

ORIGINAL PAPER

PREDICTORS AND MANAGEMENT ALGORITHM OF BONE DEMINERALIZATION IN JUVENILE IDIOPATHIC ARTHRITIS

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ABSTRACT

Introduction. Juvenile idiopathic arthritis (JIA) is a persistent type of arthritis with no defined cause, that starts before the age of 16 years and lasts for at least 6 weeks.

The objective of the study was to determine the predictors of bone demineralization and develop an algorithm to optimize the diagnostic management of bone demineralization in juvenile idiopathic arthritis.

Material and methods. The study was carried out in the Department of Rheumatology, Public Healthcare Institution – Mother and Child Institute, Chisinau, Republic of Moldova. The study included 84 children with JIA. The number of painful and swollen joints, the global evaluation of the disease by the doctor (GEDD) and the global evaluation of the disease by the patient (GEDP) were determined, as well as via the Childhood Health Assessment Questionnaire (CHAQ). Furthermore, paraclinical tests, which included a complete blood count, acute-phase markers of inflammation (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)), alkaline phosphatase, calcium levels, bone metabolism profile (osteocalcin, pyrilinks, total 25-OH-vitamin D), imaging examinations (osteoarticular radiography, ultrasound bone

RÉSUMÉ

Prédicteurs et algorithme de conduite en déminéralisation osseuse dans l'arthrite juvénile idiopathique

Introduction. L'arthrite juvénile idiopathique (AJI) se réfère à un type persistant d'arthrite sans cause définie, qui débute avant l'âge de 16 ans et dure 6 semaines au minimum.

L'objectif de l'étude a été de déterminer les prédicteurs de la déminéralisation osseuse et de développer un algorithme pour optimiser le comportement diagnostique de la déminéralisation osseuse dans l'arthrite juvénile idiopathique.

Matériel et méthodes. L'étude a eu lieu dans la Division de Rhumatologie, Établissement Public de Santé – Institut de la Mère et de l'Enfant, Chisinau, République de Moldova. Le nombre d'articulations douloureuses, d'articulations tuméfiées et l'évaluation générale de la maladie ont été déterminées par le médecin et le patient ainsi que le questionnaire d'évaluation fonctionnelle de l'enfant (CHAQ). Les indicateurs paracliniques ont été identifiés, y compris l'analyse générale du sang, des marqueurs d'inflammation de phase aiguë (vitesse de sédimentation érythrocytaire (VSE), la protéine C-réactive (CRP)), le taux de phosphatase

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densitometry), and dual-energy X-ray absorptiometry, were performed.

Results. The predictive factors for impaired bone mineralization in children with JIA were identified through logistic regression. Thus, of all predictive factors analyzed, a score of 14 factors was obtained as part of the research questionnaire, such as pain in the cervical region, thoracolumbar pain, bone pain, hair loss, posture disorder, sedentary lifestyle, dietary calcium and phosphorus deficiency, rickets at a young age, atraumatic fractures, Steinbrocker radiologic stage, Sharp score, and pyrilinks. An algorithm was developed to optimize the diagnostic management of bone demineralization in children with JIA.

Conclusions. Quantitative ultrasound is a screening method for bone mineral status, while dual-energy X-ray absorptiometry has been confirmed as the “gold” method for assessing bone mineralization in the pediatric and adult populations.

Keywords: juvenile idiopathic arthritis, impaired bone mineralization, diagnostic algorithm, predictors.

List of abbreviations:

CHAQ – Childhood Health Assessment Questionnaire
 CRP – C-reactive protein
 DAS – Disease Activity Score
 BMD – Bone mineral density
 DPD – Deoxypyridinoline
 DXA – Dual-energy X-ray absorptiometry
 ESR – Erythrocyte sedimentation rate
 GCS – Glucocorticosteroids
 GEDD – Global evaluation of disease by the doctor
 GEDP – Global evaluation of disease by the patient
 IL – Interleukin
 ISCD – International Society for Clinical Densitometry
 JIA – Juvenile idiopathic arthritis
 NPJ – Number of painful joints
 NSJ – Number of swollen joints
 OP – Osteoporosis
 PYR – Pylinx
 QUS – Quantitative ultrasound
 SD – Standard deviation
 TNF – Tumor necrosis factor

