Evaluation of Metabolic and Biochemical Abnormalities in Pediatric Population With Nephrocalcinosis in Southwestern Iran

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Abstract- This retrospective study aimed to evaluate the metabolic and biochemical abnormalities in children with nephrocalcinosis to identify its important risk factors and better understand the disease pathophysiology. Data were collected from the medical records of 163 children diagnosed with nephrocalcinosis. Their clinical and laboratory characteristics at admission were recorded, and a 24-hour urinalysis was performed to measure parameters such as calcium, oxalate, citrate, uric acid, magnesium, and cystine. Family history of kidney stones and parental consanguinity were present in 58.8% and 58.2% of patients, respectively. The most common underlying conditions were hyperparathyroidism (24%), distal renal tubular acidosis (16.6%), and medullary sponge kidney (12.9%). The main abnormalities included hypocitraturia (65.2%), hypercalciuria (51.9%), hypomagnesuria (44.6%), hyperoxaluria (39.1%), hyperuricosuria (31.5%), vitamin D deficiency (30.06%), and metabolic acidosis (27%). Patients with kidney stones and failure to thrive had higher rates of hypercalciuria. Metabolic acidosis was more common in those with parental consanguinity and vitamin D deficiency. Renal failure at final follow-up was more evident in older patients, those with parental consanguinity, hypokalemia, acidosis, and hyperparathyroidism. End-stage renal disease was more frequent in patients with consanguineous parentage, hyperparathyroidism, hypokalemia, and acidosis. Parental consanguinity, family history of kidney stones, and urinary metabolic disorders are important risk factors for pediatric nephrocalcinosis. This highlights the need for genetic counseling, screening, and monitoring of biochemical abnormalities. Early diagnosis and timely treatment are crucial to maintain glomerular function and prevent kidney failure.

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Keywords: Pediatric; Nephrocalcinosis; Risk factor; Consanguinity; Metabolic disorders

Introduction

Nephrocalcinosis refers to the abnormal deposition of calcium oxalate (CaOx) or calcium phosphate (CaPi) within the renal parenchyma, typically involving the renal medulla (in 98% of patients) or, rarely, the cortex (2% of patients) (1). Medullary nephrocalcinosis is common in patients with monogenic metabolic disorders, predisposing them to calcium kidney stones (2). Cortical nephrocalcinosis is usually associated with severe destructive diseases of the cortex, such as chronic glomerulonephritis and chronic pyelonephritis] (2,3).

Over the past two decades, a significant increase in the incidence of pediatric nephrocalcinosis and urolithiasis has been observed, although the exact reasons for this rise are still unknown. Several risk factors have been reported to be associated with pediatric kidney stones, including metabolic disturbances (e.g., idiopathic hypercalciuria and hyperoxaluria), hereditary tubular disorders, monogenic causes, anatomical abnormalities,

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urinary tract infections, and iatrogenic causes such as vitamin D intoxication (4,5).

Renal tubular acidosis (RTA) is the major underlying metabolic mechanism of nephrocalcinosis. Chronic metabolic acidosis stimulates bone dissolution and weakens renal reabsorption of calcium, while increasing the delivery of sodium to the cortical collecting duct, eventually leading to hypokalemia and hypercalciuria. Accordingly, rectification of type 1 RTA-related biochemical abnormalities is the mainstay treatment for nephrocalcinosis (6). The present study aims to investigate the metabolic and biochemical abnormalities in children with nephrocalcinosis to identify its important risk factors. Furthermore, our findings can provide a better understanding of the disease pathophysiology and risk factors for adverse outcomes.

Materials and Methods

Study design and population

This retrospective study analyzed the medical records of 163 patients with nephrocalcinosis who were referred to the nephrology clinical centers in Ahvaz, Iran over a 6-year period. Data were collected from November 22, 2021, to February 15, 2022, and the study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical Code: IR.AJUMS.HGOLESTAN.REC.1400.116).

Children younger than 18 years diagnosed with nephrocalcinosis by kidney sonography were included in the study. Premature children treated with furosemide were excluded due to its possible effect on urinary proteins and sodium transport.

Medullary nephrocalcinosis was diagnosed by two consecutive ultrasonographies, showing echogenic renal pyramids. Cortical nephrocalcinosis was revealed as calcifications in the renal cortex, while nephrolithiasis was characterized by freely mobile renal calculi in the collecting duct system (1).

