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Assessment of bone mineral density and bone turnover markers in patients with juvenile idiopathic arthritisy

S.G. Soliman, D.A. Nofal, A.A. Labeeb, R.S. El Zaiat, D.S. Fotoh

Menoufia University, Egypt

Correspondence:
Dalia Ahmed Nofal, Menoufia University
Address: Shebin El Kom,
32511 Menoufia, Egypt
E-mail: Dalia.saad@med.menofia.edu.eg

Juvenile idiopathic arthritis (JIA) is one of the most common chronic inflammatory diseases occurring in childhood, associated with decreased bone mineral density (BMD) and increased risk of osteopenia and osteoporosis, which increases the fracture risk. Aim of the work: to assess BMD and bone turnover markers (serum osteocalcin for bone formation and C terminal telopeptide of type 1 collagen for bone resorption) in JIA patients and their relation to disease activity. This study included 50 patients with JIA (female:male – 20:30). The study was approved by the Ethical Research Committee and Institutional Review Board of the Faculty of Medicine, Menoufia University, Egypt (Approval number: 19519INTPH48). Written informed consent was obtained from each patient or the parents.
These patients were diagnosed with JIA according to the criteria of classification of the International League of Associations for Rheumatology. BMD was measured by Dual-energy X-ray absorptiometry (DEXA) of the lumbar spine using the Z-score. The results were correlated with JIA disease duration, disease activity, bone turnover markers and serum level of vitamin D. Clinical disease activity was evaluated by juvenile arthritis disease activity score (JADAS-27). There was a significant negative correlation between DEXA Z-score and disease activity (p-value < 0.001), bone turnover markers (p-value < 0.001), and duration of JIA (p-value < 0.05). There was a significant difference between vitamin D level and DEXA Z-score; DEXA Z-score was lower in vitamin D deficient patients. JIA patients with higher disease activity are at a higher risk of osteopenia and osteoporosis. Well-timed and efficient treatment of JIA and proper control of disease activity may help to improve the bone status and reduce the incidence of osteoporosis. Consequently, valuable targeted interventions are essential to preserve bone health during JIA.

Key words: *bone mineral density, bone turnover markers, osteoporosis, juvenile idiopathic arthritis*

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Childhood is a very important time to build a strong musculoskeletal system. Factors influencing bone structure and quality are genetic background, organ function, chronic systemic illnesses, medications, and muscular disorders as well as metabolic disorders [1].

Juvenile idiopathic arthritis (JIA) is one of the most common chronic inflammatory diseases that occur in children and adolescents under the age of 16 years [2]. In patients with JIA, as happens in other children with chronic diseases, bone accrual may be inhibited by direct and indirect mechanisms [3].

The disease itself, as well as many other factors, is associated with decreased bone mineral density (BMD) in JIA patients such as low physical activity, reduced joint motility [4], delayed pubertal maturation, malnutrition, early onset of JIA, and its treatments [5]. Decreased BMD is associated with an increased risk of osteopenia and osteoporosis, which increases the risk of fracture [6].

Osteoporosis arises when the amount of bone resorbed exceeds the amount of newly formed bone, resulting in a net loss of bone mass, according to the World Health Organization [7].

Increasing awareness among pediatricians to identify risk factors and the clinical conditions or diseases that could lead to the development of osteoporosis made their screen for the possibility of asymptomatic osteoporosis in children with rheumatological disease [7].

Dual-energy X-ray absorptiometry (DEXA) of the lumbar spine using the Z-score is the gold standard method for the measurement of BMD in the pediatric age group. As bone density varies with age, Z-score is used in the pediatric population and not the T-score, which is usually used in adults [7].

Bone turnover markers are tools that detect the dynamics of bone remodeling concerning the bone formation and resorption [7]. This study aimed to assess BMD and bone turnover markers (serum osteocalcin for bone formation and C terminal telopeptide of type 1 collagen (CTX) for bone resorption) in JIA patients and their relation to disease activity.

MATERIAL AND METHODS

An observational cross-sectional study included 50 patients diagnosed and assessed clinically as JIA.

They were randomly recruited from Physical Medicine, Rheumatology, and Rehabilitation Clinic, Menoufia University Hospitals during the years 2020–2022. The study included both sexes. Twenty patients were females (40%) and thirty were males (60%). Their age ranged from 6 to 16 years. Their disease duration ranged from 1.5 to 8 years.

