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BONE MINERAL DENSITY IN CHILDREN WITH IDIOPATHIC HYPERCALCIURIA

GĘSTOŚĆ MINERALNA KOŚCI U DZIECI Z HIPERKALCIURIĄ IDIOPATYCZNĄ

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Abstract

The aim *of the study was to evaluate bone mineral density (BMD) in the lumbar spine in children with idiopathic hypercalciuria.*

Patients and methods: *The study group included 31 children (14 boys, 17 girls) aged 5 to 17 years (mean age 9.8±4.0 years) with idiopathic hypercalciuria. All children remained on normal calcium diet, without vitamin D and citrate supplementation. We evaluated lumbar spine (L1-L4) BMD (L1-L4 BMD) (expressed as Z-score) and blood serum levels of 25-hydroxyvitamin D3 (25OHD3), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), and intact parathormone (iPTH). We also evaluated 24-hour urinary Ca, P, and sodium (Na) excretion.*

Results: *Reduced L1-L4 BMD Z-score <-1 was found in 25.8% of children, Z-score values from -1 to 1 in 64.5% of children, and Z-score >1 in 9.7% of children. Reduced 25OHD3 level (<20 ng/mL) was found in 71% of children, levels in the range of 20-30 ng/mL in 22.6% of children, and levels >30 ng/mL in 6.4% of children. Seven out of 8 children with L1-L4 BMD Z-score <-1 were found to have 25OHD3 deficiency (level <20 ng/mL). Among children with reduced lumbar spine BMD, most were girls at the mean age of 13.8 years. Ca and P levels were normal in all children. We did not find significant differences in 25OHD3, Ca, and P levels in relation to gender and age. We found a positive correlation between L1-L4 BMD Z-score and serum 25OHD3 level. Concomitant nephrolithiasis was found in 50% of patients with reduced lumbar spine BMD.*

Conclusions: *Reduced lumbar spine BMD in patients with idiopathic hypercalciuria seems to be related to vitamin D3 deficiency.*

Key words: hypercalciuria, bone mineral density, vitamin D3, children, densitometry

Streszczenie

Celem pracy *była ocena gęstości mineralnej kości kręgosłupa lędźwiowego u dzieci z hiperkalciurią idiopatyczną.*

Pacjenci i metody: *Grupę badaną stanowiło 31 dzieci (14 chłopców, 17 dziewczynek) w wieku od 5 do 17 lat (9,8±4,0 lata) z hiperkalciurią idiopatyczną. Wszystkie badane dzieci pozostawały na diecie normowapniowej, bez suplementacji witaminy D ani cytrynianów. Analizowano gęstość mineralną kości odcinka lędźwiowego kręgosłupa L1-L4 BMD (przedstawioną w postaci Z-score) oraz oceniano stężenia w surowicy krwi:, wapnia (Ca), fosforu (P), fosfatazy zasadowej (ALP), parathormonu (iPTH), 25OHD3. W dobowej zbiórce moczu i porcji moczu oceniano wydalanie Ca, P i sodu (Na).*

Wyniki: *Obniżenie gęstości mineralnej kości w odcinku lędźwiowym L1-L4 BMD z-score <-1 stwierdzono u 25,8% dzieci, w zakresie od (-1) do 1 stwierdzono u 64,5% dzieci, >1 u 9,7% dzieci. Obniżony <20 ng/ml poziom 25OHD3 stwierdzono u 71% dzieci, 20-30 ng/ml u 22,6% i >30 ng/ml u 6,4%. U 7 z 8 dzieci*

z L1-L4 BMD z-score <-1, stwierdzono niedobór 25OHD3 (stężenie <20 ng/ml). Spośród dzieci z obniżoną gęstością mineralną kości w odcinku lędźwiowym większość stanowiły dziewczynki w średnim wieku 13,8 lat. Stężenia Ca, P były prawidłowe u wszystkich badanych. Nie stwierdzono znamiennych różnic stężeń 25OHD3, Ca, P w zależności od płci i wieku. Stwierdzono dodatnią korelację między L1-L4 BMD Z-score a stężeniem witaminy D3 w surowicy krwi. U 50% pacjentów z obniżoną gęstością mineralną kości w odcinku lędźwiowym obserwowano współwystępowanie kamicy nerkowej.