Variables and measurements

Demographic, clinical, and laboratory characteristics of patients at the referral time were assessed and recorded. Weight and height were checked according to the CDC growth charts, and weight-for-age lower than the 5th percentile and length-for-age below the 5th percentile were considered as abnormal growth or failure to thrive (FTT) (7).

The metabolic evaluation of each patient was based on blood and 24-hour urine tests. Abnormal values were detected according to the published criteria for children with urolithiasis: hypercalciuria >4 mg/kg/day, hyperoxaluria >50 mg/1.73 m²/day, hyperuricosuria >815 mg/1.73 m²/day, cystinuria >75 mg/1.73 m²/day, hypocitraturia <320 mg/1.73 m²/day, and hypomagnesemia <88 mg/m²/day (8,9). Proteinuria, hematuria, and pyuria were assessed through urinalysis. The random urine calcium-to-creatinine ratio (uCa/Cr) was estimated based on age-specific reference values (10).

Significant kidney failure was defined as a creatinine concentration more than 1.5-2 times the average value for age and gender (eGFR <60 ml/min/1.73m²) (11). Metabolic acidosis was defined as a plasma bicarbonate concentration below 20 mmol/L, and hypokalemia as a potassium level lower than 3.5 mEq/L (3 mmol/L) (12,13). Vitamin D deficiency and hypervitaminosis D were defined as levels below 20 nmol/L and above 100 nmol/L, respectively (14). Normocalcemic hyperparathyroidism was diagnosed by a serum PTH level higher than 65 pg/ml, and hypoparathyroidism by a PTH level lower than 10 pg/ml (15).

Statistical analysis

Quantitative and qualitative variables were presented as mean±SD and frequency (%), respectively. Associations between variables were evaluated using Fisher's exact test, t-test, or Mann-Whitney test, as appropriate. $P<0.05$ was considered statistically significant, and the data were analyzed using SPSS version 26.

Results

Demographic and medical features

Totally, 163 eligible patients diagnosed with nephrocalcinosis were completely analyzed. Eighty-one patients (3.86±3.55 years) were female and 82 cases (4.83±4.66 years) were male, without any significant difference in mean age of diagnosis ($P=0.14$). The family history of kidney stones and consanguineous marriages were found in 58.8% (n=96) and 58.2% (n=95) of patients, respectively. (Table 1).

Table 1. Demographics, clinical characteristics and metabolic/biochemical abnormalities in patients with nephrocalcinosis

Variables		Mean±SD and/or frequency (%)
Age, year		4.35 ±4.16
Female		3.86 ±3.55
Male		4.83 ±4.66
Gender	**Female**	81 (49.7)
	Male	82 (50.3)
Age at diagnosis (mean, year)		4.3
Family history of kidney stones		96 (58.8)
Parental consanguinity		95 (58.2)
Failure to thrive (WFA <5th)		74 (45.4 %)
Short stature (LFA <5th)		69 (42.3)
Underlying diseases	**Hyperparathyroidism**	39 (24%)
	dRTA	27 (16.6)
	MSK	21 (12.9)
	Idiopathic hypercalciuria	18 (11)
	Bartter syndrome	6 (3.7)
	Hypervitaminosis D	3 (1.8)
	PKD	3 (1.8)
	pRTA	1 (0.6)
Biochemical characteristics	**Vitamin D deficiency**	49 (30.06)
	Hypervitaminosis D	3 (2)
	Hypokalemia (<3 mEq/L)	33 (20.2)
	Metabolic acidosis	44 (27)
	Metabolic alkalosis	6 (3.6)
	Renal failure	29 (17.8)
	Hyperparathyroidism	39 (24)
	Hypoparathyroidism	20 (12.3)
Abdominal pain		63 (38.7 %)
Polydipsia		47 (28.8 %)
UTI		33 (20.2 %)
Dysuria		27 (16.6 %)
Enuresis		8 (13.3 %)
SNHL		7 (4.3 %)
Hypokalemic paralysis		8 (4.9 %)
Carpopedal spasm		3 (1.8 %)
Hematuria		22 (15.7 %)
Proteinuria		8 (5.7 %)
Pyuria		32 (22.9 %)
eGFR <60 at diagnosis (ml/min/1.73m2)		29 (17.8 %)
Urolithiasis		71 (43.6 %)
Serum creatinine level in the first visit		0.6±0.2 mg/dL (ranged 1_1.5 mg/dL)
Serum creatinine level in the last visit		1± 0.8 mg/dL (ranged 0.2_5 mg/dL)

dRTA: distal renal tubular acidosis, pRTA: proximal renal tubular acidosis, MSK: Medullary sponge kidney, PKD: Polycystic kidney disease, WFA: weight-for-age, LFA: length-for-age, UTI: urinary tract infection, SNHL: sensorineural hearing loss, PTH: Parathyroid hormone

