuria. Increased consumption of animal protein is associated with an increased incidence of calcium oxalate stones in the population [25-28]. Considering the nutritional habits in the infant period, since the use of breast milk or formula constitutes the main diet during this period, the effect of the diet on stone formation may be due to the difference between breast milk and the composition of the formula. Some differences between breast milk and formula may make the form a risk factor for stone formation [29, 30]. There is no study in the literature investigating the relationship between stone formation and diet and the time of starting supplementary foods in children under 2 years of age. Our study observed that the rate of those who were fed only formula in babies with stones was 18% and 20% in the control group. However, no statistically significant difference was found between the patient and the control groups regarding formula use. According to this result, it can be said that breast milk, formula, and mixed nutrition in the patient and control groups were not different under the age of 2 years.

The presence of stone history in the family is important, and it is determined that the history is positive in 12-68% of the patients. When the family history of stones was examined, it was found 49% in the patient group and 30% in the control group, and this was statistically significant. Most of the children with stones have a family history of stones. Family history of stone is a serious risk factor leading to stone development in the child [31-34]. In the study of Amancio *et al*., including 106 patients, it was found that 85% of those with a family history of stone had a positive family history [35]. According to the data of our study, the family history of stones in the patient group (49%) was found to be significantly higher than the control group (30%). However, when the patients were divided into two groups as younger than six months and older, it was found that the family history of those younger than six months was similar to the control group without stones, whereas the family history was significantly increased in those older than six months compared to the control group. In this case, it can be said that urinary tract stone disease detected after six months is accompanied by positive family history. Although there is no concrete data about these families, it was learned in their history that they were fed a diet rich in salt. For this reason, we thought that it is necessary to inform children and families with a family history of stones about nutrition and diet and to warn them about salt restrictions.

Normally, breast milk contains an average of 1.2-6 IU/100 mL of vitamin D [36]. Standard formulas contain 40-60 IU/100 mL of vitamin D. This difference may pose a risk for the stone. Since patients taking the standard formula can also use vitamin D, this may further increase the risk. The fact that the formulas are rich in calcium, phosphorus, oxalate, sulfate, and C – D – B6 vitamins and their separation from breast milk may also be risk factors for stone development [29, 30]. In addition, the differences in socio-cultural and educational levels may cause problems in the preparation of the formula, and the risk of urolithiasis may increase with increased solute load and increased vitamin D due to intense formulas. All-term newborns in our country take vitamin D from the age of 15 days. The last recommended adequate vitamin D intake in 2008 by the American Academy of Pediatrics was 400 IU/day [37, 38]. In our study, although active vitamin D was not measured in the patient and control groups, there was no significant relationship between vitamin D use and stone formation. These results may be because a dose not exceeding 400 U/day was used in our patients and control group. However, when the patients were divided into two groups as younger as and older than six months, it was found that the use of vitamin D in patients was similar to the control group. In this case, it can be said that urinary system stone disease detected before or after six months is not associated with the use of vitamin D at a normal maintenance dose of 400 IU/day.

Studies have shown that the majority of patients with nephrolithiasis in early childhood have one or more metabolic disorders [38, 39]. These metabolic disorders may be in the form of an increase in urine concentrations of solutes such as calcium, phosphorus, oxalate, uric acid, and cystine or a decrease in citrate in the urine. Hypercalciuria is the most common metabolic cause in most studies of pediatric stone disease. In some of the studies conducted in Turkey, hypocitraturia and hyperuricosuria were found to be other common metabolic disorders in addition to hypercalciuria [40-42]. Inappropriate, excessive vitamin D supplementation and formula feeding may cause hypercalciuria. It has been reported that hyperuricosuria may occur in breastfed babies whose fluid needs cannot be met [7,9,24]. Especially in a study conducted in China reported that the risk of kidney stones increased in babies fed with a formula containing melamine [43]. It is observed that 17-20% of children with hypercalciuria have stone development within 5 years, and it is the most common metabolic disorder associated with stone etiology in infants [44, 45]. The most important nutritionally important factor in the pathogenesis of idiopathic hypercalciuria is a diet rich in sodium and protein [46, 47]. In our study, 89 patients (89%) had normal calcium/creatinine levels, while 11 patients (11.0%) had a high calcium/creatinine ratio. In addition, breast milk alone, formula alone, and the formula plus a diet rich in sodium and protein may be involved in stone etiogenesis in infants who are fed alone and mixed-fed infants. The frequencies of abnormal calcium/creatinine ratios in babies who are fed only breast milk, formula alone, and mixed-fed babies were evaluated. There was no significant difference. However, when all patients are examined, the negative correlation between the duration of breastfeeding and the urinary calcium/creatinine ratio and a positive correlation with the urinary sodium/ potassium ratio shows that breast milk decreases calcium excretion in the first months and increases sodium excretion. This situation suggests that breast milk has an effect preventing stone formation.

