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THE ROLE OF ULTRASOUND DENSITOMETRY FOR SCREENING DIAGNOSTICS OF OSTEOPENIA IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Juvenile idiopathic arthritis (JIA) in children remains one of the most severe medical and social problems in the world. One of the complications of the disease is the development of osteopenic syndrome (OS) with the possible formation of osteoporosis. Therefore, in the process of monitoring patients with JIA, it is necessary to monitor the structural and functional state of bone tissue.

The aim of the study *was to determine the role of ultrasound densitometry (UD) for the screening diagnosis of OS in children with JIA.*

Materials and methods: *examined 63 children with JIA aged 5 to 18 years. All patients underwent a general clinical examination and determination of the serum content of 25 hydroxyvitamin D (25 (OH) D) and UD to assess the mineral density of bone tissue.*

Results. *In children with JIA, 41.76 % of cases were diagnosed with OS of various degrees of severity, which corresponds to the results of many studies conducted using such a "gold standard" of diagnosis as dual-energy X-ray absorptiometry (DXA). At the same time, osteopenia I degree was diagnosed in 20.0 % of cases, II degree – in 35.0 % of cases, III degree – in 30.0 % of cases, and in 3 patients (15.0 %) the Z-index was below -2 .5, which meets the criteria for osteoporosis. It was established that children with OS were older than children without this syndrome, significantly more often complained of pain in the joints, morning stiffness and restriction of movements, and during examination, joint deformity was more often detected in them. In addition, children with OS were characterized by a significantly lower level of 25 (OH)D in blood serum (17.3 [14.3, 25.8] vs 28.8 [20.6, 46.3] ng/ml; p< 0.05).*

Conclusions. *UD can be used for screening diagnosis of OS in children with JIA. The ease of use of ultrasound densitometry devices, the absence of radiation exposure of the child, the possibility of conducting an examination at the bedside, and the low cost are clear advantages of this method of examining bone mineral density compared to DXA*

Keywords: *ultrasound densitometry, juvenile idiopathic arthritis, osteopenic syndrome, osteoporosis, densitometry, children*

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1. Introduction

Juvenile idiopathic arthritis (JIA) in children remains one of the serious medico-social global problems due to its increasing prevalence, chronic course of the pathological process with periods of exacerbation and remission, high risk of complications and early disability of patients [1]. The incidence of JIA ranges from 0.83 to 23 cases per 100,000 pediatric population per year. According to medical statistics, more than 3,000 children with this disease are registered in Ukraine [2].

One of the complications of the disease is the development of osteopenia (or osteopenic syndrome) with the possible formation of osteoporosis, which can lead to osteopathies and fractures, mainly vertebrae [3, 4]. In JIA, osteoporosis is divided into periarticular (mainly in the epiphyses) and generalized (in all parts of the skeleton). Periarticular OP is an early radiographic sign of JIA and a predictor of bone destruction, while generalized OP is an indicator reflecting the chronicity and intensity of systemic inflammatory processes [5]. It has been proven that persistent inflammation, excessive production of pro-inflammatory cytokines, side effects of drugs together, and impaired motor activity lead to systemic disorders of bone metabolism [6]. The influence of disease factors leads to a decrease in the absorption of calcium, a violation of the hydroxylation of vitamin D, which contributes to a decrease in the rate of bone mass accumulation and, in the future, to a progressive decrease in the bone mineral density (BMD), including in adult life [7, 8]. Therefore, in the process of observing patients with JIA, it is necessary to monitor the structural and functional state of bone tissue for timely prevention of osteopenic syndrome and correction of detected disorders.

To date, there are several methods of BMD research which differ in their technique and evaluated anatomical areas and have advantages and disadvantages [9].

In pediatric practice, as in adults, dual-energy X-ray absorptiometry (DXA) is the "gold standard" for the study of bone mass and the diagnosis of osteoporosis [10]. Although X-ray densitometry is the most sensitive method for detecting changes in the density of bone tissue, at the same time, it is not an ideal method for monitoring the state of bones in children in dynamics due to the influence of radiation exposure and age restrictions (allowed to be used from the age of 5) [5]. In addition, the use of DXA is quite limited due to the high cost of equipment, the need for highly trained personnel to correctly interpret the obtained data, and the lack of centres that perform this procedure, which makes it difficult to use this method as a screening tool [11].

