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Skeletal Status at Diagnosis in Children with Hematologic Malignancy – Pilot Study*

Stan kośćca u dzieci podczas rozpoznania choroby limfoproliferacyjnej – badanie pilotażowe

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Abstract

Background. The hematologic malignancy may adversely affect bone metabolism irrespective of its primary location.
Objectives. The aim of the study was to assess skeletal status in children at the moment of diagnosing a lymphoproliferative disease.
Material and Methods. The authors assess bone mineral density (BMD) in 25 children with hematologic neoplasm. BMD was determined by densitometry with dual X-ray absorptiometry (DXA) using the total body and spine programmes. In addition, a quantitative ultrasound assay (QUS) of the calcaneus was performed and the following were assessed: speed of sound (SOS), broadband ultrasound attenuation (BUA) and the stiffness factor. 25 children considered to be healthy (at the same mean age and pubertal stage) were the control group.
Results. At the time of diagnosis two children with acute lymphoblastic leukemia had osteoporosis with vertebral compression fracture and another three had low BMD. BMD in spine projection (Spine BMD) was lower ($p < 0.016$) than in age-matched controls. The authors found a positive correlation between BMD in the total body programme (Total BMD) of a DXA and the QUS parameters.
Conclusions. In examined group of children with newly diagnosed hematologic malignancy early changes regarding a decrease in mineral density, are visible in the bone which is metabolically active, what can be confirmed by the results of a DXA in the spine projection. The authors confirm diagnostic applicability of QUS for the assessment of bone density in these patients (**Adv Clin Exp Med 2010, 19, 4, 531–535**).

Key words: bone metabolic disease, hematologic neoplasms, children.

Streszczenie

Wprowadzenie. Proces nowotworowy niezależnie od swojego pierwotnego umiejscowienia może zaburzać metabolizm kostny.
Cel pracy. Ocena ilościowa tkanki kostnej u dzieci, u których rozpoznano chorobę limfoproliferacyjną.
Materiał i metody. U 25 pacjentów z rozpoznanym nowotworem oceniono gęstość mineralną kośćca (*bone mineral density* – BMD), wykorzystując badanie densytometryczne metodą absorpcjometrii promieniowania X o podwójnej energii (DXA) w programie *total body* (ocena całego ciała) i *spine* (ocena kręgosłupa lędźwiowego). Przeprowadzono także ilościowe badanie ultradźwiękowe kości piętowej (*quantitative ultrasound assay* – QUS), określając: prędkość przechodzenia ultradźwięków (SOS), szerokopasmowe tłumienie ultradźwięków (BUA) oraz współczynnik *Stiffness*. Grupę porównawczą stanowiło 25 zdrowych osób w tym samym wieku i w podobnej fazie dojrzewania płciowego w stosunku do grupy badanej.
Wyniki. Dwoje pacjentów chorych na ostrą białaczkę limfoblastyczną miało osteoporozę z kompresyjnym złamaniem kręgów, troje innych zmniejszone BMD. W grupie badanej BMD w projekcji *spine* było mniejsze niż w grupie porównawczej ($p < 0{,}016$). U pacjentów z nowotworem wykazano statystycznie istotną dodatnią korelację między

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gęstością mineralną kości w programie *total body* badania densytometrycznego a wszystkimi trzema wskaźnikami badania ultradźwiękowego.
Wnioski. U badanych pacjentów ze świeżo rozpoznaną chorobą limfoproliferacyjną wczesne zmiany dotyczące zmniejszenia gęstości mineralnej ujawniają się w kości bardzo aktywnej metabolicznie, czego dowodem może być wynik badania densytometrycznego w projekcji *spine*. Potwierdzono przydatność diagnostyczną badania ultradźwiękowego kości piętowej (QUS) w ocenie gęstości mineralnej kości w tej grupie pacjentów (**Adv Clin Exp Med 2010, 19, 4, 531–535**).

Słowa kluczowe: choroba metaboliczna kości, choroba limfoproliferacyjna, dzieci.