INTRODUCTION

Juvenile idiopathic arthritis (JIA), as defined by the International League of Associations for Rheumatology (ILAR)¹, refers to a persistent type of arthritis with no defined cause that starts before the age of 16 and lasts for at least 6 weeks¹. JIA is the most common rheumatic disease in children, that can significantly impair joint function, resulting in

alkaline et de calcium, profil du métabolisme osseux – ostéocalcine, pyriliens, 25-OH-vitamine D totale; examens d'imagerie – radiographie ostéoarticulaire, densitométrie osseuse échographique et absorptiométrie à rayons X en double énergie.

Résultats. Par régression logistique, des facteurs prédictifs du trouble de la minéralisation osseuse chez les enfants atteints d'AJI ont été identifiés. Ainsi, un score a été obtenu à partir de 14 facteurs parmi tous ceux analysés, faisant partie du questionnaire de recherche, soit: douleurs dans la région cervicale, douleurs thoraco-lombaires, maux de dos, chute de cheveux, déformation de la posture, mode de vie sédentaire, insuffisance alimentaire en calcium et en phosphore, rachitisme à un jeune âge, fractures atraumatiques, stade radiologique selon Steinbrocker, score de Sharp et pyrilinks. Un algorithme a été développé pour optimiser le comportement diagnostique de la déminéralisation osseuse chez les enfants atteints d'AJI.

Conclusions. L'échographie quantitative est considérée comme une méthode de dépistage de l'état minéral osseux, tandis que l'absorptiométrie à rayons X en double énergie a été confirmée comme la méthode « en or » pour évaluer la minéralisation osseuse pour la population pédiatrique et adulte.

Mots-clés: arthrite juvénile idiopathique, trouble de la minéralisation osseuse, algorithme de diagnostic, prédicteurs.

joint deformities, growth failure, and persistent active disease in adulthood. The disease is characterized by chronic synovial inflammation, cartilage damage, and bone erosion.

Bone fragility in the third age has its roots in childhood, during the growth period, and is assessed by several determining factors that can affect bone growth, such as juvenile inflammatory diseases. Persistent inflammation, starting in childhood, when

the development of the skeletal system and growth are not yet complete, can cause a few complications, such as growth retardation, impaired bone metabolism, eventually leading to osteopenia or osteoporosis, and fractures².

Children diagnosed with systemic diseases of the connective tissues are at a high risk of developing, over time, osteopenic or osteoporotic bone mineralization disorders through primary or secondary mechanisms. The latter include the negative effect on bone metabolism of pro-inflammatory cytokines, especially tumour necrosis factor (TNF), a series of interleukins (IL): IL-1, IL-6, IL-8, IL-12, IL-15, IL-18, and granulocyte-macrophage colony-stimulating factor^{3,4}, nutritional deficiency of vitamin D and calcium, reduced physical activity and aggressive long-term treatment with osteotoxic remedies, such as glucocorticosteroids (GCS).

Impaired bone mineralization in children has aroused a great interest in the daily practice of pediatricians in the last decade worldwide. Epidemiological data from some recent studies indicate that, in children with rheumatic diseases, a prevalence rate of vertebral fractures has been reported from 10% to 30%⁵⁻⁸, with an incidence of 6% of vertebral fractures in the 12-month period from the initiation of long-term treatment with glucocorticoids⁹. A series of studies have documented low bone mass in children with rheumatic diseases^{7, 10-14}. The decrease in bone mass may increase the risk of fractures during childhood and possibly later in adulthood because of sub-optimal accumulation of peak bone mass^{11,12}. Definite evidence of bone fragility in children with rheumatic diseases is provided by studies documenting vertebral and extremity fractures^{5-8,14,15}.