Uric acid is the product of purine metabolism and is excreted by the kidneys. Matos *et al*. showed that spot urinary uric acid/creatinine ratios are high in infancy depending on age and decrease as the child grows [48]. In our study, uric acid excretion of the babies was examined, high uric acid excretion was found in 8% of the patients with stones. But the rates of patients with abnormal uric acid/creatinine were found to be similar in babies who were fed only breast milk, formula only, and mixed feeds.

Hypocitraturia is one of the most common metabolic disorders causing urinary tract stones. Citrate, together with calcium, acts by creating soluble compounds that reduce calcium saturation in the urine and prevent calcium oxalate and calcium phosphate precipitation [49, 50]. In our study, it was observed that 17% of patients with stones had lower citrate excretion compared to normal. Since it is known that a high protein diet may be effective in the development of hypocitraturia, while in our study, the distribution of those with abnormal citrate excretion in only breast milk, formula only, and mixed-fed infant groups were evaluated, and no significant difference was found between the groups.

LIMITATIONS AND STRENGTHS OF THE STUDY

This study also has some limiting features. Although the patients were included in the study at the first two years of age, the fact that some patients were younger than six months and some older than six months restricted the evaluation of the effects of breast milk and formula on stone formation on a homogeneous group. The fact that the use of vitamin D was questioned verbally could not be a factor that objectively reveals our data, as we did not evaluate the findings reflected on the biochemistry parameters of the patients. Because the spot urine results were only in the patient group due to financial reasons, the abnormal values determined were compared with reference values according to age, but no comparison could be made with the control group included in the study as a similar age group.

CONCLUSION

Although many factors are effective in the formation of renal stones in infancy, there is not enough study in the literature about the effect of using formula alone or together with vitamin supplements on stone formation. According to the results of this study, there was no direct effect of nutrition in infancy on stone formation. However, there is a negative correlation between the duration of breastfeeding and the spot urinary calcium/creatinine ratio. And a positive correlation with the spot urine sodium/potassium ratio in patients who only breastfed suggested that breast milk may have a protective effect on stone formation in the long term. It was concluded that the use of vitamin D at a maintenance dose, such as normal 400 IU/day, was not associated with the stone formation and that positive stone history in the family was associated with stone formation, especially after the 6th month.

ACKNOWLEDGEMENTS

We thank Ms. Çağla Sarıtürk for her support on statistics.

ETHICS APPROVAL

This study was approved by the local ethics committee of Okmeydani Training and Research Hospital (date/number: 17.04.2018/867).

CONSENT TO PARTICIPATE

Informed consent was obtained from all parents of the children.

CONSENT FOR PUBLICATION

Consents for publication was obtained from the participants.

HUMAN AND ANIMAL RIGHTS

The study was conducted in accordance with the Helsinki Declaration guidelines

CONFLICT OF INTEREST

The authors declare no competing interests.

FUNDING

No financial support was received for this study.