The hematologic malignancy may adversely affect bone metabolism irrespective of its primary location [1]. In survivors low peak bone mass achieved in youth may lead to disturbances of mineralization and microstructure of the skeleton in their adult lives [2–4].

In hematological malignancies impaired bone density is the consequence of infiltration of the spongy bone by a proliferating clone [5] or of proresorptive effects of cytokines produced by neoplasm [6]. Several cases of severe osteoporosis in the course of leukaemia (7) or lymphoma [8, 9] in children have been described.

According to the literature low bone density is present in 13–41% of children and teenagers at the time of diagnosis, and osteoporosis is present in 1–8% of patients [5, 7]. In extreme cases pathological bone fractures are likely to occur, especially in children with neoplastic metastases or leukemic infiltration of bones. Since a reduced bone mineral density (BMD) predisposes to osteoporosis and bone fractures, the use of densitometry with dual X-ray absorptiometry (DXA) to evaluate BMD may be useful to identify risk patients.

For that reason the aim of the study was to evaluate BMD using DXA in children with freshly diagnosed hematologic neoplasm and to asses usefulness of quantitative ultrasound assay (QUS) as screening tool for detection reduced bone mass in these patients.

Material and Methods

The study included 50 children aged from 5 to 19 years. In 25 patients (15 girls and 10 boys) the examination was performed within one week since the diagnosis of neoplasm: acute lymphoblastic leukemia (ALL – 16), non-Hodgkin lymphoma (NHL – 4) and Hodgkin lymphoma (HL – 4), acute myeloblastic leukemia (AML – 1).

25 healthy children (12 girls and 13 boys) were the control group.

An examination assessing presence of pathological bone fractures, the body weight and height, body mass index and the pubertal stage according to Tanner scale were performed.

Bone mineral density was assessed based on a densitometric assay with dual X-ray absorptiometry (DXA) with a DPX device by Lunar (Madison, USA) using the total body (Total BMD) and spine projections (Spine BMD).

The interpretation of a densitometric assay included the absolute values of BMD expressed as g/cm^2 and the number of standard deviations normalised with relation to the average value for age and gender (the Z-score index). According to the current diagnostic guidelines for the paediatric population low bone density was defined as an BMD Z-score that was less than or equal to –2.0 and osteoporosis was diagnosed when low bone mineral density and clinically significant fracture history coexisted. Clinically significant fracture history is one or more of the following: vertebral compression fracture, long-bone fracture of the lower extremities, two or more long-bone fractures of the upper extremities [10].

In addition, a quantitative ultrasound assay (QUS) of the calcaneus with Achilles Plus Solo by GE Lunar (Madison, USA) was performed and the following were assessed: speed of sound (SOS), broadband ultrasound attenuation (BUA) and the stiffness factor. The Z-score index was calculated based on reference values for Polish children prepared by Jaworski [11].

The obtained results were characterised using descriptive statistics. The results were prepared using the Spearman rank correlation coefficient and the following tests: W Shapiro-Wilk and U Mann-Whitney's. Significance was established at $p < 0.05$.

Results

The patients and controls did not differ significantly in terms of the mean age, body mass index and pubertal stage (individual data are available at the authors).

Based on the result of the DXA test and the clinical picture low bone mass was noted in 3 and osteoporosis in 2 out of 25 tested children with a disease. Vertebral compression fracture were de-

Table 1. Mean values of DXA and QUS parameters in study group and controls

Tabela 1. Średnie wartości parametrów DXA i QUS w grupie badanej i porównawczej

Parameter (Parametr)	Study group (Grupa badana) (mean ± SD)	Controls (Grupa porównawcza) (mean ± SD)	p
Total (BMD – g/cm^2)	0.95 ± 0.16	0.97 ± 0.12	NS
Total body (Z-score)	0.06 ± 0.99	–0.004 ± 0.74	NS
Spine (BMD – g/cm$^{2)}$	0.78 ± 0.29	1.03 ± 0.54	NS
Spine (Z-score)	–0.94 ± 1.45	–0.04 ± 0.84	0.016
Stiffness (Z-score)	–0.79 ± 1.87	–0.31 ± 1.42	NS
SOS (Z-score)	–0.85 ± 1.83	–0.04 ± 3.05	NS
BUA (Z-score)	–0.57 ± 1.63	0.14 ± 1.67	NS

p – significance level.
p – poziom istotności.