The pathogenesis of impaired bone metabolism in patients with rheumatic diseases is multifactorial and involves an excessive activation of osteoclastogenesis and reduced bone formation. Important studies providing information on focal bone loss were conducted by Bromley, Hummel, Gravallesse et al, who suggest that the synovial tissue in rheumatic diseases is rich in cells, descendants of monocytes/macrophages, which, through appropriate stimuli, can induce their differentiation into preosteoclasts and, finally, into fully functional osteoclasts¹⁶⁻²⁰.

Another type of bone loss found in patients with rheumatic diseases is periarticular osteopenia associated with inflamed joints. The third type of bone loss specific to JIA is generalized axial and appendicular osteopenia, which has been determined using various bone mass assessment techniques^{21,22}. There is compelling evidence that reduced bone mass is associated with an increased risk of hip fracture or vertebral fracture²²⁻²⁵.

The clinical manifestations of impaired bone mineralization are diverse, such as spinal pain, permanent vertebral deformities, and vertebral fractures²⁶⁻²⁸. In the pediatric population, fractures are common; 50% of children have at least one fracture^{29,30}, and approximately a quarter of children have recurrent fractures³¹.

Pyridinoline, pyrilinks (PYR), and deoxypyridinoline (DPD) are markers of collagen degradation. PYR is predominantly present in the connective tissue.

Dual-energy X-ray absorptiometry (DXA) of the lumbar spine or whole body is the gold standard for measuring bone mineral density (BMD) in the pediatric age group, as recommended by the International Society for Clinical Densitometry (ISCD) in 2007³², with the 2013 ISCD recommendations update³. The BMD assessment via this technique uses the Z-score, which expresses the number of standard deviations (SD) that refers to the patient's BMD deviations from the mean BMD in healthy children of the same age and sex³².

THE OBJECTIVE OF THE STUDY was to determine the predictors of bone demineralization and develop an algorithm to optimize the diagnostic management of bone demineralization in JIA.

MATERIAL AND METHODS

The prospective study was carried out in the Department of Rheumatology, Public Healthcare Institution – Mother and Child Institute, Chisinau, Republic of Moldova, between November 2014 – December 2018. The patients' parents signed a written consent to participate in the study. The study was approved by the Ethics Committee of the institute (approval number 66, June 8, 2015). The study included 84 children diagnosed with JIA, using the classification criteria adopted at the Congress of the World League of Rheumatology Associations (1997) in Durban (Republic of South Africa)³³.

The inclusion criteria were as follows: children with the diagnosis of JIA, systemic, oligoarticular and polyarticular forms; consent of the patient's parents or legal guardian, and the child's consent (age ≥ 14 years) to participate in the study.

The exclusion criteria were as follows: patients with other rheumatic diseases (reactive arthritis, scleroderma, systemic lupus erythematosus, systemic vasculitis, and dermatomyositis), the disagreement of the patient's parents or legal representatives, as well as of the children.

The control group included 27 healthy children.

The prospective study included 84 children with JIA (57 girls and 27 boys). Polyarticular JIA was found

in 32 children, systemic JIA in 10 children, oligoarticular JIA in 42 children. The average age of the patients included in the study was 11 years. The disease duration at the time of inclusion in the study was on average 45.90 ± 44.42 months (lasting from 1 month to 170 months).

The clinical data and paraclinical tests were assessed throughout and at the end of the study. The clinical indices included the number of painful joints (NPJ) and the number of swollen joints (NSJ), the global evaluation of the disease by the doctor (GEDD), and the global evaluation of the disease by the patient (GEDP)³⁴. The Childhood Health Assessment Questionnaire (CHAQ) was used to assess the physical function of children, as proposed by the American College of Rheumatology³⁵. The CHAQ score included 13 questions. Special scores were added to the score obtained in questions 1-10, and the score gained from questions 11-13 was added to the index obtained. The paraclinical tests included a complete blood count, acute-phase markers of inflammation (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)), alkaline phosphatase and calcium levels, bone metabolism profile (osteocalcin, pyrilinks, total 25-OH-vitamin D), imaging examinations (osteoarticular radiography, ultrasound bone densitometry), and dual-energy X-ray absorptiometry.

