ORIGINAL ARTICLE

CHARACTERISTICS OF CERTAIN INDICES OF MINERAL METABOLISM IN CHILDREN WITH KIDNEY CALCULI

DOI: 10.36740/WLek202201215

Iryna S. Lembryk, Oksana V. Tymoshchuk, Lesia Ya. Ivanyshyn, Oksana V. Kuzenko, Inna V. Shlimkevych, Olena A. Holodnykh

IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

ABSTRACT

The aim: To study the violations of bone density indices in patients with kidney calculi.

Materials and methods: 175 children with different types of kidney calculi were examined and treated in Ivano-Frankivsk Regional Children's Consultative Polyclinics and Hospital, from 2016 to 2019 inclusively. Comprehensive metabolic panel involved by means of generally accepted biochemical methods. Sonography of the urinary tract was carried out. Voiding cystourethrography and excretory urography were performed. Bone mineral density was evaluated by means of ultrasonic densitometry. Statistical processing of the obtained data was carried out according to standard methods of variation statistics.

Results: In patients with kidney calculi, oxaluria and oxalate-calcium nephropathy (60.0% and 30.0%, $p < 0.05$) occurred most frequently. Signs of syndrome of undifferentiated connective tissue dysplasia - postural malformation (50.0%), thoracic kyphosis (25.0%), and stigmas of dysembryogenesis (25.0%) were noticed. In the majority of children with oxalate-calcium nephropathy, levels of the bone alkaline and acid phosphatase isoenzymes in a blood serum were significantly high, indicating severity of the resorption and disorders in development of the bone tissue. In these children, decreased fraction of ionized calcium, hypomagniemia and hypophosphatemia were observed.

Conclusions: Children with oxalate-calcium nephropathy are in group of risk for osteopenic syndrome.

KEY WORDS: children, kidney calculi, bone density

Wiad Lek. 2022;75(1 p.2):232-236

INTRODUCTION

It is notorious that the malformation of bone tissue occurs with most congenital and acquired renal diseases, including kidney calculi. It may even result in fractures, malfunction of the cardiovascular system, as well as the development of chronic kidney disease (CKD) along with impaired renal function, which may be fatal in adulthood [1,2].

The analysis of recent literature data shows that more than half of children with oxalate nephropathy have syndrome of connective tissue dysplasia in the form of scoliosis, osteochondrosis, reactive arthritis or arthralgia, and hip dysplasia [3,4].

Some researchers explain this with the fact that oxalic acid is the end-product in the exchange of a number of amino acids (serine, glycin, hydroxyproline), which are involved in the metabolism of connective tissue [5,6]. It is on record that bone remodeling also occurs in *tubulointerstitial nephritis*, especially at the stage of pre-azotemic stage in CKD [7].

Previously conducted scientific studies on this issue have approved the presence of osteopenic syndrome in more than half of patients with tubulopathies accompanied by urinary tract infections, such as chronic pyelonephritis [7,8].

Therefore, from this perspective, the study of specific parameters of mineral metabolism in children with kidney calculi, affecting the condition of bone tissue, will be of significant prognostic value.

THE AIM

The aim of investigation is to study the violations of bone density in children with kidney calculi.

MATERIALS AND METHODS

All children underwent comprehensive thorough inspection, including BMI, in accordance with the modern protocols for examination and treatment of urinary tract diseases. Criteria worked out by Ivanov D.D., Korzh O.M.: obvious excess amount of salt crystals in urine; sonographic echo-positive admixtures in kidney calyces and presence of isolated disuria were also taken into account for confirmation of kidney calculi. Comprehensive metabolic panel, in addition to common indicators, involved the determination of total blood calcium level connected with blood plasma proteins, as well as its ionized fraction, magnesium and phosphates by means of generally accepted biochemical methods. For the analysis of partial renal functions and metabolic disturbances, excretion of uric acid, calcium, phosphorus, oxalic acid in urine were estimated by recalculation of daily excretion per kilo-