Wnioski: *Obniżenie gęstości mineralnej kości w odcinku lędźwiowym kręgosłupa u pacjentów z hiperkalciurią idiopatyczną wydaje się zależeć od niedoborów witaminy D3.*

Słowa kluczowe: hiperkalciuria, gęstość mineralna kości, witamina D3, dzieci, densytometria

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INTRODUCTION

Idiopathic hypercalciuria (IH) is the most common metabolic disturbance in children, found in 2.2-6.4% of the paediatric population depending on the geographical region [1, 2, 3]. It is defined as urinary calcium excretion above 4 mg/kg/24 h with normal serum calcium level. It is considered the most common cause of calcium-containing kidney stones in children. Hypercalciuria is present in 40-60% of patients with recurrent nephrolithiasis [4]. Pathogenesis of IH includes genetic and environmental factors, such as lifestyle and nutrition, including high salt diet [5, 6]. Studies in hypercalciuric rats showed an increased vitamin D receptor (VDR) density in effector tissues (bone, kidneys, intestine), explaining relatively increased tissue sensitivity to 1,25(OH)2D3. Excessive tissue response to vitamin D3 may result in all abnormalities characteristic for IH (increased intestinal calcium absorption, reduced renal calcium reabsorption, increased calcium mobilization from bones) [7].

Previous studies indicated that long-term hypercalciuria may contribute to bone mass deficit [8. 9. 10] but the mechanism of this defect has not been clarified. Potential pathogenetic factors include excessive prostaglandin E2 (PGE-2) synthesis, and increased activity of bone resorption-stimulating cytokines (interleukin-1, interleukin-6, tumour necrosis factor). Strategies to prevent development of osteopenia/osteoporosis in these patients have not been established [11, 12].

Of note, the highest accumulation of bone mass occurs in childhood and adolescence, peaking at the end of the second decade of life [13]. Each disturbance of this process may be a risk factor for osteopenia, osteoporosis, and bone fractures during adult life. Thus, elucidation of the mechanism of osteopenia/osteoporosis in children with IH might lead to preventive strategies reducing the risk of bone fractures during adult life [1, 12, 14, 15, 16, 17, 18].

The aim of the study was to evaluate bone mineral density (BMD) in the lumbar spine in children with idiopathic hypercalciuria, potentially leading to identification of young patients at risk of osteoporosis.

MATERIAL AND METHODS

The study group included 31 children (14 boys, 17 girls) aged 5 to 17 years (mean 9.8±4.0 years) with IH admitted to our Department from May 2014 to January 2014. All children had normal renal function as evaluated using the Schwartz formula (glomerular filtration rate [GFR] >90 mL/min/1.73m^2) [19].

We included children above 5 years of age on normal calcium diet with a history of increased urinary calcium excretion (≥4 mg/kg/24 h). Exclusion criteria included hypercalcemia, tubular acidosis, nephrocalcinosis, chronic renal failure, bone metabolic diseases (e.g., primary hyperparathyroidism), anatomic defects of the lumbar spine, long-term immobilization, therapy with drugs affecting bone metabolism (glucocorticoids, diuretics). None of the children received vitamin D preparation, calcium, multivitamin supplements, cod liver oil, and citrates.