RESULTS

The analysis of the clinical symptomatology of possible bone mineralization disturbances in the children with JIA included in the study determined that the most frequent manifestations, in most cases, were as follows: long tubular bone pain (83.34%), nail fragility (63.1%), back pain of the thoracolumbar (59.52%) and cervical regions (38.1%), followed by nail thinning (32.53%), and posture disorder (24.1%).

The analysis of the dietary factors in the children included in the study revealed a nutritional deficiency of phosphorus and calcium in approximately half of the children: 52.63% of children with phosphorus deficiency and 59.26% of children with calcium deficiency, with a higher prevalence among girls.

Sedentary lifestyle presented statistically significant values in the experimental group, distributed by gender, and in the group of patients undergoing GCS treatment. Thus, 8 (29.63%) boys and 6 (10.71%) girls confirmed a sedentary behavior ($p < 0.05$, $\chi^2 = 4.648$, $gl = 1$), respectively, 4 (7.55%) children not undergoing steroid treatment and 10 (37.04%) subjected to GCS therapy ($p = 0.01$, $\chi^2 = 10.755$, $gl = 1$).

The analysis of the manifestations of rickets at a young age, carried out based on the data from the outpatient records, also determined statistically

significant results in patients subjected to GCS treatment: 11 (39.29%) children with rickets undergoing GCS treatment and 2 (3.77%) children who did not receive GCS treatment ($p < 0.001$, $\chi^2 = 17.148$, $gl = 1$).

The analysis of pyrilinks values (PYR) in the experimental group ($n = 63$) revealed statistically significant differences, with a mean of 33.38 ± 19.16 nmol deoxypyridinoline/mmol ($p = 0.00$, 95% CI 28.55 -38.20). These high values confirm an intense process of bone resorption in children with JIA, compared to the mean values of PYR in the control group - 12.24 ± 11.35 nmol deoxypyridinoline/mmol (CI 95% 7.75-16.73).

Statistically significant differences were found between the mean values of osteocalcin in the experimental group, which accounted for 9.86 ± 8.12 ng/mL, and the control group ($n = 27$) - 13.50 ± 8.02 ng/mL ($p = 0.05$, 95% CI 7.87-11.86). Normal osteocalcin values were found in 61 children (< 22 ng/mL), of which 18 (29.55%) boys and 43 (70.5%) girls ($p < 0.05$, $\chi^2 = 5.302$, $gl = 1$). Elevated osteocalcin values (> 22 ng/mL) were found in 5 children, predominantly boys - 4 (80%) cases and only 1 (20%) girl.

The bone metabolism status was analyzed by assessing the serum level of total 25-OH-vitamin D in children with JIA. Thus, 2 (25%) children with polyarticular JIA had values of total vitamin D suggestive of a severe deficiency, followed by 1 (12.5%) child with systemic JIA. In the experimental group, 55% of the children ($n = 30$) had total vitamin D values suggestive of a moderate deficiency: 6 (75%) children with polyarticular JIA, 4 (80%) children with oligoarticular JIA, and 3 (37.5%) with systemic JIA ($p > 0.05$). Only 20.7% of the children in the experimental group ($n = 30$) had an optimal level of total vitamin D, of which 4 (50%) children had the systemic form and 1 (20%) child had the oligoarticular form of JIA.

The imaging exam comprised the analysis of the most relevant indicators, such as the Steinbrocker radiologic stage, the Sharp score, the number of joint erosions and joint space narrowing, and the osteoporotic index.

A number of 8 children with JIA were examined by dual-energy X-ray absorptiometry (DXA) of the entire skeleton and subjected to ultrasound bone density assessment, presenting a BMD Z-score < -2.0 . Mean values suggestive of osteoporosis were found in children with systemic JIA with a BMD Z score = -3.2 ± 0.5 , children with disease duration > 24 months, with average values of Z BMD = -3.0 ± 0.6 , and those subjected to a long-term GCS treatment, with a BMD Z-score = -2.9 ± 0.6 , statistically insignificant data. Children with polyarticular JIA and children with disease duration < 24 months presented mean Z-score values suggestive of osteopenia: -2.4 ± 1.0 and, correspondingly, -1.8 ± 0.9 .