The clinical findings of patients included polydipsia (28.8%), dysuria (16.6%), sensorineural hearing loss (SNHL) (4.3%), carpopedal spasms (1.8%), hypokalemic paralysis (4.9%), and urinary tract infection (UTI) (20.2%). Totally, 49.7 % of patients had decelerated or arrested physical growth. Seventy-two patients (45.4%) had weight-for-age less than 5th percentile and 42.2% had a height less than 5th percentile. The first ultrasonography indicated that 56.4% of patients had merely nephrocalcinosis while 43.6% of them had nephrocalcinosis with stones. (Table 1).

The most common underlying diseases in patients were respectively hyperparathyroidism (24%), distal RTA [dRTA] (16.6%), medullary sponge kidney (12.9%), idiopathic hypercalciuria (11%), and Bartter syndrome (3.7%), followed by polycystic kidney disease (1.8%), hypervitaminosis D (1.8%), and proximal RTA (0.6%). Other rare underlying diseases included sanjad

sakati syndrome (n=4), Williams syndrome (n=1), osteogenesis imperfecta (n=1), Wilms' tumor (n=1), one case of leukemia who underwent chemotherapy. In 39.9% of patients, hyperoxaluria, hyperuricosuria, hypocitraturia and hypomagnesuria were observed in the absence of underlying diseases. In 13 cases, no underlying disease or predisposing factor was found (8%).

Biochemical blood analysis indicated that 30.06%, 20.2% (n=33), 27% (n=44), 3.6% (n=6), 17.8% (n=29), 24% (n=39), 12.3% (n=20), and 2% (n=3) of patients had respectively vitamin D deficiency, hypokalemia, metabolic acidosis, metabolic alkalosis, renal failure, hyperparathyroidism, hypoparathyroidism, and hypervitaminosis D (Table 1).

Moreover, 24-hour urine analysis test conducted for 92 patients indicated that hypocitraturia, hypercalciuria, hypomagnesuria, hyperoxaluria, and hyperuricosuria were respectively found in 65.2%, 51.9%, 44.6%, 39.1%, and 31.5% of patients. Cystinuria was positive in only one case (1.1%). Random urinary Ca/Cr ratio was also measured in 155 cases, of which 76 (49%) had levels above normal ratio (Table 1).

The first ultrasonography indicated that 56.4% of patients had merely nephrocalcinosis while 43.6% of them had nephrocalcinosis with nephrolithiasis. In the follow-up ultrasound of 127 patients, nephrocalcinosis remained in 52.8% of patients, including 15% nephrocalcinosis with stones without reducing the number of stones and 11% nephrocalcinosis with a reduction in the number and size of stones. Eventually, 21.3% of patients had improved. The improvement of nephrocalcinosis in the last ultrasound was significantly higher in cases with nephrocalcinosis plus nephrolithiasis than those with only nephrocalcinosis (P<0.001).

Renal failure at the final follow-up was significantly more evident in patients with older age at the time of nephrocalcinosis diagnosis, parental consanguinity, hypokalemia, acidosis, and hyperparathyroidism than others (P<0.05).

Associations between clinical and biochemical characteristics

Family history of kidney stones had a significant correlation with the potassium level (P=0.04) and history of UTI (P=0.03). UTI had a significant correlation with the age of diagnosis of nephrocalcinosis (P=0.02). Moreover, parental consanguinity had a significant correlation with metabolic acidosis (P=0.002), hypokalemia (P=0.001), hyperoxaluria (P=0.028), FTT (P<0.001), and kidney failure (P<0.001). Also, renal failure was significantly associated with hypocitraturia (P=0.009) and nephrolithiasis (P=0.006). The incidence rate of hypokalemia was significantly higher in patients of consanguineous parentage (P=0.001), but it was less in patients with family history of nephrolithiasis (P=0.01). (Table 2).