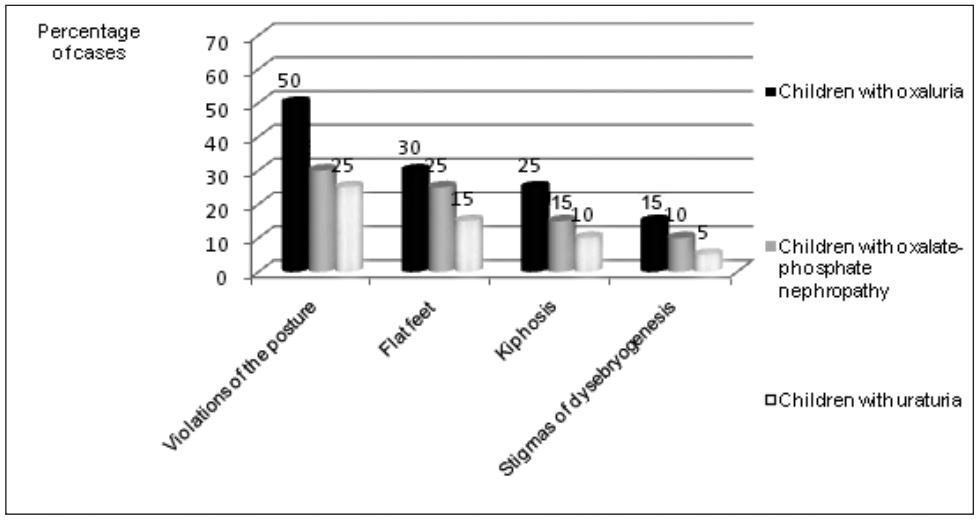

Fig. 1. Signs of the syndrome of undifferentiated connective tissue dysplasia in children with kidney calculi, depending on its type, n=175

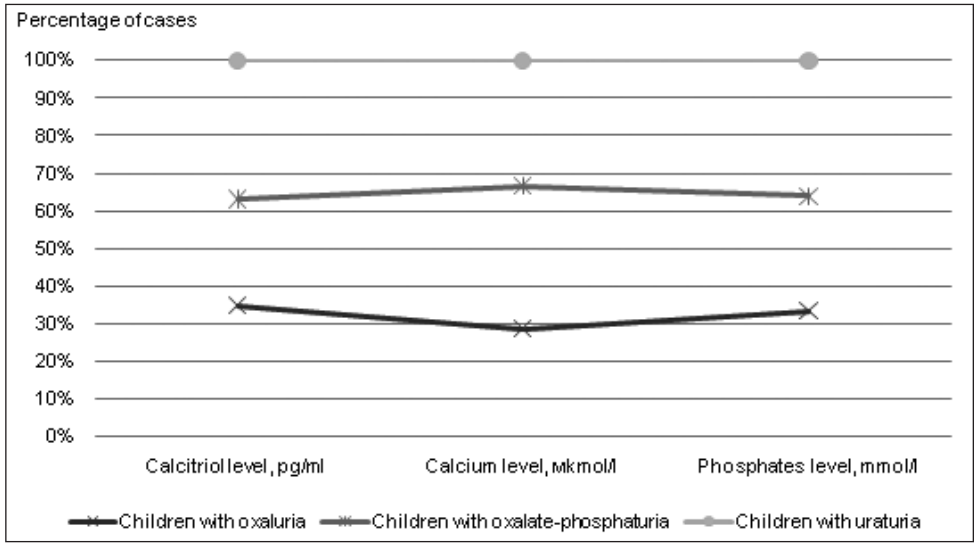

Fig 2. Assessment of calcitriol, calcium and phosphate levels in children with kidney calculi, n=175

gram of weight per day (mg / kg / day). Determination of alkaline phosphatase activity in serum was based on the kinetic method with p-nitrophenylphosphate DEA buffer. Detection of acid phosphatase activity in the bloodserum was conducted at analyzer «ARCHITECT 3 - 8000 Abbott Diagnostics» (USA) with usage of kit «Abbott» (USA). Vitamin D metabolite – the calcitriol index was studied with the help of ELISA test exemplified by analyzer using EUROIMMUN test system (Germany), while the parathormone activity was studied by ECLIA test (SINEVO laboratory) on analyzer and using the Cobas 6000, Roche Diagnostics (Switzerland) test system.

Sonography of the kidneys and urinary tract was carried out with the help of aparatus Esaote mylab seven (Italy). Voiding cystourethrography and excretory urography were performed by means of aparatus «Spectrap».