In several countries, experts use quantitative ultrasound research, which uses sound waves of 20 kHz. With the help of ultrasound densitometers, it is possible to study the average velocity of ultrasound waves passing through bone and soft tissue, to indirectly characterize the quality of the bone structure, and to determine the BMD index. The advantages of ultrasound densitometry over DXA are relative availability, low cost, and lack of radiation exposure, which makes it ideal for use in children [11]. There are several types of devices, each of which measures the speed of transmission and the amplitude of the ultrasound signal in certain areas of the skeleton. Depending on the type of bone being examined, ultrasonic densitometers are divided into calcaneal densitometers, which assess the state of trabecular bone tissue, and axial densitometers, which allow assessing the state of tubular bones (radius, tibia, phalanx of the finger) [10].

However, the place of quantitative ultrasound in pediatric practice remains uncertain.

The aim of the research – to determine the role of ultrasound densitometry for the screening diagnosis of OS in children with JIA.

2. Materials and methods

The research was conducted based on the pediatric department of specialized medical care of the communal non-profit enterprise "City Children's Clinical Hospital No. 6 of the Dnipro City Council" from December 2021 to March 2024.

To achieve the goal, 63 children with JIA aged from 5 to 18 years (average age – 13.0 [9.0; 16.0] years) who were treated in the pediatric department of specialized medical care in Dnipro were examined. Among the examined children were 22 boys (34.9 %) and 41 girls (65.1 %). The average age of the boys was 13.0 [8.0; 16.0] years, girls – 13.0 [11.0; 16.0] years old.

The criteria for inclusion in the study were children under 18 years of age with a confirmed diagnosis of JIA and the consent of the patient and his parents to participate in the study.

Verification of the diagnosis of JIA was carried out based on its diagnostic criteria in accordance with the "Unified clinical protocol of medical care for children with juvenile arthritis" (order of the Ministry of Health of Ukraine No. 832 dated 22.10.2012). The clinical variant of juvenile arthritis is established according to the ILAR classification of juvenile arthritis (ILAR 2nd edition, 2001).

The scope of the conducted research included a comprehensive examination of patients: a thorough study of the anamnesis of the disease and life, physical examination, conducting general clinical, laboratory and instrumental research methods.

Laboratory methods of research included determining the content of vitamin D (VD) metabolite – 25 hydroxyvitamin D (25 (OH)D) in blood serum by enzyme immunoassay. A value of 25(OH)D above 30 ng/ml is considered a sufficient level of VD, from 21 to 29 ng/ml – insufficient VD and below 20 ng/ml – a deficiency of VD.

BMD was assessed in all patients using a Sunlight Omnisense 9000 ultrasound densitometer.

To assess BMD, the absolute speed of sound (SoS), expressed in meters per second (m/s), and the Z-criterion were evaluated - the difference between the result of the measurement of the sound speed of SoS for the patient and the peak average value of SoS for the population (one with the patient's age and of the same sex), expressed in units of the population standard deviation. According to WHO, a Z-criterion value above -1.0 indicates normal BMD, a Z-criterion value from -1.1 to -2.5 is considered as osteopenic syndrome, and a Z-criterion value below -2.5 indicates about the presence of osteoporosis.

Statistical processing of the obtained results was carried out using the "STATISTICA 6.1" application program package (serial number - AGAR909E415822FA). Quantitative and qualitative indicators were evaluated. Quantitative parameters were checked for compliance with Gauss's law using the Kolmogorov-Smirnov test with the Lilliefors and Shapiro-Wilk corrections. Given that quantitative indicators had a non-parametric type of distribution, their description was carried out using the median and interquartile range (Me [25 %; 75 %]). Qualitative data were described as n (%). Quantitative data were compared using the non-parametric Mann-Whitney (U) test, and qualitative data were compared using Pearson's $\chi 2$ test with Yates' correction for continuity. When testing statistical hypotheses, the critical p-value was chosen to be <0.05.

The study was conducted with the permission of the local Commission on Biomedical Ethics (protocol of the meeting of the Commission on Biomedical Ethics of the communal non-profit enterprise "City Children's Clinical Hospital No. 6" of the Dnipro City Council" No. 2511/21-1 dated November 25, 2021) in accordance with the fundamental moral-ethical principles, requirements for compliance with the rights, interests and personal dignity of research participants, which are ensured the following regulatory documents: the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine, Quality Clinical Practice (GCP), UNESCO's General Declaration on Bioethics and Human Rights, the Constitution of Ukraine (Articles 3, 21, 24, 28, 32), Fundamentals of Legislation of Ukraine on health care (Articles 43.1, 44.1).

3. Research result

Among the clinical forms, the oligoarticular variant of the disease prevailed, occurring in 65.1 % (n=41)

of cases. The polyarticular variant occurred in 34.9 % (n=22) of cases (Fig. 1).