Table 2. Metabolic risk factors in patients with nephrocalcinosis and their subgroups

	Overall Percentage	Family History of Calculus		Parental Consanguinity		MSK	
Metabolic Risk Factors	**Percentage**	**Percentage**	***P***	**Percentage**	***P***	**Percentage**	***P***
Hypercalciuria	51.9%	51.2%	0.016	60%	0.81	15%	0.44
Hypocitraturia	65.2%	66.7%	0.92	56.7%	0.54	18.3%	0.2
Hypomagnesuria	44.6%	65.9%	0.93	57.3%	0.9	14.6%	0.9
Hyperuricosuria	31.5%	62.1%	0.56	55.2%	0.91	10.3%	0.74
Hyperoxaluria	39.1%	72.2%	0.33	69.4%	0.02	13.9%%	0.95

End-stage renal disease (ESRD) was significantly more frequent in cases with remained nephrocalcinosis than those who have been improved (P=0.02). ESRD was significantly more prevalent in patients of consanguineous parentage (P=0.001), hypokalemia (P=0.007) and acidosis (P=0.008). Also, the incidence of ESRD in patients with hyperparathyroidism was significantly higher than those with hypoparathyroidism and/or normal PTH (P=0.02). ESRD had a significant positive correlation with the age of nephrocalcinosis diagnosis (P=0.032). There was also a significant negative correlation between ESRD and bicarbonate (P=0.04). Moreover, primary renal disease (PRD) was more prevalent in cases of nephrocalcinosis than in cases of nephrocalcinosis plus nephrolithiasis (P=0.006). Also, PRD was significantly higher in patients with leukocyturia and hematuria (P<0.05). PRD had a significant negative correlation with bicarbonate level (P=0.03). But PRD had no significant correlation with other factors (P>0.05) (Table 3).

Table 3. Associations between clinical and biochemical characteristics of patients with nephrocalcinosis

Variables		Mean±SD	*P*
Potassium level, mmol/L	**Patients with a family history of kidney stones**	0.7+3.9	0.04
	Patients without a family history of kidney stones	0 5+3.7	
Average age of diagnosis (yr)	**Patients with a history of UTI**	3.1±2.8	0.02
	Patients without a history of UTI	4.6±4.4	
	Patients with ESRD	7.4±5.5	0.032
	Patients without ESRD	4.2±3.9	
Parathyroid hormone, pg/mL	**Patients with metabolic acidosis**	5.5±4.7	0.044
	Patients without metabolic acidosis	3.9±4	
	Boys	39 ± 43	0.026
	Girls	74 ± 126	
Blood bicarbonate level, mEq/L	**Patients with ESRD**	19±6.5	0.04
	Patients without ESRD	22±5.6	
	Patients with PRD	20±6	0.03
	Patients without PRD	22±5	
	Patients with normal growth	6.5±20	<0.001
	Patients with FTT	4.1±24	
	Patients with short stature	19.9±6.6	0.001
	Patients with normal height	23.9±3.9	
Urinary Ca/Cr ratio	**Hypokalemic cases**	18.4±7.4	0.001
	Patients with normal potassium level	23.4±4.4	
	Patients with hypoPP	18±8	0.038
	Patients without hypoPP	22±5	
	Patients with normal growth	0.42±0.4	0.047
	Patients with FTT	1.3±0.8	
	Patients with metabolic acidosis	0.45±0.3	0.029
	Patients without metabolic acidosis	0.76±1.1	
	Patients with hypercalciuria	0.7±0.8	0.04
	Patients without hypercalciuria	0.4±0.4	
	Patients with hyperuricosuria	0.6±0.6	0.026
	Patients without hyperuricosuria	0.3±0.2	
Potassium, mmol/L	**Patients with normal growth**	3.9±0.5	0.005
	Patients with FTT	3.6±0.75	
	Patients with short stature	3.5±0.74	0.01
	Patients with normal height	4±0.49	
Vitamin D, ng/mL	**Patients with metabolic acidosis**	3.3±0.68	<0.001
	Patients without metabolic acidosis	4±0.54	
24-hour urine oxalate, mg/24 hrs	**Patients with hypocitraturia**	21± 11	0.046
	Patients without hypocitraturia	33± 25	
24-hour urine magnesium, mg/24 hrs	**Patients with metabolic acidosis**	43±28	0.045
	Patients without metabolic acidosis	11.6±18	
	Patients with metabolic acidosis	69.4±80	0.025
	Patients without metabolic acidosis	40±22	
	Patients with high urine Ca/Cr ratio	62±56	0.002
	Patients with normal Ca/Cr ratio	18.6 ±30.9	
24-hour urine uric acid, mg/24 hrs	**Patients with leukocyturia**	35±14	0.028
	Patients without leukocyturia	53±53	
	Boys	320±162	0.002
	Girls	203±104	
24-hour urine citrate, mg/24 hrs	**Patients with hypomagnesuria**	215±92	0.04
	Patients without hypomagnesuria	283±165	
Creatinine, mg/dL	**Patients with hypercalciuria**	82±130	0.013
	Patients with normal calcium	24±52	
24-hour urine Ca, mg/24 hrs	**Patients with hyperuricosuria**	0.5±0.1	0.039
	Patients without hyperuricosuria	0.7±0.3	
	Patients with hypomagnesuria	75±48	0.003
	Patients without hypomagnesuria	132±89	