The predictive factors of impaired bone mineralization were identified by logistic regression in children with JIA. Thus, of all the factors analyzed, a score from 14 factors was obtained as part of the research questionnaire, comprising pain in the cervical region, thoracolumbar pain, backache, hair loss, posture disorder, sedentary lifestyle, dietary calcium and phosphorus deficiency, rickets at a young age, atraumatic fractures, Steinbroker radiologic stage, Sharp score, and pyrilinks (Table 1) (Fig. 1).

Following the analysis of the research data, an algorithm was developed to optimize the diagnostic management of bone demineralization in children with juvenile idiopathic arthritis (Fig. 2).

The main limitation of the study is related to the small number of patients.

DISCUSSION

JIA is a severe disease that leads to severe impairment of functional ability up to physical disability because of osteoarticular injuries, leading to premature death caused by systemic diseases, thus having a great medical, social, and economic impact.

Impaired bone mineralization is a current and important issue in public health, especially among chronic diseases in children, which, according to several studies^{26,36-41}, has continuously increased in the

last decades. Children with JIA are at risk of developing permanent joint damage because of chronic inflammation and the breakdown of cartilage and bone.

A cross-sectional study conducted by Dey et al.⁴² analyzed the BMD in children with JIA by associating risk factors, with the following results: dietary deficiency of calcium and vitamin D and reduced physical activity.

Table 1. Predictive factors for impaired bone mineralization in juvenile idiopathic arthritis

Nr.	Predictive factors	χ^2	P
1	Pain in the cervical region	16,356	.000*
2	Sharp score	12,472	.000*
3	Thoracic-lumbar pain	9,685	.002*
4	Dietary phosphorus deficiency	8,052	.005*
5	Sedentary lifestyle	8,886	.003*
6	Bone pain	7,134	.008*
7	Atraumatic fractures	5,509	.019*
8	Rickets at an early age	5,486	.019*
9	BMD DEXA Z-score	5,507	.019*
10	Hair loss	6,574	.010*
11	Posture disorder	4,474	.034*
12	Pyrilinks	2,211	.137
13	Steinbroker radiologic stage	3,941	.047*
14	Dietary calcium deficiency	3,905	.048*

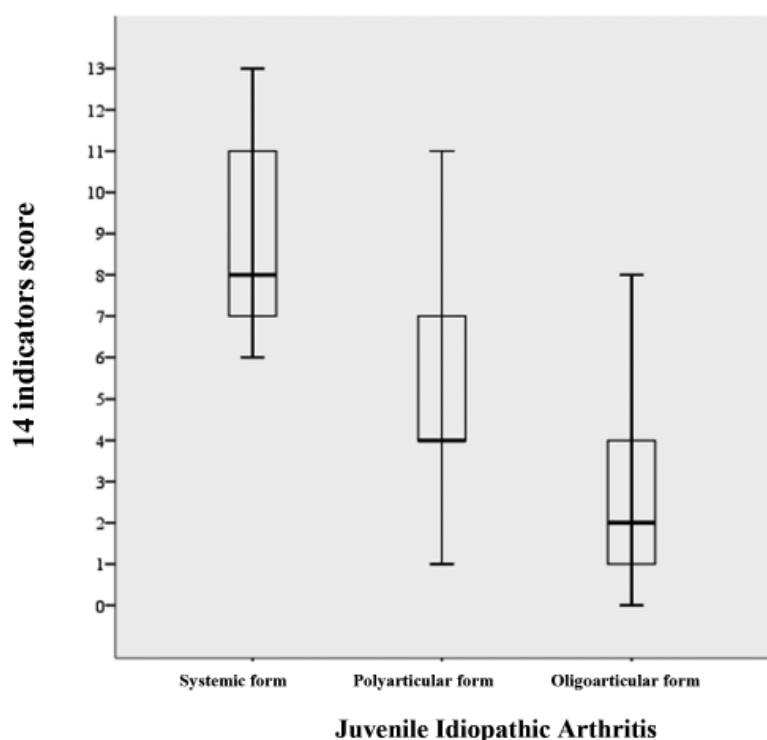


Figure 1. Distribution of the score of predictive factors according to the clinical form of JIA