Patients were diagnosed with JIA according to the criteria of classification of the International League of Associations for Rheumatology (ILAR) [8], with a disease duration of more than one year, all patients are under medical treatment for JIA, and patients' ages ranged from (5 to 16) years old.

Patients with a history of receiving corticosteroids, patients receiving concomitant osteotoxic drugs not prescribed for JIA and cause affection of BMD e.g. heparin, warfarin, anticonvulsants, thyroid hormone, and cancer therapy, patients having any other autoimmune diseases, patients with a history of other chronic diseases causing osteoporosis e.g. (endocrinal, hematologic, and renal diseases), and patients with neurological disorders e.g. cerebral palsy and spasticity were excluded from the study. The study was approved by the Ethical Research Committee and Institutional Review Board of the Faculty of Medicine, Menoufia University, Egypt (Approval number: 19519INTPH48). Written informed consent was obtained from each patient or the parents.

All patients were subjected to demographic data recording (age, sex, height, weight, and body mass index), history taking, and clinical examination, including general examination [9] and local examination of joints [10].

Assessment of disease activity was done using the juvenile arthritis disease activity score (JADAS-27) [11], which includes 4 items: physician global assessment of disease activity measured on a 0–10 visual analog scale (VAS) where 0 – no activity and 10 – maximum activity, parent/patient global assessment measured on a 0–10 VAS where 0 – very well and 10 – very poor, number of active joints, and erythrocyte sedimentation rate (ESR) normalized to a (0 to 10) scale.

JADAS 27 = Active joint count + physician global + parent global + ESR. The total JADAS score range from 0–57 [11].

All the patients underwent a DEXA scan on the lumbar spine using the lunar DPX DEXA System (analysis version 14.10) manufactured by General Electric GE Healthcare from the United States. The technologist performing the scan is responsible for proper positioning of the patient, selecting regions of interest (ROI), and careful evaluation of the DEXA results [12]. The reported pediatric DEXA value is expressed as a percentile or a standard deviation score, the Z-score by the same radiologist.

Radiography (X-ray on lumbar spine) is a valuable imaging tool for detecting vertebral fractures in children and adolescents [13].

The standard method for assessment of the height and shape of the T4 to L4 vertebral bodies is lateral thoracic and lumbar spine radiographs. The summation caused by overlying structures such as intra-thoracic organs and the patient's shoulders makes the visualization of the vertebral levels from T1 to T3 difficult and so they are excluded from the routine assessment. The normal physiological wedging that may be seen in the mid-thoracic vertebrae (T5 to T7) should not be mistaken for fracture [14].

All patients were tested for complete blood count (CBC), ESR, C-reactive protein (CRP) titer, albumin/creatinine ratio, serum calcium (total and ionized), phosphorus, magnesium, parathyroid hormone, 25-hydroxyvitamin D3, and bone turnover markers: serum osteocalcin for bone formation and CTX for bone resorption.

Human C – telopeptide of type 1 collagen kit was used which is measured by Enzyme-Linked Immunosorbent Assay (ELISA); using Bio-Rad PR4100 ELISA reader, from Germany. Samples for CTX-I were collected in the morning hours in the fasted state (fasting for 12 hours). CTX-I exhibits a circadian rhythm in the blood which remains unchanged in various scenarios [15].

According to the International Society for Clinical Densitometry, a Z-score of -2.0 or lower is defined as below the expected range for age, and a Z-score above –2.0 is within the expected range for age [15]. In the pediatric population, osteoporosis is a clinical diagnosis. Patients with a BMD Z-score less than or equal to –2.0 in combination with a clinically significant fracture are diagnosed to have osteoporosis [16].

Regarding disease activity score (JADAS 27), there was a cutoff score of 1 for classifying a patient as having the inactive disease for all JIA categories with a cutoff point for the classification of minimal disease activity of 1: 2 for oligoarticular JIA and 1: 3.8 for polyarticular JIA. Children with systemic arthritis, rheumatoid factor (RF) positive polyarthritis, RF-negative polyarthritis, or extended oligoarthritis were included in the polyarthritis group. The oligoarthritis group included patients with persistent oligoarthritis. Patients with JIA classified in the remaining ILAR categories were assigned to the polyarthritis or oligoarthritis group based on the number of joints affected during the disease course (> 4 or < 4, respectively). Values above the cutoff points for classification of active disease state (JADAS > 3.2 and JADAS > 5.2 for oligoarticular and polyarticular JIA, respectively) [17].