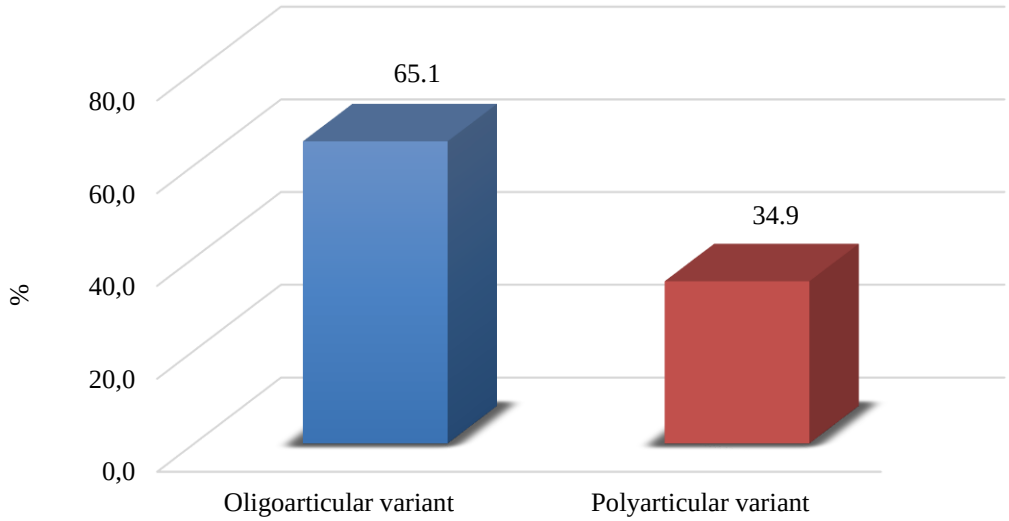

Fig. 1. Clinical forms of JIA in children

Children with oligoarticular and polyarticular variants were comparable in age (Table 1). Thus, the median age of children with an oligoarticular variant was 13.0 [10.0; 16.0] years versus 14.0 [8.0; 17.0] years old in children with a polyarticular variant of the disease (p>0.05). It was established that the onset of the disease occurred at an earlier age in children with a polyarticular variant than in children with an oligoarticular variant (3.5 [2.0; 10.0] versus 6.5 [3.0; 13.0] years, p≤0.1). However, the average duration of the disease was not significantly different in children of both groups (p>0.05). Nor did the indicators of physical development differ.

Table 1

Characteristics of children with oligo- and polyarticular variants of the disease

Indicator	Oligoarticular variant (n=41)	Polyarticular variant (n=22)	p
Age, years, Me [25 %;75 %]	13,0 [10,0; 16,0]	14,0 [8,0; 17,0]	>0,05
Age of disease debut, years, Me [25 %;75 %]	6,5 [3,0; 13,0]	3,5 [2,0; 10,0]	<0.05
Length of illness, months	66,0 [42,0; 90,0]	72,0 [48,0; 144,0]	>0,05
Height, cm, Me [25 %;75 %]	157,0 [138,0; 165,0]	156,5 [140,0; 166,0]	>0,05
Body weight, kg, Me [25 %;75 %]	43,0 [29,0; 55,0]	42,5 [31,0; 58,5]	>0,05
BMI, kg/m^2, Me [25 %;75 %]	16,8 [15,0; 18,8]	18,4 [15,8; 21,0]	>0,05

Ultrasound densitometry was performed in 48 patients with JIA, according to which 20 patients (41.7 %) were diagnosed with OS of various degrees of severity. According to WHO criteria, osteopenia I degree (–1.0 SD < Z-index > –1.5 SD) was diagnosed in 20.0 % of cases (n=4), II degree (–1.5 SD ≤Z- index ≥ –2.0 SD) – in 35.0 % of cases (n=7), III degree (–2.0 SD ≤ ≤ Z- index ≥ –2.5 SD) – in 30.0 % of cases (n=6) and in 3 patients (15.0 %) the Z-index was below –2.5, which corresponds to the criteria of osteoporosis (Fig. 2).

Clinical and, anamnestic and laboratory-instrumental data were compared in children with and without OS (Table 2). It was established that children with OS were older than children without this syndrome (15.0 [13.0; 17.0] vs. 13.0 [9.0; 15.0] years; p<0.1), but did not differ statistically in terms of age of onset and duration of the disease.