ESRD, End-stage renal disease; PRD, Primary renal disease; FTT, failure to thrive; hypoPP, hypokalemic periodic paralysis

The failure to thrive (FTT) showed a significant negative correlation with the levels of bicarbonate and potassium, but a positive correlation with urinary Ca/Cr ratio (P<0.05). Moreover, FTT was significantly more frequent in patients with polydipsia (P=0.024), hypercalciuria (P=0.035), metabolic acidosis (P<0.001), hypokalemia (P<0.001), and patients of consanguineous parentage (P<0.001). FTT was not seen in patients with nocturnal enuresis (P=0.04) (Table 3).

Results of a 24-hour urine analysis showed that hypercalciuria is more frequent in cases of nephrocalcinosis plus nephrolithiasis than nephrocalcinosis alone (P=0.046). Hypocitraturia was more prevalent in girls (P=0.048) and patients with kidney failure (P=0.009). Hyperoxaluria was significantly higher in patients of consanguineous parentage (P=0.028). Nocturnal enuresis was significantly more in cases with hyperoxaluria (P=0.03). Hematuria was more prevalent in cases with hypocitraturia (P=0.046). Hypocitraturia had a significant correlation with vitamin D level (P=0.046). But hypocitraturia had no significant correlation with other factors (P>0.05) (Table 3).

Patients with nephrocalcinosis plus hypokalemia were more likely to get kidney failure (P=0.007). Hypokalemia had a significant correlation with blood bicarbonate level (P=0.001), whereas hypokalemia had no significant association with gender, dysuria, PTH, hypercalciuria, etc. (P>0.05). In other respect, hypokalemic periodic paralysis (hypoPP) had a significant negative correlation with bicarbonate level (P=0.038). But hypoPP had no significant correlation with other factors (P>0.05).

Metabolic acidosis was significantly higher in nephrocalcinosis patients of consanguineous parentage (P=0.043), vitamin D deficiency (P=0.029), and polydipsia (P=0.008). Metabolic acidosis and hypokalemia were more common in patients with SNHL (P=0.009, P=0.005). Also, metabolic acidosis was significantly lower in cases with family history of nephrolithiasis (P=0.015). Moreover, the mean age of diagnosis in cases with metabolic acidosis was significantly higher than those without acidosis (P=0.044). Metabolic acidosis had a significant negative correlation with urinary Ca/Cr ratio (P=0.029) and potassium (P<0.001), but a positive correlation with 24-hour urine levels of oxalate (P=0.045) and magnesium (P=0.025). Metabolic acidosis was also significantly correlated with the etiology of nephrocalcinosis (P<0.001). But it had no significant correlation with sex and other urinary metabolic disorders (P>0.05).

The mean PTH level in girls was significantly more than boys (P=0.026). Hyperparathyroidism was more frequent in girls with nephrocalcinosis while hypoparathyroidism was more evident in boys (P=0.006). The mean levels of 24-hour urine uric acid were significantly higher in boys (P=0.002). Moreover, hypocitraturia and urinary infection were more prevalent in girls (P=0.048; P<0.001). But gender had no significant correlation with other conditions (P>0.05).

Random urine Ca/Cr ratio had a significant positive relationship with 24-hour urine magnesium (P=0.002). But it had no eligible correlation with other factors (P>0.05). The mean level of urine Ca/Cr ratio in cases with hypercalciuria was significantly higher than those without hypercalciuria (P=0.04). Also, hypercalciuria had a significant positive correlation with 24-hour urine citrate (P=0.013), whereas hypercalciuria had no significant correlation with other factors (P>0.05).

Hyperuricosuria had a significant negative correlation with creatinine level (P=0.039) while a positive correlation with urine Ca/Cr ratio (P=0.026). But hyperuricosuria had no significant correlation with other factors (P>0.05).

Hypomagnesuria had significant negative correlations with 24-hour urine levels of Calcium (P=0.003) and uric acid (P=0.04). But hypomagnesuria had no significant correlation with other factors (P>0.05). Also, leukocyturia had a significant negative correlation with 24-hour urine magnesium (P=0.028). But it had no significant correlation with other factors (P>0.05).