Statistical analysis

Data were collected, tabulated, and statistically analyzed using an IBM-compatible personal computer with Statistical Package for the Social Sciences (SPSS) version 23 [18]. Qualitative data were expressed as number (N) and percentage (%), while quantitative data were expressed as mean ($\bar{x}$), standard deviation (SD), and range (minimum-maximum). For quantitative data, Mann–Whitney tests [19] and Kruskal–Wallis tests were used. Spearman correlation was used to show a correlation between two continuous not normally distributed variables [20]. Significant test results were quoted as two-tailed probabilities. The significance of the obtained results was judged at the 5% level ($p > 0.05$).

RESULTS

This study included 50 patients, 20/50 females (40%) and 30/50 males (60%). The mean age was 12.81 ± 3.15 years, ranging from 6–16 years.

This study showed that 36% of patients had low BMD (Z-score ≤ 2) and 64% of patients had normal BMD (Z-score > –2) by DEXA of the lumbar spine. On the other hand, no patient was given a diagnosis of osteoporosis (BMD Z-score ≤ –2 with a significant fracture history) and an X-ray of the lumbar spine was normal in 100% of the patients (*table 1*).

Regarding vitamin D classification, 40% of patients had a normal level, 34% of patients had an insufficient level and 26% of patients had a deficient level of vitamin D (*table 2*).

There was a highly significant difference between types of JIA and DEXA Z-score; DEXA Z-score is lower in plyarticular RF +ve type and enthesitis-related type than other types. It also showed a significant difference between vitamin D level and DEXA Z-score; DEXA Z-score is lower in vitamin D deficient patients (*table 3*).

There was a significant positive correlation between disease activity (JADAS-27) and bone turnover markers (serum osteocalcin with *p*-value < 0.05 and serum CTX with *p*-value <0.001 (*table 4*, *figure*).

Also this study showed a significant negative correlation between disease activity (JADAS-27) and vitamin D level (*p*-value < 0.05) (*table 4*).

There was a significant negative correlation between BMD (DEXA Z-score) and duration of JIA (*p*-value < 0.05), disease activity (JADAS-27) (*p*-value < 0.001), and bone turnover markers (*p*-value < 0.001) (*table 5*).

DISCUSSION

Low BMD is a common finding in children with JIA associated with an increased risk of osteopenia

Table 1
Radiological parameters in the patients (*n* = 50)

Radiological parameters	Distribution
DEXA Z-score (lumbar spine): Range Mean ± SD	 –1.3...–3.8 –1.94 ± 0.69
Classification of BMD according to Z-score, *n* (%): low BMD (Z-score < –2) normal (Z-score > –2)	 18 (36) 32 (64)
X-ray (lumbar spine), *n* (%): normal	 50 (100

Note. SD – standard deviation, range (minimum–maximum).

Table 2
Vitamin D level in patients (*n* = 50)

Vitamin D	Distribution
Vitamin D, ng/ml: range mean ± SD	 10–32.8 25.19 ± 6.24
Vitamin D classification, *n* (%): normal (> 30 ng/ml) insufficient (21–29 ng/ml) deficient (< 20 ng/ml)	 20 (40) 17 (34) 13 (26)

Table 3
Comparison between BMD (DEXA Z-score) versus types of JIA, and vitamin D level

Parameter	DEXA Z-score			
	Mean ± SD	Range	Test of significance	*p*-value
Type of JIA: polyarticular RF +ve polyarticular RF –ve systemic onset oligoarticular enthesitis related	 –2.60 ± 0.12 –1.60 ± 0.09 –1.36 ± 0.05 –1.51 ± 0.09 –2.53 ± 1.07	 –2.4... –2.7 –1.5... –1.7 –1.3... –1.4 –1.4... –1.6 –1.6... –3.8	39.459 (Kruskal–Wallis test)	< 0.001**
Vitamin D: normal insufficient deficient	 –1.64 ± 0.35 –2.059 ± 0.52 –2.25 ± 1.04	 –1.3... –2.4 –1.5... –2.7 –1.3... –3.8	6.017 (Kruskal–Wallis test)	0.049*