In all children, we evaluated lumbar spine (L1-L4) BMD (L1-L4 BMD) by dual energy X-ray absorptiometry (DXA) using a Discovery A bone densitometry system (Hologic). Results were expressed as Z-scores. Serum levels of 25-hydroxyvitamin D3 (25OHD3) (reference range 20-60 ng/mL) [20], calcium (Ca) (reference range 2.13-2.63 mmol/L), phosphorus (P) (reference range 0.95-1.65 mmol/L), alkaline phosphatase (ALP) (reference range 80-280 U/L), and intact parathormone (iPTH) (reference range 10-65 pg/mL) were determined in fasting blood samples. Twenty-four hour urinary Ca, P, and sodium (Na) excretion was evaluated. Serum Ca, P, and ALP levels and urinary Ca, P, Na, and creatinine excretion was measured using a dry-chemistry method (MicroSlide, VITROS 5600, Ortho-Clinical Diagnostics Johnson & Johnson). iPTH level was measured by the immunoenzymatic method using the Immulite 2000xPi system, and 25OHD3 level was measured by the chemiluminescence method using the ARCHITECT i1000SR system (Abott Diagnostics).

We evaluated the prevalence of reduced BMD in children with idiopathic hypercalciuria and its relation with gender, age, concomitant nephrolithiasis, haematuria, and the evaluated biochemical parameters.

The study protocol was approved by the Bioethics Committee at the Medical University of Warsaw. We obtained an informed consent for participation in the clinical study from parents and children aged >16 years of age.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistica 9.0 PL software (StatSoft, College Station, TX, USA). Normal distribution of variables was verified using the Shapiro-Wilk test. Data were shown as ranges, medians (for non-normally distributed variables) or mean values and standard deviations (for normally distributed variables). The Student t test for independent samples and the Mann-Whitney U test were used. Correlations between variables were evaluated using the Pearson linear correlation coefficient or the Spearman test for non-normally distributed variable. P<0.05 was considered significant.

RESULTS

Table I shows clinical characteristics of the studied children. The mean L1-L4 BMD Z-score in the study group was -0.27±1.04 (range from od -2.1 to 2.2). Reduced BMD (Z-score <-1) was found in 8/31 children (25.8%). The distribution of densitometry findings is shown in Table II. Among 8 children with reduced BMD (L1-L4 BMD Z-score <-1.0), girls were 62.5% at the mean age of 13.8 years. Children with L1-L4 BMD Z-score <-1 were older than children with normal BMD (median age 12 years, range 6-1.7 years vs. median 10.5 years, range 5-17 years, respectively, P= 0.057). Coexisting nephrolithiasis was found in 4/8 patients with reduced lumbar spine BMD (Tab. II). A low-energy metatarsal or forearm fracture occurred in 2 children. Children with nephrolithiasis were significantly older (median age 11.07 years, range 5±17) than children without nephrolithiasis (median age 8.3 years, range 5±13) (P=0.022).

In children with haematuria, L1-L4 BMD Z-score was significantly lower than in children without haematuria (-1.4±0.50 vs. -0.1±0.99, respectively, P=0.016).

Among children with L1-L4 BMD Z-score <-1, a history of haematuria was found significantly more frequently compared to children with L1-L4 BMD Z-score >-1 (3/8 vs. 1/23, respectively, P<0.001).

The Pak test to evaluate the type of hypercalciuria was performed in 19 (63%) children. The majority of them had absorptive hypercalciuria (14/19, or 73%) (Tab. II). We found no effect of the type of hypercalciuria on the L1-L4 BMD Z-score (P=0.479).

Median serum 25OHD3 level in our study group was 17.2 ng/mL (range 9.7-40). A reduced 25OHD3 level (<20 ng/mL) was found in 22 children (71%), and 8 of them (36.4%) had reduced lumbar spine BMD (L1-L4 BMD Z-score <-1). Serum 25OHD3 level was lower

Table I Clinical data in children with idiopathic hypercalciuria (IH) (n=31).

Tabela I. Dane kliniczne dzieci z hiperkalciurią idiopatyczną (HI) (n=31).