Discussion

The most common clinical underlying risk factors of nephrocalcinosis in the present study population were respectively hyperparathyroidism, dRTA, medullary sponge kidney, and idiopathic hypercalciuria, which confirmed the previous reports (16-18). Moreover, the most common underlying urinary abnormalities associated with nephrocalcinosis were respectively hypocitraturia, hypercalciuria, hypomagnesuria, hyperoxaluria, and hyperuricosuria. In this regard, most of the present results were in agreement with the results of Kari *et al.*,'s study in the pediatric population of Riyadh, Saudi Arabia (19). However, cystinuria was a rare urinary abnormality in our study population. This discrepancy may be due to genetic, dietary, or lifestyle differences between the two populations.

A significant number of our patients simultaneously had hypomagnesaemia-hypercalciuria-nephrocalcinosis.

Hypercalciuria along with low amounts of crystal formation inhibitors such as citrate and magnesium can lead to nephrocalcinosis and urolithiasis. Also, the urinary acidification disturbances and urine volume can affect the interactions of the aforementioned ions to promote crystal formation (20).

A significantly high rate of our study population had a family history of kidney stones and/or had been born from consanguineous marriages. This signifies the importance of genetic and family history in the occurrence of pediatric nephrocalcinosis. Such a strong correlation between family history of urolithiasis and/or history of consanguinity have been also reported in several previous studies (21-24). The most common monogenic causes found in familial nephrolithiasis/nephrocalcinosis were primary hyperoxaluria types 1 and 2 (AGXT, GRHPR), hypomagnesemia/renal/ophthalmological abnormalities (CLDN12), Bartter syndrome type 2 (SLC12A1), and infantile hypercalcemia/hypophosphatemia/nephrolithiasis (SLC34A1) (25). Gefen *et al.*, found that primary hyperoxaluria type 3 (HOGA1) and cystinuria type A (SLC3A1) were the most common diagnoses in the nephrolithiasis group, while SLC34A3 carrier and primary hyperoxaluria type 1 (AGXT) were the most common diagnoses in the nephrocalcinosis group (26).

The present study did not find any correlation between pediatric nephrocalcinosis and gender. By contrast, Alhasan et al. have recently reported that nephrolithiasis was significantly more prevalent in male and nephrocalcinosis in female patients (24). Additionally, we found that FTT (45.4 %) and short stature (42.3 %) were the most common clinical symptoms in nephrocalcinosis patients, which confirms the recent Choi *et al.*,'s report (27).

A high rate of our patients had vitamin D insufficiency/deficiency and abnormal PTH levels. Prevalence of vitamin D deficiency in children with chronic kidney disease (CKD) has been reported to be 50-92%, and a negative correlation has been found between 25(OH)D concentrations and CKD stage (28). This complication can occur for several reasons such as secondary hyperparathyroidism and increased catabolism of vitamin D metabolites, loss of vitamin D metabolites during proteinuria, low dietary intake, and inadequate sunlight exposure (29,30). Shroff *et al.*, evaluated the preventive effects of vitamin D supplementation on secondary hyperparathyroidism, and reported that children who received ergocalciferol until achieving 25(OH)D concentrations >30 ng/mL developed secondary hyperparathyroidism with a significantly greater delay compared to those who consumed placebo (31). Furthermore, there is evidence of a significant association between vitamin D deficiency and increased arterial calcification and tightness in CKD patients. Also, vitamin D has shown anti-hypertensive and anti-proteinuria effects, implying that it may have cardioprotective effect and/or prevent the CKD progression (32).

In the present study, a significant percentage of children with nephrocalcinosis had metabolic acidosis (27%), which significantly correlated with the consanguineous, vitamin D deficiency and polydipsia. The most common causes of pediatric metabolic acidosis are sepsis, gastroenteritis, diarrhea and subsequent hypovolaemia, and hypoxia (19,33). Chronic metabolic acidosis causes hypercalciuria in patients through stimulation of bone resorption and disruption of renal calcium reabsorption. Subsequently, a low urinary citrate excretion (due to hypokalemia or metabolic acidosis) is further exacerbated and nephrocalcinosis progresses (34,35).

Asymptomatic or clinically silent kidney stones are possibly serious because, in their expected passage, they may cause infection, obstruction and renal impairment. The purpose of this study was to determine the prevalence of silent kidney stones in a sample of Baghdad population and consider how this value could affect the justification for a screening system.