Among the children of both groups, the oligoarticular variant of the disease prevailed, which occurred in 60.0 % of cases in children with OS and in 57.7 % of cases in children without it. Patients with OS were significantly more likely to complain of joint pain (90.0 % vs. 30.8 %; p<0.05), morning stiffness (95.0 % vs 38.5 %, p<0.05) and movement limitations (65.0 % vs 26.9 %; p<0.05), and joint deformity was detected during examination (80.0 % vs 42.3 %; p<0.05).

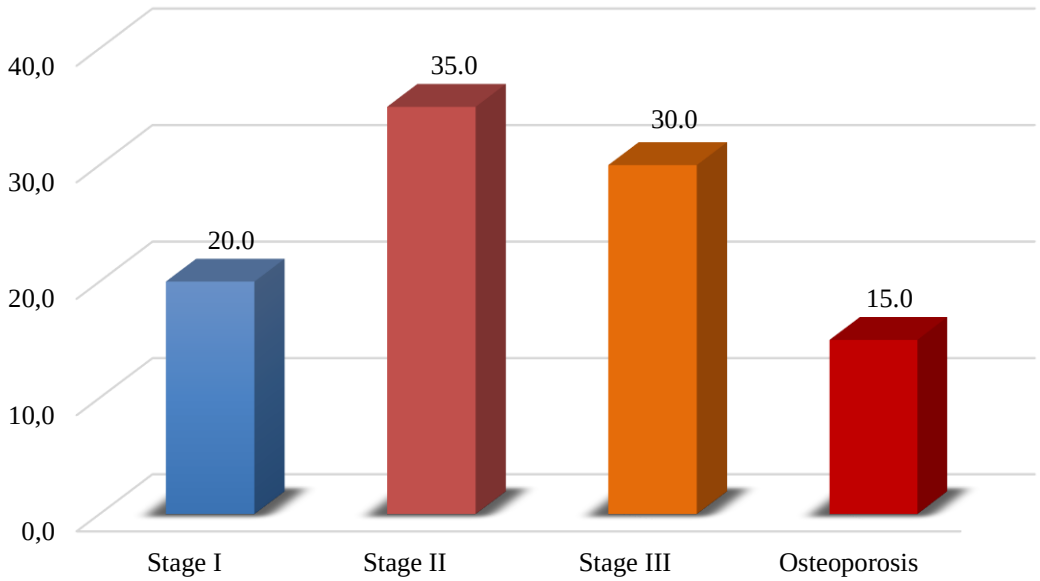

Fig. 2. The structure of the osteopenic syndrome in children with JIA

Table 2

Characteristics of children with and without osteopenic syndrome

Characteristic	Children with OS (n=20)	Children without OS (n=26)	p
Age, years, Me [25 %;75 %]	15.0 [13.0; 17.0]	13.0 [9.0; 15.0]	<0.05
Height, cm, Me [25 %;75 %]	159.5 [150.0; 166.0]	153.5 [140.0; 165.0]	>0.05
Weight, kg, Me [25 %;75 %]	46.5 [34.5; 58.3]	42.5 [31.5; 56.0]	>0.05
BMI, kg/m^2, Me [25 %;75 %]	17.9 [16.8; 21.9]	17.8 [15.0; 20.7]	>0.05
Age of disease debut, Me [25 %;75 %]	8.0 [4.0; 12.5]	6.0 [3.0; 9.0]	>0.05
Length of illness, months, Me [25 %;75 %]	66.0 [36.0; 90.0]	60.0 [36.0; 108.0]	>0.05
Polyarticular variant, n (%)	8 (40.0 %)	11 (42.3 %)	>0.05
Oligoarticular variant, n (%)	12 (60.0 %)	15 (57.7 %)	>0.05
Methotrexate dose, Me [25 %;75 %]	20.0 [15.0; 20.0]	15.0 [15.0; 20.0]	<0.05
Duration of methotrexate prescription, months, Me [25 %;75 %]	60.0 [36.0; 84.0]	48.0 [36.0; 108]	>0.05
Arthralgia, n (%)	18 (90.0 %)	8 (30.8 %)	<0.05
Morning stiffness, n (%)	19 (95.0 %)	10 (38.5 %)	<0.05
Movement restrictions, n (%)	13 (65.0 %)	7 (26.9 %)	<0.05
Deformation of the joints, n (%)	16 (80.0 %)	11 (42.3 %)	<0.05
Joint contractures, n (%)	6 (30.0 %)	4 (15.4 %)	>0.05
Vitamin D, ng/ml, Me [25 %;75 %]	17.3 [14.3; 25.8]	28.8 [20.6; 46.3]	<0.05
Parathyroid hormone, ng/ml, Me [25 %;75 %]	41.1 [33.8; 61.9]	43.6 [35.5; 50.6]	>0.05
Densitometry, Z-index, Me [25 %;75 %]	–1.9 [–2.4; –1.5]	–0.4 [–0.7; 0.6]	<0.05

It was also established that patients with OS received a higher therapeutic dose of methotrexate (20.0 [15.0; 20.0] vs 15.0 [15.0; 20.0]; p<0.05), but the duration of its use did not differ significantly (60.0 [36.0; 84.0] vs. 48.0 [36.0; 108]; p>0.05).