*Note * – significant (p < 0.05); ** – highly significant (p < 0.001).*

Table 4
Correlation between JADAS-27 versus laboratory parameters

Laboratory parameters	JADAS-27	
	r_{rho}	*p*-value
Vitamin D, ng/ml	–0.428	0.002*
Bone turnover markers, ng/ml: serum osteocalcin Serum CTX	 0.389 0.702	 0.005* < 0.001**

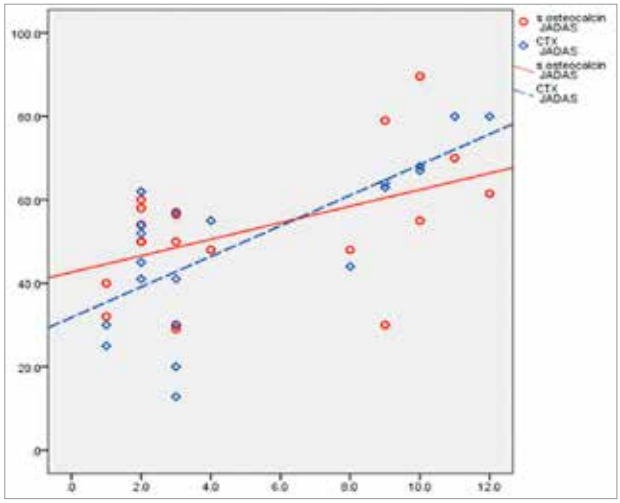
*Note * – significant (p < 0.05); ** – highly significant (p < 0.001).*

Table 5
Correlation between BMD (DEXA Z-score) versus bone turnover markers and clinical parameters

Parameter		DEXA Z-score	
		r_{rho}	*p*-value
Bone turnover markers, ng/ml	Serum osteocalcin	–0.488	< 0.001**
	CTX	–0.843	< 0.001**
Clinical parameters	Duration of JIA, years	–0.384	0.006*
	Disease activity (JADAS-27)	–0.864	< 0.001**

*Note * – significant (p < 0.05); ** – highly significant (p < 0.001).*

Figure
Correlation between JADAS and bone turnover markers



and osteoporosis, which increases the risk of fracture. DEXA of the lumbar spine using the Z-score is the gold standard method for the measurement of BMD in the pediatric age group. Bone turnover markers are tools that detect the dynamics of bone remodeling concerning the bone formation and resorption [7].

This study aimed to assess BMD and bone turnover markers (serum osteocalcin for bone formation and CTX for bone resorption) in JIA patients and their relation to disease activity.

The present study included 50 JIA patients with a mean age of 12.81 ± 3.15 and with mean disease duration of 3.63 ± 2.11 years. The selection of patients was based on the criteria of classification of the ILAR [8].

The results of this study showed that 36% of patients had low BMD (Z-score ≤ 2) and 64% of patients had normal BMD (Z-score > –2) by DEXA scan on the lumbar spine. On the other hand, no patient was given a diagnosis of osteoporosis (BMD Z-score ≤ –2 and a significant fracture history) and an X-ray of the lumbar spine was normal in all patients.

On the other side Zavala et al. [21], showed in an observational cross-sectional study of Spanish JIA patients from 5 to 16 years old that the population prevalence estimation of low BMD was less than 5% and concluded that low BMD prevalence in JIA patients in their population was low. This difference may be due to the different nutritional habits of the Egyptian population, low physical activity, and lack of sun exposure.

In this study there was a highly significant difference between types of JIA and DEXA Z-score, DEXA Z-score is lower in plyarticular RF +ve type with a mean –2.60 ± 0.12 and enthesitis-related type with a mean –2.53 ± 1.07. The mean Z-score in other types of JIA was –1.60 ± 0.09 in polyarticular RF –ve type, –1.36 ± 0.05 in systemic-onset type, and –1.51 ± 0.09 in oligoarticular type. This means that the polyarticular RF +ve type has the highest score putting them at high fracture risk.

This comes in agreement with a study by Kuntze et al., in which Z-scores were significantly lower in patients with polyarticular JIA and those with spondyloarthropathy [22].