Characteristics of children with IH ***Charakterystyka dzieci z HI n%***	**n**	**%**
Gender/*Płeć*		
Girls/*Dziewczynki*	17	54.8
Boys/*Chłopcy*	14	45.2
Initial clinical signs		
Początkowe objawy kliniczne		
Hematuria/*Krwinkomocz*	4	12.9
Abdominal pain/*Ból brzucha*	7	22.5
Kidney colic/*Kolka nerkowa*	6	19.4
Urolithiasis/*Kamica*	13	41.9
Other*/*Inne*	8	25.8
Family history of urolithiasis ***Kamica nerkowa w rodzinie***	**12**	**38.7**

*Dysuric signs, urinary tract infections, nocturnal eneuresis, daytime eneuresis

**Objawy dyzuryczne, ZUM, nietrzymanie moczu nocne i dzienne*

Table II. Distribution of densytomteric studies results, coexisting nephrolithiasis and types of idiopathic hypercalciuria.

Tabela II. Rozkład wyników badania densytometrycznego, współistniejącej kamicy nerkowej oraz typów hiperkalciurii idiopatycznej.

	Z-score L1-L4 BMD	**Urolithiasis** ***Kamica***	**Type of hypercalciuria** ***Typ hiperkalciurii***		
			Absorptive ***Absorpcyjna***	**Renal** ***Nerkowa***	**Mixed** ***Mieszana***
	Total Razem n=31	n=13	n=19		
Z-score range *Zakres Z-score*	n (%)				
<-1.0	8 (25.8)	4 (30.8)	5	-	1
-1.0-1.0	20 (64.5)	8 (61.5)	7	1	2
>1.0	3 (9.7)	1 (7.7)	2	1	-

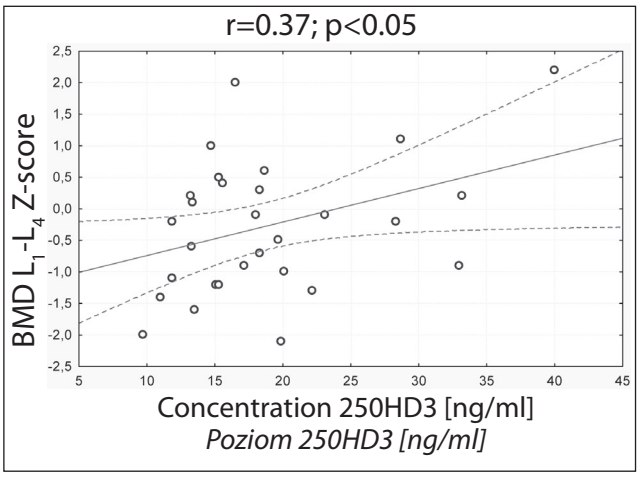

Fig. 1. Correlations of L1 - L4 BMD Z-score and serum 25OHD3.

Ryc. 1. Korelacje wartości L1-L4 BMD Z-score i stężenia 25OHD3 w surowicy.

in children with L1-L4 BMD Z-score <-1 compared to children with L1-L4 BMD Z-score >-1 (median 14.3 ng/mL, range 9.7-22.2 vs. median 18.3 ng/mL, range 11.9-40, respectively, P=0.055). All children in our study group had normal blood serum Ca (mean 2.53±0.1 mmol/L) and P (mean 1.45±0.165 mmol/L) levels. Blood serum ALP activity (mean 213.69±74.86 U/l) was increased in 4 children (12.9%), and two of them had reduced lumbar spine BMD (L1-L4 BMD Z-score <-1.0). An increased blood serum iPTH level (median 27.01 pg/mL, range 7.2-85.9) was found in one child (3.2%) with normal BMD and a reduced blood serum 25OHD3 level (18 ng/mL).

The mean 24-hour urinary Ca excretion in our study group was 4.80±2.07 mg/kg/24 h, the mean urinary P excretion was 21.71±9.94 mg/kg/24 h, and the median Na excretion was 3.045 mmol/kg/24h (range 0.75-12.69).