Diagnostic algorithm in children with suspected osteopenia/osteoporosis

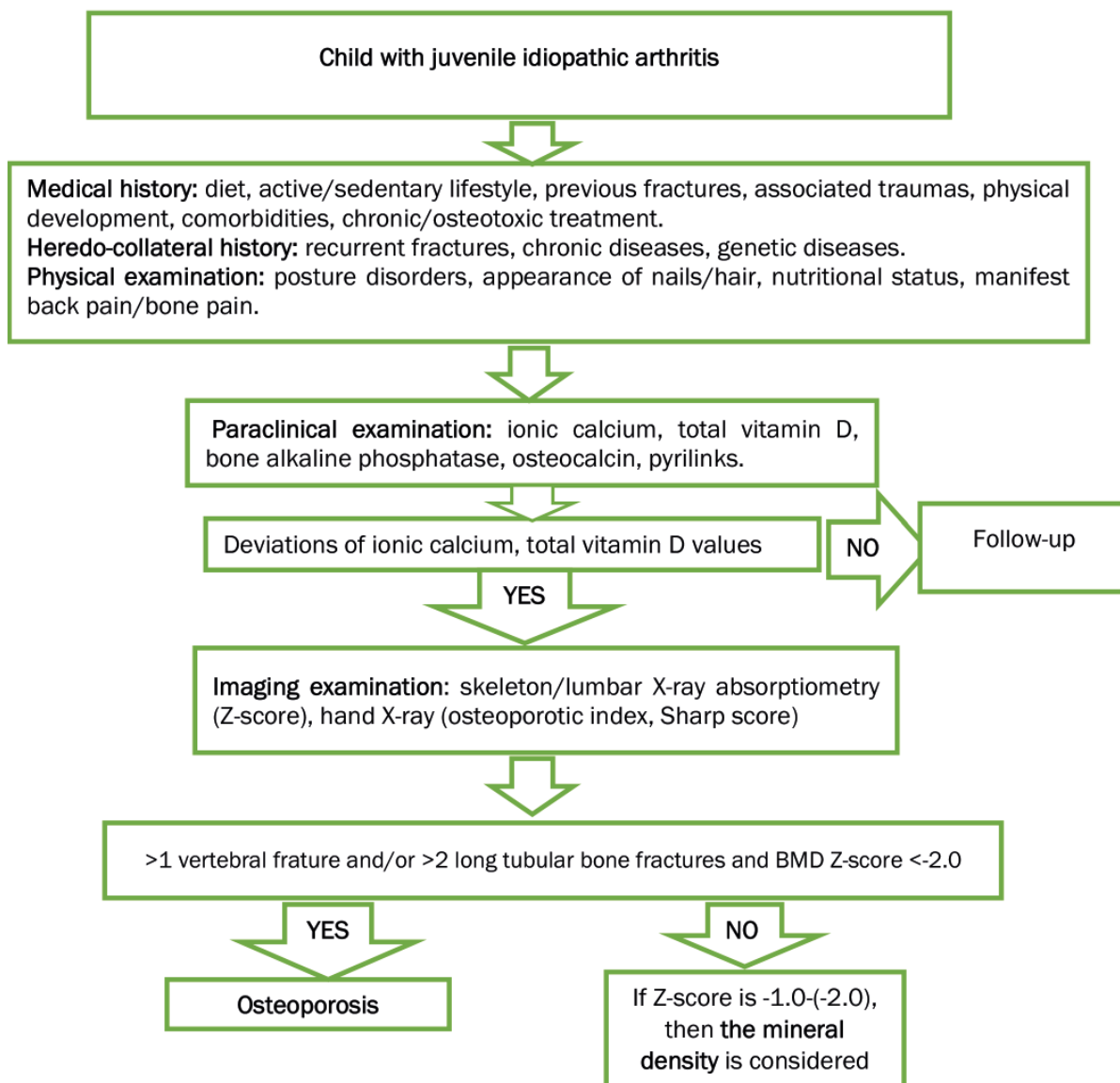


Figure 2. Diagnostic algorithm of bone mineralization disturbances in JIA

Lien et al. studied bone mineral content and BMD in the whole skeleton, lumbar spine, and femoral neck of 105 adolescents with an early onset of JIA and a mean disease duration of 14.2 years. The researchers found that 41% of the patients had low total bone mineral content, which was closely correlated with the average decrease in weight and height, the duration and activity of the disease, and the number of joints involved¹³.