Bone mineral density was evaluated by means of ultrasonic densitometry on a Sunlight MiniOnniTM device. It was performed to 50% of patients, in particular girls, whose body mass index was more than 20. Ultrasonic densitometry involved evaluation of the following indicators: absolute sound speed (SS), expressed in meters per second (m/s), and Z-score, that is, the difference between the result of patient's SS measurements and the peak mean value of SS among the population (of the same age and sex with the patient), expressed in units of standard deviation of statistical population. Undoubtedly, osteopenic syndrome, as well as its indicators, still remains an urgent issue in modern medicine.

According to WHO criteria, Z-score which is more than 1.0 is considered to be normal condition of bone tissue; the value of Z-criterion between -1.0 and -2.5 is considered as an osteopenic syndrome, and Z-score below -2.5 indicates the presence of osteoporosis [9].

Our scientific research was conducted due to the Declaration of Helsinki (52nd WMA, General Assembly, Edinburgh, Scotland, October 2000), and all diagnostic procedures have been approved by the local ethical committee.

Informed consent (in two separate forms) has been obtained for all patients and their parents. It has declared that studies have been performed following human rights, and they are not harmful, safe and available for usage.

Statistical processing of the obtained data was carried out and verified according to standard methods of variation statistics (Software package by Microsoft 6.0): mean value by parameter M, statistical reliability and statistical criterion ($p<0.05$).

Table I. Specific indicators of blood metabolic panel in children with kidney calculi, n=205

Specimen/units	Healthy children, n=30	Children with kidney calculi, n=175		
		Children with oxaluria, n=105	Children with oxalate-calcium nephropathy, n=53	Children with uraturia, n=17
Total protein, g/l	72.51±2.40	63.69±1.66*	66.36±2.51*	67.41±2.31*
Albumin, g/l	43.65±1.52	37.45±1.30*	39.48±1.41*	38.39±1.14
Globulin, g/l	28.34±1.30	28.52±2.02*	25.07±1.40	26.40±1.80*
Uric acid, mmol/L	7.31±1.02	8.54±1.01*	8.92+2.01*	9.01+1.01*
Kreatinine, mmol/L	98.21±2.32	103.17±1.12*	101.21±1.22*	102.23±1.32*
ALT, mmol/L•hour	0.40±0.01	0.63±0.06*	0.52±0.11	0.57±0.07
ALP (bone fragment), U/L	85.37±9.85	108.89±10.25*	80.11±12.54*	99.76±11.25*
ALP, U/L	231.41±20.56	266.42±38.73	302.38±30.99	278.38±21.99
Magnesium (whole blood), mmol/L	0.71±0.3	0.95±0.2	0.88±0.1	0.78±0.2
Statistical significance	p<0.05	p<0.05	p<0.05	p<0.001

Table II. Specific indicators of calcium-phosphorus metabolism in patients with kidney calculi, n=205, M±m

Indicators of calcium-phosphorus metabolism	Healthy children n=30	Children with oxaluria, n=105	Children with oxalate-calcium nephropathy, n=53	Children with uraturia, n=17
Total serum calcium cocentration (whole blood), mmol/L	2.23±0.03	1.88±0.01*	2.07±0.01**	2.18±0.01
Ionized calcium level, mcmol/L	1.16±1.32	0.98±1.21	1.23±1.23	1.19±1.14
Serum phosphate level, mmol/L	1.21±0.03	1.19±80.05	1.32±0.10	1.33±0.08
Parathormone level, pg/ml	12.31±0.02	13.22±0.01	12.67±0.02	12.47±0.03
Statistical significance	p<0.001	p<0.05	p>0.05	p<0.001

Table III. Estimation of bone mineral density Z-scores

Disease	Z-score < -2,5		Z-score from -2,5 to -1		Z-score > 2,5		Z-score >1,0	
	Absolute number	%	Absolute number	%	Absolute number	%	Absolute number	%
Oxaluria, n=105	5	4.8	26	24.7	25	23.8	49	46.7
Oxalate-calcium nephropathy, n=53	15	28.3	21	39.6	10	18.9	7	13.2
Uraturia, n=17	-	-	5	29.4	6	35.3	6	35.3

RESULTS

Thorough physical examination of patients revealed the signs of undifferentiated connective tissue dysplasia apart from non-specific dysuric symptoms (75.0%) and signs of chronic non-specific intoxication (25.0%) (Figure 1).