NS – not significant.
NS – różnica nieistotna statystycznie.

BMD – bone mineral density.
BMD – gęstość mineralna kości.

SOS – speed of sound.
SOS – prędkość przechodzenia ultradźwięków.

BUA – broadband ultrasound attenuation.
BUA – szerokopasmowe tłumienie ultradźwięków.

tected in 2 patients with ALL in whom osteoporosis was diagnosed.

Mean values of DXA and QUS parameters in patients and healthy controls are presented in Table 1. A statistically significant difference regarding the mean value of the Z-score index for the spine programme of DXA was found: in the study group it was significantly lower, although it was within the norm. The mean values of other parameters did not differ statistically between groups and were within the range of values considered to be the norm.

Association between DXA and QUS parameters in children with lymphoproliferative disease is shown in Table 2. Positive correlation between the bone mineral density in the total body programme in the DXA and all the three parameters of QUS was demonstrated; similar relationships were not observed for the spine programme.

Discussion

The authors found that at diagnosis two children with ALL had osteoporosis with pathological vertebral fracture and another three had low bone mineral density. This confirm early deleterious effects on the bone.

Demonstrating a statistically significant lower Spine BMD in study group when compared to the controls was important and needed to be emphasised, although it was within the norm. As reported earlier by van der Sluis et al. [12], the authors found that a malignancy has a negative effect on the bone which is metabolically active. Trabecular bone has a higher metabolic rate and changes in BMD will occur earlier in Spine BMD than in Total BMD.

Arisoki et al. presents conclusions which are different from own; in their study, which included 28 children with freshly diagnosed neoplasm, all densitometric indices assessing bone mass did not differ from the results of healthy peers (13).

An interesting fact is that a positive correlation was discovered between bone mineral density in the total body programme of a DXA and the QUS parameters. Similar relationship was observed by Ahuja et al. [14]. Those authors suggest that BUA may serve as a reliable screening tool to detect reduced bone mass in pediatric patients with leukemia [13]. Currently this examination has been used as a screening examination of bone mass.

Table 2. Relationship between the Z-score index of DXA and QUS in patients with neoplasm – Spearman correlation coefficients (r)

Tabela 2. Współczynnik korelacji Spearmana (r) między (Z-score) dla parametrów DXA i QUS

QUS parametr (Z-score)	DXA parametr (Z-score)			
	Total body		Spine	
	r	p	r	p
Stiffness	0.60	0.007	0.40	NS
SOS	0.60	0.009	0.37	NS
BUA	0.46	0.046	0.23	NS

p – significance level.
p – poziom istotności.

NS – not significant.
NS – różnica nieistotna statystycznie.

QUS – quantitative ultrasound assay.
QUS – badanie ultradźwiękowe.

DXA – Dual X-ray absorpiometry.
DXA – absorpcjometria promieniowania X o podwójnej energii.

SOS – speed of sound.
SOS – prędkość przechodzenia ultradźwięków.

BUA – broadband ultrasound attenuation.
BUA – szerokopasmowe tłumienie ultradźwięków.

The results the authors obtained indicate that in children with a haematological malignancy there are bone disturbances at the early stage of the disease. Early changes of the skeleton may additionally be intensified in the course of treatment, prolonged limitation of physical activity, leading to decreased bone mass (15). It explains why it is necessary to perform global assessment of the skeletal system, as early as at the time of diagnosing a neoplastic disease.

The authors concluded that in examined group of children with newly diagnosed hematologic malignancy early changes regarding a decrease in mineral density, are visible in the bone which is metabolically active. The authors confirm diagnostic applicability of QUS for the assessment of bone density in these patients.

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