The study carried out by Burnham et al, which included 1,939 children with JIA and approximately 200,000 children in the control group, determined a clinically significantly increased risk of nonvertebral fractures in the first group (6.7% in patients versus 3.3% in controls)⁴³.

The Canadian STOPP (Steroid-Associated Osteoporosis in the Pediatric Population) study evaluated the health of the spine in 134 children with rheumatic diseases within 30 days of starting glucocorticosteroid treatment, revealing vertebral fractures in 7% of patients; 2 (9%) children with systemic JIA developed vertebral fractures, while nonvertebral fractures were observed in 28 children with other forms of JIA. Children with accidental vertebral fractures showed a greater decrease in lumbar spine BMD Z-score during the first 6 months in the study conducted by Huber et al. and a prevalence of 29–45% later during the treatment, with an incidence of up to 33% in the first years of corticosteroids administration^{39,44}.

The study carried out by Southwood (2008), assessing imaging changes in the diagnosis and monitoring of children with JIA, established that the changes specific to the pediatric population are the premature closure of the growth zone, epiphyseal deformation, and growth asymmetry⁴⁵.

The study by Hassan et al. certified osteopenic/osteoporotic bone mineralization disturbances in children with JIA by DXA examination, especially in those with oligoarticular and systemic forms. In the same study, children with longer disease duration showed more pronounced osteopenic/osteoporotic bone mineral status disturbances⁴⁶.

CONCLUSIONS

The assessment of bone metabolism disturbances in children with JIA by determining bone formation markers established that the process of bone resorption is amplified, which is revealed by an increase in pyrilinks, without altering bone formation.

The Sharp score was determined as a risk factor and shows a positive association with the development of osteopenic/osteoporotic bone mineralization disturbances in pediatric JIA patients.

Ultrasound bone densitometry identified predominantly osteopenic changes, while dual-energy X-ray absorptiometry found osteoporotic changes in bone structure.

Quantitative ultrasound is a screening method for bone mineral status, while dual-energy X-ray absorptiometry has been confirmed as the “gold” method for assessing bone mineralization in the pediatric and adult populations.

RECOMMENDATIONS

1. An early assessment of risk factors for bone demineralization is recommended in children with JIA, according to the developed screening algorithm.
2. In children with JIA who present clinical data of bone demineralization, it is necessary to evaluate the bone remodeling markers such as osteocalcin, pyrilinks, and 25-OH vitamin D to assess the subsequent diagnostic management of osteoporosis, establish the treatment, and minimize the risk of fractures.
3. In all children with JIA, vitamin D should be administered from the onset of the disease in appropriate doses, according to the results of the serum 25-OH vitamin D evaluation, with a tailored follow-up.
4. The radiological profile should be determined by assessing the Sharp score and detecting joint

lesions as a predictor of the risk of developing osteopenia/osteoporosis.

5. In all children with confirmed JIA, it is recommended to perform quantitative ultrasound (QUS), which is considered a screening imaging method for changes in bone mineral density, and dual-energy X-ray absorptiometry (DXA) by assessing the BMD/BMI Z score – the “gold” method to confirm osteopenia/osteoporosis.

Authors' Contributions:

N.R., S.F., A.C., L.M.N. were responsible for clinical diagnosis, paraclinical investigations, treatment decisions, and follow-up of the patients. N.R., A.C. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Compliance with Ethics Requirements:

“The authors declare no conflict of interest regarding this article”

“The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008 (5), as well as the national law. Informed consent was obtained from the patients included in the study.”

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