As we can see, postural disorders (50.0%), thoracic kyphosis (25.0%) and *stigmas of dysembryogenesis* (25.0%) were the most common disorders among children with oxaluria.

Among the postural disorders, scoliosis of the cervico-thoracic and thoracic-lumbar parts of spine were the most common (50.3% and 49.7%, p <0.05). However, flat-feet, predominantly that of longitudinal arch, occurred in children with oxalate-calcium nephropathy. Our records show that children with oxaluria and uraturia (80.0% and 75.0%, p>0.05) were the most stigmatized. Deflected nasal septum (70.0%), broad nasal bridge (25.0%), and "adherent" ear-lobes (5.0%) were the most common external *stigmas of dysembryogenesis*. Additionally, the signs of joint hypermobility and delicate pale (parchment-like) skin with clearly visualized vascular pattern were observed in children with oxaluria and uraturia (65.0% and 57.0%, p>0.05).

Asthenic body habitus in patients with oxaluria and oxalate-phosphate nephropathy also indicated the syndrome of undifferentiated connective tissue dysplasia (80.0% and 65.0%, p<0.05). However, increased body weight (BMI of 25.5 ± 0.1 and 18.4 ± 0.1, p <0.05) is more common in chil-

dren with uraturia as compared to the patients with oxaluria. Thorough laboratory-instrumental examination of patients with different types of dysmetabolic nephropathy confirmed the violation of mineral metabolism indicators (Table I).

The data above shows that the majority of children with oxaluria and oxalate-calcium nephropathy have the significantly elevated serum levels of bone isoenzymes of alkaline and acid phosphatase, indicating an increased intensity of the processes of bone tissue resorption and development.

Signs of hypo- and dysproteinemia were observed in patients with oxaluria, which can be explained by the presence of underlying pathology (chronic non-obstructive pyelonephritis). Hypomagnesemia was also more common in patients with oxaluria, while the increase in urea levels occurred more frequently in patients with uraturia.

In order to obtain a complete clinical and laboratory picture patients with micronephrolithiasis were assigned a number of laboratory indicators, which more or less would evidence the disorders of calcium-phosphorus metabolism (Table II).

The findings presented in the table indicated imbalance of calcium-phosphorus metabolism (decreased levels of ionized calcium against the background of normal levels of total serum calcium, hypophosphatemia along with increased parathormone activity) only in patients with oxaluria and oxalate-calcium nephropathy. In our opinion, these particular children should be considered as risk group for the osteopenic syndrome development.

We have also conducted the analysis of particular values of calcium-phosphorus metabolism against the background of disorders of vitamin D-calcitriol metabolite synthesis (Figure 2).

Estimation of bone mineral density according to the findings provided by densitometry is presented in Table III.

Densitometry shows signs of osteopenic syndrome and normal bone tissue in children with oxaluria. Oxalate-calcium nephropathy was characterized by the signs of osteopenic syndrome and early symptoms of osteoporosis. Patients with uraturia most commonly belonged to the cohort of examined patients with normal bone tissue and early signs of osteopenia.

Sonograms of kidneys and urinary tract typically revealed duplication and splitting of the pyelocaliceal system (60.0%), lumbar dystopia of one or another kidney (30.0%), and hypermobile kidneys (10.0%). Most often these changes were observed in patients with oxaluria and uraturia (75.0% and 65.0%, $p>0.05$).

Voiding cystourethrography revealed *vesicoureteral reflux* in 35.0% of patients with kidney calculi. Cystitis in combination with urethritis (80.0%) was most commonly observed in patients with uraturia. The results of excretory urography revealed the development of kidney and urinary tract abnormalities only in a small percentage of the examined patients (15.0%).

DISCUSSION

Micronephrolithiasis remains a burden issue of pediatric neprology worldwide, and a large number of cases is accompanying with decreased bone density mineralization [6,7,9-11]. But factors predisposal to development of bone diseases in these patients are still unclear,especially in children with signs of undifferential connective tissue dysplasia [2,9,10]

Nowadays scientists make a focus on association between idiopathic hypercalciuric stone formers and bone disease. Also influence of contributing factors at progress of chronic kidney disease in adults is under supervision. Making analysis of available pediatric literature data we have noticed a lack of issues concerning this correlation [1,8,10,11]. Some authors [2,3,5,9] came to the conclusion that decreased bone mineral density, increased level of uric acid and signs of metabolic syndrome are significantly associated with appearance of chronic kidney disease but in adults [2-4]. Decreased bone density is also encountered in patients with oxalate-calcium stones [2,3,6]. So, further prospective cohort studies in pediatric patients are required to determine factors, which might prevent a progression of metabolic kidney diseases.