REFERENCES

[1] Sas DJ. An update on the changing epidemiology and metabolic risk factors in pediatric kidney stone disease. Clin J Am Soc Nephrol 2011; 6: 2062-2068. https://doi.org/10.2215/CJN.11191210

[2] Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney Stones among children: a 25-year population-based study. J Urol 2012; 188: 247-252. https://doi.org/10.1016/j.juro.2012.03.021

[3] Matlaga BR, Schaeffer AJ, Novak TE, Trock BJ. Epidemiologic insights into pediatric kidney stone disease. Urol Res 2010; 38: 453-457. https://doi.org/10.1007/s00240-010-0327-9

[4] Rizvi SA, Naqvi SA, Hussain Z, Hashmi A, Hussain M, Zafar MN, Sultan S, Mehdi H. Pediatric urolithiasis: developing nation perspectives. J Urol 2002; 168: 1522-1525. https://doi.org/10.1016/S0022-5347(05)64509-0

[5] Ertan P, Tekin G, Oger N, Alkan S, Horasan GD. Metabolic and demographic characteristics of children with urolithiasis in Western Turkey. Urol Res 2010; 39: 105-110. https://doi.org/10.1007/s00240-010-0306-1

[6] Oner A, Demircin G, Ipekçioğlu H, Bülbül M, Ecin N. Etiological and clinical patterns of urolithiasis in Turkish children. Eur Urol 1997; 31: 453-458. https://doi.org/10.1159/000474506

[7] Baştuğ F, Gündüz Z, Tülpar S, Poyrazoğlu H, Düşünsel R. Urolithiasis in infants: evaluation of risk factors. World J Urol 2013; 31: 1117-1122. https://doi.org/10.1007/s00345-012-0828-y

[8] Alpay H, Gokce I, Ozen A, Bıyıklı N. Urinary stone disease in the first year of life: is it dangerous? Pediatr Surg Int 2013; 29: 311-316. https://doi.org/10.1007/s00383-012-3235-y

[9] Jobs K, Rakowska M, Paturej A. Urolithiasis in the pediatric population-current opinion on epidemiology, patophysiology, diagnostic evaluation and treatment. Dev Period Med 2018; 22: 201-208.

[10] Önal B, Kırlı EA, Canpolat N, Taşdemir M, Gürbüz A, Özman O, Sever L, Bilge I, Çalışkan S. Different approaches among physicians to treat pediatric stone disease: a survey-based study. Arch Argent Pediatr 2021; 119: 83-90. https://doi.org/10.5546/aap.2021.eng.83

[11] Sas DJ. Dietary risk factors for urinary stones in children. Curr Opin Pediatr 2020; 32: 284-287. https://doi.org/10.1097/MOP.0000000000000886

[12] Mohamed J, Riadh M, Abdellatif N. Urolithiasis in infants. Pediatr Surg Int 2007; 23: 295-299. https://doi.org/10.1007/s00383-007-1889-7

[13] Nicoletta JA, Lande MB. Medical evaluation and treatment of urolithiasis. Pediatr Clin North Am 2006; 53: 479-91. https://doi.org/10.1016/j.pcl.2006.03.001

[14] Alzaheb RA. A Review of the factors associated with the timely initiation of breastfeeding and exclusive breastfeeding in the Middle East. Clin Med Insights Pediatr 2017; 11: 1179556517748912. https://doi.org/10.1177/1179556517748912

[15] Gertosio C, Meazza C, Pagani S, Bozzola M. Breastfeeding and its gamut of benefits. Minerva Pediatr 2016; 68: 201-212.

[16] Greer F. Do breast fed infants need supplemental vitamins. Pediatr Clin N Am 2000; 48: 415-423. https://doi.org/10.1016/S0031-3955(08)70034-8

[17] Bozkurt HB, Çetin T, Sarıca K. The Possible Beneficial Effect of Breastfeeding on the Clinical Course of Urolithiasis Detected During Infancy. Breastfeed Med 2020; 15: 84-89. https://doi.org/10.1089/bfm.2019.0236

[18] Drach GW. Metabolic evaluation of pediatric patients with stones. Urol Clin North Am 1995; 22: 95-100. https://doi.org/10.1016/S0094-0143(21)01019-3