The study found that the prevalence of clinically silent nephrolithiasis was 3.4%, which the authors concluded does not support a global screening program, but may justify targeted screening for higher risk groups such as males over 50 with a positive family history (36). Accordingly, monitoring and correcting the biochemical abnormalities associated with metabolic acidosis is one of the main therapeutic strategies to prevent nephrocalcinosis progression.

A series of correlations were discovered between various abnormalities and factors in this study, which provides a broad pathophysiology insight about nephrocalcinosis for physicians and researchers. Hypocitraturia had a significant negative correlation with vitamin D level.

Our findings showed that the mean levels of bicarbonate and potassium in patients with FTT were significantly lower than those with normal growth. Whereas the level of urinary Ca/Cr ratio in patients with FTT was significantly higher than those with normal growth. Also, Random urine Ca/Cr ratio had a positive relationship with 24-hour urine magnesium.

Hyperuricosuria had a positive correlation with urine Ca/Cr ratio but a negative correlation with Cr level. Hypomagnesuria had a negative correlation with both 24-hour urine uric acid and Ca levels. Moreover, leukocyturia had a negative correlation with 24-hour urine magnesium.

Present study showed that renal failure at the final follow-up was significantly more evident in patients with older age at the time of nephrocalcinosis diagnosis, parental consanguinity, hypokalemia, acidosis, and hyperparathyroidism (21-24,33). Therefore, early diagnosis of disease by ultrasound and examination of its underlying etiology and timely treatment of related complications can help preserve glomerular function and prevent ESRD. Moreover, measurement and monitoring of the levels of potassium and blood gas in patients are recommended.

The present study identifies parental consanguinity, family history of nephrocalcinosis, and various urinary and metabolic disorders as important risk factors associated with pediatric nephrocalcinosis. These findings signify the importance of genetic counseling and screening of consanguineous couples, as well as the need for close monitoring and correction of biochemical abnormalities in affected children.

Additionally, the study revealed a series of correlations between different abnormalities and factors, providing broader pathophysiological insights about nephrocalcinosis and urolithiasis for physicians and researchers. These observations could inform more effective prevention and management strategies for these conditions.

However, the retrospective nature of the study and the limited sample size represent important limitations. To accurately elucidate the pathophysiology of pediatric nephrocalcinosis and its associated risk factors, further prospective and multicenter studies are required.

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References

1. Vaidya SR, Yarrarapu SNS, Aeddula NR. Nephrocalcinosis. [Updated 2022 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
2. Dickson FJ, Sayer JA. Nephrocalcinosis: A Review of Monogenic Causes and Insights They Provide into This Heterogeneous Condition. Int J Mol Sci 2020;21:369.
3. Hooda AK, Narula AS, Raychaudhury N, Chatterji S. Renal cortical nephrocalcinosis following acute renal failure due to polytrauma. Ren Fail 2007;29:231-3.
4. Shavit L, Jaeger P, Unwin RJ. What is nephrocalcinosis? Kidney Int 2015;88:35-43.
5. Lin TH, Lu HJ, Lin CH, Lee MD, Chang BP, Lin CC, et al. Nephrocalcinosis in children who received high-dose vitamin D. Pediatr Nephrol 2022;37:2471-8.
6. Palmer BF, Kelepouris E, Clegg DJ. Renal Tubular Acidosis and Management Strategies: A Narrative Review. Adv Ther 2021;38:949-68.
7. Mei Z, Ogden CL, Flegal KM, Grummer-Strawn LM. Comparison of the prevalence of shortness, underweight, and overweight among US children aged 0 to 59 months by using the CDC 2000 and the WHO 2006 growth charts. J Pediatr 2008;153:622-8.
8. Zakaria M, Azab S, Rafaat M. Assessment of risk factors of pediatric urolithiasis in Egypt. Transl Androl Urol 2012;1:209-15.
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;22:201-8.
10. Poyrazoğlu HM, Düşünsel R, Yazici C, Durmaz H, Dursun I, Sahin H, et al. Urinary uric acid: creatinine ratios in healthy Turkish children. Pediatr Int 2009;51:526-9.
11. Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein SL. Pediatric nephrology, 7th ed. Springer: Berlin, Heidelberg, 2015.
12. Jung B, Martinez M, Claessens YE, Darmon M, Klouche K, Lautrette A, et al. Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. Ann Intensive Care 2019;9:92.
13. Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. Endocr Connect 2018;7:R135-46.
14. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr 2020;74:1498-513.
15. Rajkumar V, Levine SN. Normocalcemic Hyperparathyroidism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
16. Monet-Didailler C, Chateil JF, Allard L, Godron-Dubrasquet A, Harambat J. Néphrocalcinose de l'enfant.