On the contrary, the BMD Z score in the lumbar spine showed a statistically significant correlation with the systemic subtype of JIA in a study by El Badri et al. [23]. Also, Shin et al., reported that patients with systemic JIA had lower BMD values [4]. Also, a study by Hassan et al., concluded that children with JIA who have oligoarticular and systemic onset of JIA patients were more susceptible to low BMD [24]. These differences in our results may be explained by the small number of patients included in some of the subgroups.

The present study showed that 40% of patients have normal vitamin D levels (> 30 ng/ml), 34% have an insufficient level (21–29 ng/ml) and 26% have deficient vitamin D levels (< 20 ng/ml).

El Badri et al., reported also that a deficiency of 25-OH-vitamin D (< 10 ng/ml) was found in 4 (10%) patients [23]. Although in other studies, vitamin D levels in JIA patients were normal [26, 27]. These differences may be due to deficient assessment of the dietary and environmental effects (sun exposure) on study participants.

In the present study, there was a significant difference between vitamin D level and DEXA Z-score; DEXA Z-score is lower in vitamin D deficient patients with a mean –2.25 ± 1.04.

Also, in another study by El Badri et al., 75% of the patients with vitamin D deficiency (< 10 ng/ml) had a low BMD [23].

In the present study, there was a significant positive correlation between disease activity (JADAS-27) and serum osteocalcin (p-value < 0.05), and a highly significant positive correlation between disease activity (JADAS-27) and serum CTX (p-value < 0.001).

This comes in concordance with a study done by Janicka-Szczepaniak et al., that reported that the concentrations of CTX were higher in patients with a positive JADAS27 score, in other words, with higher disease activity [28].

Our results showed a highly significant difference between vitamin D levels regarding disease activity (JADAS). This means that disease activity is higher in vitamin D deficiency.

This comes in concordance with Çomak et al., a study in which disease activity was calculated with JADAS-27. There was a significant negative correlation between vitamin D levels and disease activity (p = 0.01) [29]. There was a suggestion that vitamin D deficiency may be a possible modifiable risk factor affecting the disease activity in JIA [29].

Similarly, Janicka-Szczepaniak et al., concluded that 25(OH) D deficiencies were associated with higher JIA disease activity [28]. Also, Rudenko et al., reported that there was a relationship between serum 25(OH) D and disease activity in patients with early inflammatory polyarthritis [30]. In agreement with this Mouterde et al., reported that disease activity and disability scores were inversely related to 25(OH) D levels [31].

In the present study, there was a highly significant negative correlation between BMD (DEXA Z-score) and bone turnover markers (p-value < 0.001).

Also, Zavala et al., stated that there was an increase in bone turnover in patients with lower BMD values [21].

On the other hand, Janicka-Szczepaniak et al. reported that there were no associations between markers of bone turnover and DEXA results [28]. Also, Qu et al., stated that there was a positive correlation between BMD and osteoprotegerin levels in JIA patients [32]. These differences from our results may be explained by a high biological and circadian variability of bone turnover markers.

In this study, there was a significant negative correlation between BMD (DEXA Z-score) and duration of JIA, and this is explained by that the more disease duration the more chance for high disease activity with higher inflammatory markers, and long periods of immobility and decreased physical activity.

This is in concordance with a study by Hassan et al., which concluded that patients with a longer duration of JIA at diagnosis had more osteopenia and osteoporosis than those with a short duration of disease [24]. Also, another study by Islam et al., reported that the disease duration had a positive relationship with lower BMD in JIA patients [33].

This study showed a highly significant negative correlation between BMD (DEXA Z-score) and JADAS-27.

This is in concordance with a study by Dey et al., in which BMD had a slight negative correlation with disease activity measures (active joint count, JADA score, ESR, and CRP) [34]. Also, another study by Sumi et al., concluded that there was an association between decreased bone mineralization in JIA and low bone formation that is related to disease severity [35]. BMD was significantly lower in patients with high disease activity [34].

CONCLUSION

JIA patients with higher disease activity are at a higher risk of osteopenia and osteoporosis. DEXA Z-score provides a useful noninvasive technique to assess BMD in JIA patients and will increase our diagnostic accuracy and provide invaluable tools for assessing different therapies. Well-timed and efficient treatment of JIA and proper control of disease activity may help to improve the bone status and reduce the incidence of osteoporosis.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

ORCID
Nofal D.A. ORCID: https://orcid.org/0000-0001-5673-2831
Fotoh D.S. ORCID: https://orcid.org/0000-0002-5805-0081

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