[19] Edvardsson V, Elidottir H, Indridason OS, Palsson R. High incidence of kidney stones in Icelandic children. Pediatr Nephrol 2005; 20: 940-944. https://doi.org/10.1007/s00467-005-1861-5

[20] Ozokutan BH, Kucukaydin M, Gunduz Z, Kabaklioglu M, Okur H, Turan C. Urolithiasis in childhood. Pediatr Surg Int 2000; 16: 60-63. https://doi.org/10.1007/s003830050016

[21] Basaklar AC, Kale N. Experience with childhood urolithiasis, report of 196 cases. Br J Urol 1991; 67: 203-205. https://doi.org/10.1111/j.1464-410X.1991.tb15110.x

[22] Dursun I, Poyrazoglu HM, Dusunsel R, Gunduz Z, Gurgoze MK, Demirci D, Kucukaydin M. Pediatric urolithiasis: an 8-

year experience of single centre. Int Urol Nephrol 2008; 40: 3-9.
https://doi.org/10.1007/s11255-007-9234-6

[23] Novak TE, Lakshmanan Y, Trock BJ, Gearhart JP, Matlaga BR. Sex prevalence of pediatric kidney stone disease in the United States: an epidemiologic investigation. Urology 2009; 74: 104-107.
https://doi.org/10.1016/j.urology.2008.12.079

[24] Daudon M, Doré JC, Jungers P, Lacour B. Changes in stone composition according to age and gender of patients: a multivariate epidemiological approach. Urol Res 2004; 32: 241-247.
https://doi.org/10.1007/s00240-004-0421-y

[25] Taylor EN, Curhan GC. Diet and fluid prescription in stone disease. Kidney Int 2006; 70: 835-839.
https://doi.org/10.1038/sj.ki.5001656

[26] Taylor EN, Fung TT, Curhan GC. DASH-Style diet associates with reduced risk for kidney stones. J Am Soc Nephrol 2009; 20: 2253-2259.
https://doi.org/10.1681/ASN.2009030276

[27] Nouvenne A, Meschi T, Prati B, Guerra A, Allegri F, Vezzoli G, Soldati L, Gambaro G, Maggiore U, Borghi L. Effects of a low-salt diet on idiopathic hypercalciuria in calcium-oxalate stone formers: a 3-mo randomized controlled trial. Am J Clin Nutr 2010; 91: 565-570.
https://doi.org/10.3945/ajcn.2009.28614

[28] Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med 1997; 126: 497-504.
https://doi.org/10.7326/0003-4819-126-7-199704010-00001

[29] Hoppe B, Roth B, Bauerfed C, Langman BC. Oxalate, citrate, and sulfate concentration in human milk compared with Formula preparations: Influence on urinary anion excretion. J Pediatr Gastroenterol Nutr 1998; 27: 383-386.
https://doi.org/10.1097/00005176-199810000-00002

[30] Campfield T, Braden G, Flynn-Valone P, Clark N. Urinary oxalate excretion in premature infants: Effect of human milk versus formula feeding. Pediatrics 1994; 94: 674-678.
https://doi.org/10.1542/peds.94.5.674

[31] Erbagci A, Erbagci AB, Yilmaz M, Yagci F, Tarakcioglu M, Yurtseven C, Koyluoglu O, Sarica K. Pediatric urolithiasis evaluation of risk factors in 95 children. Scand J Urol Nephrol 2003; 37: 129-133.
https://doi.org/10.1080/00365590310008866

[32] Tabel Y, Akin IM, Tekin S. Clinical and demographic characteristics of children with urolithiasis: single-center experience from eastern Turkey. Urol Int 2009; 83: 217-221.
https://doi.org/10.1159/000230027

[33] Hoppe B, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. Pediatr Nephrol 2010; 25: 403-413.
https://doi.org/10.1007/s00467-008-1073-x

[34] Ece A, Ozdemir E, Gurkan F, Dokucu AI, Akdeniz O. Characteristics of pediatric urolithiasis in south-east Anatolia. Int J Urol 2000; 7: 330-334.
https://doi.org/10.1046/j.1442-2042.2000.00207.x