Néphrologie Thérapeutique 2021;17:58-66.
17. Vervaet BA, Verhulst A, d'Haese PC, De Broe ME. Nephrocalcinosis: new insights into mechanisms and consequences. Nephrol Dial Transplant. 2009;24:2030-5.
18. Floege J, Johnson RJ, Feehally J. Comprehensive clinical nephrology E-book. Elsevier Health Sciences; 2010.
19. Kari JA, Shalaby MA, Qari FA, Albanna AS, Alhasan KA. Childhood nephrolithiasis and nephrocalcinosis caused by metabolic diseases and renal tubulopathy: A retrospective study from 2 tertiary centers. Saudi Med J 2022;43:81-90.
20. Benigno V, Canonica CS, Bettinelli A, von Vigier RO, Truttmann AC, Bianchetti MG. Hypomagnesaemia–hypercalciuria–nephrocalcinosis: a report of nine cases and a review. Nephrol Dial Transplant 2000;15:605-10.
21. Amancio L, Fedrizzi M, Bresolin NL, Penido MG. Pediatric urolithiasis: experience at a tertiary care pediatric hospital. J Bras Nefrol 2016;38:90-8.
22. Alemzadeh-Ansari MH, Valavi E, Ahmadzadeh A. Predisposing factors for infantile urinary calculus in south-west of Iran. Iran J Kidney Dis 2014;8:53-7.
23. Ertan P, Tekin G, Oger N, Alkan S, Horasan GD. Metabolic and demographic characteristics of children with urolithiasis in Western Turkey. Urol Res 2011;39:105-10.
24. Alhasan KA, Shalaby MA, Albanna AS, Temsah MH, Alhayek Z, Abdalla MS, et al. Comparison of Renal Stones and Nephrocalcinosis in Children: Findings From Two Tertiary Centers in Saudi Arabia. Front Pediatr 2022;9:736308.
25. Daga A, Majmundar AJ, Braun DA, Gee HY, Lawson JA, Shril S, et al. Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis. Kidney Int 2018;93:204-13.
26. Gefen AM, Sethna CB, Cil O, Perwad F, Schoettler M, Michael M, et al. Genetic testing in children with nephrolithiasis and nephrocalcinosis. Pediatr Nephrol 2023;38:2615-22.
27. Choi N, Kim SH, Bae EH, Yang EM, Lee KH, Lee SH, et al. Long-term outcome of Bartter syndrome in 54 patients: A multicenter study in Korea. Front Med (Lausanne) 2023;10:1099840.
28. Shroff R, Knott C, Rees L. The virtues of vitamin D—but how much is too much? Pediatr Nephrol 2010;25:1607-20.
29. Michaud J, Naud J, Ouimet D, Demers C, Petit JL, Leblond FA, et al. Reduced hepatic synthesis of calcidiol in uremia. J Am Soc Nephrol 2010;21:1488-97.
30. Grant WB, Boucher BJ, Bhattoa HP, Lahore H. Why vitamin D clinical trials should be based on 25-hydroxyvitamin D concentrations. J Steroid Biochem Mol Biol 2018;177:266-9.
31. Shroff R, Wan M, Gullett A, Ledermann S, Shute R, Knott C, et al. Ergocalciferol Supplementation in Children with CKD Delays the Onset of Secondary Hyperparathyroidism: A Randomized Trial. Clin J Am Soc Nephrol 2012;7:216-23.
32. Shroff R, Wan M, Rees L. Can vitamin D slow down the progression of chronic kidney disease? Pediatr Nephrol 2012;27:2167-73.
33. Bhowmick R. Normal Anion Gap Metabolic Acidosis in Pediatric Acute Diarrhea: A Menace or an Innocent Bystander? Indian J Crit Care Med 2022;26:1235-6.
34. Alexander RT, Cordat E, Chambrey R, Dimke H, Eladari D. Acidosis and Urinary Calcium Excretion: Insights from Genetic Disorders. J Am Soc Nephrol 2016;27:3511-20.
35. Frías Ordoñez JS, Urrego Díaz JA, Lozano Triana CJ, Millán GL. Distal Renal Tubular Acidosis: Case Series Report and Literature Review. Revista Colombiana de Nefrología 2020;7:97-112.
36. Tahir NL, Hassan QA, Kamber HM. The Prevalence of a Clinically Silent Nephrolithiasis in Baghdad Population: An Initial Ultrasound Screening Study From Iraq. Acta Med Iran 2019;57:51-6.