BMD indicators in children with OS were –1.9 [–2.4; –1.5] versus –0.4 [–0.7; 0.6] in children without this syndrome (p<0.05).

A study of the level of 25 (OH)D in blood serum as an important diagnostic criterion of OS showed that it was significantly lower in children with OS than in children without OS and was 17.3 [14.3; 25.8] against 28.8 [20.6; 46.3] ng/ml; (p<0.05). However, parathyroid hormone levels did not significantly differ in children of both groups and amounted to 41.1 [33.8; 61.9] against 43.6 [35.5; 50.6] ng/ml (p>0.05).

4. Discussion of research results

Due to rapid technological developments over the last decade, the use of ultrasound densitometry techniques for BMD studies has increased significantly. However, the reliability of this research method in relation to traditional radiographic methods of measuring bone mass in childhood is debated [9].

The main problem with the use of ultrasound densitometers in inflammatory rheumatic diseases is that they differ technologically in terms of the anatomical areas of measurement and the use of different ultrasound

mechanisms, such as trabecular transverse transmission (used on the calcaneus), cortical transverse transmission (used on the phalanges of the fingers) and cortical axial transmission (applies to the phalanges of the fingers, radius and tibia) [9, 12]. Therefore, it is impractical to compare measurements obtained directly by different technologically different devices.

To date, the calcaneus is the only measurement site that has achieved an acceptable level of scientific validation for the clinical use of ultrasound densitometry devices in the treatment of osteoporosis. However, not all heel devices can be used in the pediatric population due to inappropriate sensor sizes. Therefore, other peripheral areas of the skeleton, such as the radial and tibial bones, are proposed to assess the condition of bones in children. However, their scientific validity for measuring bone mineral density, especially of the distal radius, remains controversial. An international consensus definition of osteopenia and osteoporosis using ultrasound densitometers is also still missing [9, 12]. However, several studies in both adults and children demonstrate that ultrasound devices for quantifying BMD are as reliable as DXA. Thus, the study of U. O. Abrahamovych et al. (2017) confirmed the high sensitivity of the ultrasound method of instrumental diagnosis of osteoporosis in adult patients with systemic lupus erythematosus compared to X-ray osteodensitometry and DXA [11]. The study of M. Delshad et al. (2021) found reliable positive correlations between the results of ultrasound densitometry and DXA in healthy children [13]. In the study of S. Cerar et al. (2023) defined the role of quantitative ultrasound for the screening diagnosis of severe metabolic bone diseases in newborns, as well as for the assessment of further bone development, including monitoring the response to treatment [14].

Our study also confirmed that OS is a fairly common complication of JIA in children and is 39.6 %. The data obtained by us using ultrasound densitometry coincide with the results of many studies conducted using such a "gold standard" of diagnostics as DXA [3, 10].

Therefore, ultrasound densitometry can reasonably be used as an alternative to expensive, radiation-exposed DXA for the screening diagnosis of OS in children with JIA. Its advantages are speed, safety, painlessness, lack of radiation and low cost.

The limitation of the conducted study was the impact of full-scale military operations on the territory of Ukraine on the collection of information, which significantly limited the sample of patients for the study.

Prospects for further research are to study biochemical markers characterizing the speed and character of bone tissue metabolism processes in children with JIA to develop algorithms for predicting and preventing the development of OS and osteoporosis in the future.

5. Conclusions

1. Ultrasound bone densitometry can be used as a screening method for the diagnosis of OS to separate patients who should be referred for DXA, thereby saving unnecessary medical costs.

2. The ease of use of ultrasound densitometry devices, the absence of radiation exposure to the child, the possibility of conducting the examination at the bedside, and the low cost are clear advantages of ultrasound densitometry compared to X-ray densitometric methods such as DXA.

3. Early detection and timely correction of osteopenic conditions in children with JIA will reduce not only the risk of fractures but also the development of osteoporosis in adulthood.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

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Data availability

The manuscript has no associated data.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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