[35] Amancio L, Fedrizzi M, Bresolin NL, Penido MG. Pediatric urolithiasis: experience at a tertiary care pediatric hospital. J Bras Nefrol 2016; 38: 90-98.
https://doi.org/10.5935/0101-2800.20160014

[36] Fallahzadeh MH, Zare J, Al-Hashemi GH, Derakhshan A, Basiratnia M, Arasteh MM Fallahzadeh MA, Fallahzadeh MK. Elevated serum levels of Vitamin D in infants with urolithiasis. Iran J Kidney Dis 2012; 6: 186-191.

[37] Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008; 122: 398-417.
https://doi.org/10.1542/peds.2007-1894

[38] Bastug F, Dusunsel R. Pediatric urolithiasis: causative factors, diagnosis, and medical management. Nat Rev Urol 2012; 9: 138-146.
https://doi.org/10.1038/nrurol.2012.4

[39] Üntan İ, Üntan S, Tosun H, Demirci D. Metabolic risk factors and the role of prophylaxis in pediatric urolithiasis. J Pediatr Urol 2021; 17: 215.e1-215.e6.
https://doi.org/10.1016/j.jpurol.2020.12.003

[40] Tekin A, Tekgul S, Atsu N, Bakkaloglu M, Kendi S. Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. J Urol 2002; 168: 2572-2574.
https://doi.org/10.1016/S0022-5347(05)64218-8

[41] Tekin A, Tekgul S, Atsu N, Sahin A, Ozen H, Bakkaloglu M. A study of the etiology of idiopathic calcium urolithiasis in children: hypocitruria is the most important risk factor. J Urol 2000; 164: 162-165.
https://doi.org/10.1016/S0022-5347(05)67487-3

[42] Pietrow PK, Pope JC 4th, Adams MC, Shyr Y, Brock JW 3rd. Clinical outcome of pediatric stone disease. J Urol 2002; 167: 670-673.
https://doi.org/10.1016/S0022-5347(01)69121-3

[43] Wen JG, Liu XJ, Wang ZM, Li TF, Wahlqvist ML. Melamine-contaminated milk formula and its impact on children. Asia Pac J Clin Nutr 2016; 25: 697-705.

[44] Butani L, Kalia A. Idiopathic hypercalciuria in children--how valid are the existing diagnostic criteria? Pediatr Nephrol 2004; 19: 577-582.
https://doi.org/10.1007/s00467-004-1470-8

[45] Hulton SA. Evaluation of urinary tract calculi in children. Arch Dis Child 1982; 84: 320-323.
https://doi.org/10.1136/adc.84.4.320

[46] Rao PN, Prendiville V, Buxton A, Moss DG, Blacklock NJ. Dietary management of urinary risk factors in renal stone formers. Br J Urol 1982; 54: 578-583.
https://doi.org/10.1111/j.1464-410X.1982.tb13600.x

[47] Polito C, La Manna A, Maiello R, Nappi B, Siciliano MC, Di Domenico MR, Di Toro R. Urinary sodium and potassium excretion in idiopathic hypercalciuria of children. Nephron 2002; 91: 7-12.
https://doi.org/10.1159/000057598

[48] Matos V, Van Melle G, Werner D. Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis 1999; 34: 1-7.
https://doi.org/10.1016/S0272-6386(99)70380-X

[49] Kirejczyk JK, Porowski T, Konstantynowicz J, Kozerska A, Nazarkiewicz A, Hoppe B, Wasilewska A. Urinary citrate excretion in healthy children depends on age and gender. Pediatr Nephrol 2014; 29: 157515-82.
https://doi.org/10.1007/s00467-014-2806-7

[50] Del Valle EE, Spivacow FR, Negri AL. Citrate and renal stones. Medicina (B Aires) 2013; 73: 363-368.

Received on 17-12-2021 Accepted on 28-02-2022 Published on 11-03-2022

https://doi.org/10.6000/1929-4247.2022.11.01.1