We found a positive correlation between blood serum 25OHD3 level and lumbar spine BMD in our study group (fig. 1). We did not find correlation between lumbar spine BMD and the remaining blood serum and urine biochemical parameters.

DISCUSSION

In our study group of children with IH, reduced BMD (L1-L4 BMD Z-score <-1.0) was found in nearly 26% of children, which is in accordance with other reports [9, 21-24].

Garcia et al. [21] found reduced lumbar spine BMD in 22 (30.1%) of 73 children with IH. An association between hypercalciuria and reduced BMD in children was also reported twice by Perrone et al., for the first time in 1992 [22] when they found osteopenia in 4 (20%) of 20 evaluated children, and later in 1995 [23] when they reported low lumbar spine BMD Z-score in 8 (17%) of 46 evaluated children with IH. In another study by the same author, children with permanent and transient hypercalciuria were compared, and lower bone mass was found in those with permanent IH. Freundlich et al. [10], Penido et al. [24] and Schwadereret et al. [1] found reduced BMD in 38%, 35%, and 47% children with hypercalciuria, respectively.

In our study, we found that children with reduced BMD were older than children with normal densitometry findings (mean age 11 vs. 8.5 years, respectively). Similarly, Garcia-Nieto et al. reported a negative linear correlation between L1-L4 BMD Z-score and patient age, which suggests that BMD loss initiated in childhood results in osteoporosis at a later age [21, 25]. The highest accumulation of bone mass occurs in childhood and adolescence, peaking at the end of the second decade of life [13, 26, 27] and each disturbance of this process may be a risk factor for osteopenia, osteoporosis, and bone fractures during adult life [10].

In our study, BMD reduction was found more frequently in girls, similarly to the study by Garcia Nieto et al. [21], but in contrast to studies by Freundlich et al. and other authors who found male preponderance [10].

Based on the performed analysis, we compared children with hypercalciuria only and those with hypercalciuria and concomitant nephrolithiasis and found, similarly to Schwaderer et al. [1], lower BMD in children with concomitant nephrolithiasis. It is also of note that children with nephrolithiasis were older and had worse bone densitometric parameters compared to children with isolated hypercalciuria, which is in accordance with our studies.

We also observed that a history of erythrocyturia, which might herald nephrolithiasis, was significantly more common in children with L1-L4 BMD Z-score <-1. Penido et al. and Srivastava et al. highlighted that erythrocyturia is one of the most common prodromes of IH [2, 3, 24].

In our study, we found that IH in children is most commonly due to an increased intestinal calcium absorption, which was also confirmed by other authors [28]. Several studies suggested that it may have an effect on PTH level and secondarily on bone mass reduction observed in the studied children. In all children in our study except for one, serum iPTH level was within the reference range, similarly to other studies [29].

Vitamin D3 deficiency was found in 70% of children with IH in our study. In 36% of children with IH and a reduced serum 25OHD3 level (<20 ng/mL), we also found reduced lumbar spine BMD (L1-L4 BMD Z-score <-1). Vitamin D3 deficiency in this patient population was also observed by other authors [30, 31] who did not associate this fact with a reduction of BMD. Several studies in the literature reported that low serum vitamin D3 level may be a factor predisposing to the development of renal stones [32].

Our analysis of biochemical parameters of calcium-phosphorus metabolism in the studied group of children showed no significant differences in relation to gender, age, the presence of nephrolithiasis, erythrocyturia, and L1-L4 BMD Z-score.

Hypotheses linking BMD reduction with excretion disturbances of calcium have been proposed for a long time. Despite relatively few studies in children with IH, most results are consistent with a notion that a reduction of BMD occurs, particularly within the spine. Precise mechanisms contributing to bone loss remain unknown. However, any continuing and persistent disturbances of bone growth are associated with an increased risk of osteoporosis, osteopenia, and fractures during adult life.

CONCLUSIONS

Reduced lumbar spine BMD in patients with idiopathic hypercalciuria seems to be related to vitamin D3 deficiency.

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