CONCLUSIONS

1. Minor developmental abnormalities of connective tissue, including postural disorders (50.0%), thoracic kyphosis (25.0%) and *stigmas of dysembryogenesis* (25.0%) were most commonly observed in children with oxaluria.
2. Comprehensive clinical and laboratory examination of the majority of children with dysmetabolic nephropathy indicated increased serum levels of bone isoenzymes of alkaline and acid phosphatase, as indirect indicators of abnormalities in the processes of bone tissue resorption and development.
3. Characteristic changes observed on patients' densitograms were: reduced mineralization of bone tissue, which, in combination with *stigmas of dysembryogenesis* and shifting of laboratory values, testified the prevalence of osteopenic syndrome, which was more pronounced in case of oxalate-calcium kidney calculi.

REFERENCES

1. Ketteler M., Block G.A., Evenepoel P. et al. Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder: Synopsis of the Kidney Disease: Improving Global Outcomes 2017 Clinical Practice Guideline Update. Annual International Medicine. 2018; 168 (6): 422–430.
2. Schwaderer A.L., Oduguwa A., Kusumi K. Urinary stone disease in pediatric and adult metabolic bone clinic patients. Urolithiasis. 2018; 46(2):173-178. doi: 10.1007/s00240-017-0968-z.
3. Taylor E.N., Feskanich D., Paik J.M., Curhan G.C. Nephrolithiasis and risk of incident bone fracture. J Urol. 2016; 195: 1482–1486.
4. Wang S., Zhang Y., Zhang X. et al. Upper urinary tract stone compositions: the role of age and gender. International Brazilian Journal of Urology: official journal of the Brazilian Society of Urology. 2020; 46(1): 70-80.
5. Kim J.C., Cho K.S., Kim D.K. et al. Predictors of Uric Acid Stones: Mean Stone Density, Stone Heterogeneity Index, and Variation Coefficient of Stone Density by Single-Energy Non-Contrast Computed Tomography and Urinary pH. .Journal Clinal Medicine. 2019; 8(2).

6. Pan B.-L., Loke S.-S. Chronic kidney disease associated with decreased bone mineral density, uric acid and metabolic syndrome. PLoS One. 2018;13(1): e0190985. doi: 10.1371/journal.pone.0190985.
7. Cetin N., Gencler A., Kavaz Tufan A. Risk factors for development of urinary tract infection in children with nephrolithiasis. J Paediatr Child Health. 2020;56(1):76-80. doi: 10.1111/jpc.14495.
8. EAU Guidelines on Interventional Treatment for Urolithiasis. European Urology. 2016; 69(3): 475-82. doi: 10.1016/j.eururo.2015.07.041.
9. Marushko Yu.V., Volokha T.I., Asonov A.O. Ultrasonic densitometry (axial measurement) in the diagnosis of osteopenic syndrome in children with different somatic pathologies. Sovremennaya pediatriya. 2016; 1(73): 54-58.
10. Türk C., Petřík A., Sarica K. et al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. European Urology. 2016; 69(3):468.
11. Bultitude M., Smith D., Thomas K. Contemporary Management of Stone Disease: The New EAU Urolithiasis Guidelines for 2015. European Urology. 2016; 69 (3): 483. doi: 10.1016/j.eurruro.2015.08.010.

ORCID and contributionship:
Iryna S. Lembryk: 0000-0001-7584-7407[A,C-F]
Oksana V. Tymoshchuk: 0000-0002-7225-0725 [C]
Lesia Ya. Ivanyshyn: 0000-0003-2350-3375[B]
Oksana V. Kuzenko: 0000-0001-7468-380X[C]
Inna V. Shlimkevych: 0000-0002-4094-2794[B,C]
Olena A. Holodnykh: 0000-0001-5846-6581 [E]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Iryna S. Lembryk
Ivano-Frankivks national medical university
132 Konovalcya st., 76018 Ivano-Frankivks, Ukraine
tel: +38(050) 2086350
e-mail: irunka80@ukr.net

Received: 28.12.2020
Accepted: 28.08.2021

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article