ASSESSMENT OF BONE MINERAL DENSITY IN A COHORT OF JUVENILE IDIOPATHIC ARTHRITIS PATIENTS

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Abstract. Introduction: *Low bone mass is encountered in patients with juvenile idiopathic arthritis (JIA) as a serious long-term complication of this pediatric condition and may be associated with fractures and its complications. The present study aimed to evaluate the frequency of low bone mineral density (BMD) and fragility fractures in patients with JIA in its polyarticular or oligoarticular forms. Secondary, our aim was to identify factors associated with low bone mass.* ***Patients and methods:*** *This was a retrospective study conducted on 26 patients with JIA meeting the ILAR criteria for poly or oligoarticular form. Patients were divided into two groups according to their age: group1 included patients aged over 16 years old and group 2 included patients aged under 16 years old. Sociodemographic, clinical, biological and functional data were collected by consulting patient's medical records. Bone mineral density was measured at three different sites: whole body, lumbar spine and hip using the dual-energy X-ray absorptiometry (DXA) equipment. Data were entered and analyzed using SPSS version 11.5 software.* ***Results:*** *Twenty-six JIA patients including 20 females (74.1%) and six males (22.2%) were enrolled with a mean disease duration of 20.23 years (2-54 years). The mean age was 28.2 years (7-58 years). The distribution of JIA subtypes among patients was as follows: 6 with oligoarticular JIA and 20 with polyarticular JIA. Sixteen patients (59%) practiced regular physical activity. In our series, the frequency of low bone mineral density was 41% in children with JIA and 68% in adults with JIA. Only two patients presented a fragility fracture in adulthood represented by a hip fracture following low-energy trauma and treated surgically in both cases. No patient received anti-osteoporotic treatment. In group 1, there was a significant correlation between low bone mass and weight (p = 0.020), BMI (p = 0.028), disease duration (p = 0.045), positivity of AAN (p = 0.050), disease activity (p = 0.019), oral corticosteroid (p = 0.034) and biologic treatment (p = 0.043). In-group 2, a statistically significant correlation was found between low bone mass and age at the time of JIA diagnosis (p = 0.041), weight (p = 0.03), physical activity (p = 0.05), disease duration (p = 0.021), functional impact of the disease assessed by the HAQ score (p = 0.018), oral corticosteroid therapy (p = 0.014) and biological therapy (p = 0.012).* ***Conclusion:*** *Our study showed that a combination of factors contributed to compromise bone health in patients with JIA. Fragility fractures were rare and occurring mainly in adulthood. An adequate control of disease activity, proper management of treatment, adequate calcium and vitamin D intake, as well as regular physical activity, may contribute to preserve bone health in those patients.*

Key words: *Juvenile idiopathic arthritis, osteoporosis, bone mineral density*

Introduction

Bone fragility is more prevalent among children who have chronic rheumatic diseases, such as juvenile idiopathic arthritis (JIA) [1]. JIA is one of the most common pediatric rheumatic conditions affecting joints, with estimated global incidence rates of 1 per 1000 person-years [2]. JIA includes a heterogeneous group of pediatric arthritic presentations that can be classified into seven different subtypes based on the International League of Associations for Rheumatology (ILAR) criteria [3-4].

It has been proven that patients with JIA may present with several complications among them low bone mass, which is now a well-recognized serious long-term complication of this disease and is associated with considerable morbidity and sometimes an impaired quality of life [1]. In fact, patients with JIA acquire increased life-long fracture risk when the acquisition of peak bone mass (PBM) is interrupted by their underlying disease or treatment [4]. In literature, up to 50% of adults with a history of JIA suffer from a decrease of bone mass [5].

In this study, we aimed to evaluate the frequency of low bone mass and fragility fracture in patients with polyarticular and oligoarticular JIA, and to identify risk factors for bone fragility.

Materials and Methods

This was a retrospective study conducted on 26 patients with JIA who met the ILAR criteria. Socio-

demographic, clinical, biological and functional data were collected by consulting patient medical records. Patients were divided into two groups according to their age: **Group 1** – patients aged over 16 years old; **Group 2** – patients aged under 16 years old.

The disease activity was assessed with: Disease activity score (DAS28) in group 1 and Juvenile Arthritis disease activity score (JADAS 10) in group 2.

Bone mineral density (BMD) was measured using the same dual-energy X-ray absorptiometry (DXA) equipment, at three different sites according to the age of patients: lumbar spine and hip in group 1 and the whole body in group 2. BMD was expressed as a ratio of bone mass measured in grams of calcium to the exposed bone surface area measured in square centimeters (g/cm^2) [6, 7]. DXA results were expressed based on Z-score which represents the difference between the measurement corresponding to the patient and the average value reported at the standard deviation σ of the reference population distribution. The reference value was given based on the subject age, given the variations observed in the reference populations. A Z-score of -2.0 or lower defined “low bone mass” and a Z-score above -2.0 was “normal bone mass” [10].

The data were entered and analyzed using SPSS version 11.5 software.

Our study included a descriptive and analytic part. We calculated means and standard deviations and determined the range (extreme values = minimum and maximum) for the quantitative variables. The correlation between two quantitative variables was assessed with the Pearson correlation test. The correlation between two qualitative variables was assessed with Chi-square test. The correlation between a qualitative and quantitative variable was assessed with the Mann-Whitney U test. A p value cut-off was fixed at 0.05 for significance for all statistic tests.

Results

The study included 26 patients with JIA, 20 of whom were female (74%) and 6 were male (22%). The mean age was 28.2 years (7-58 years). Eleven patients were aged under 16 years old while 15 were aged over 16 years old. The mean weight was 62.1 kg (17-82 kg). The mean height of the patients was 163.91 cm (118-178 cm). The mean body mass index (BMI) was 22.65 kg/m^2 (12.20-28.04 kg/m^2).

The distribution of the different subtypes of JIA was as follow: polyarticular JIA – 74% (n = 20), and oligoarticular JIA – 22% (n = 6).

The patients were illiterate or had primary, secondary, and university level education in 15%, 15%, 30%, and 30% of cases, respectively. Twenty patients (74%) had stunted growth and were underweight.

Sixteen patients (59%) practiced regular physical activity. While ten patients (37%) involved little physical activity.

The average age of onset of the JIA was 7.88 years (1-16 years). The mean duration of disease progression at the moment of data collect was 20.23 years (2-54 years). The disease was associated with positive ANA in 14 patients (52%). Rheumatoid factor and anti-citrullinated proteins antibodies were positive in 9 patients (33%) and 5 patients (18%), respectively.

The mean DAS28 vs score was 3.23 in group 1 and the mean JADAS10 score was 2.20 (0-10.31) in group 2.

The functional impact of the disease was assessed using the Health Assessment Questionnaire (HAQ) score in group 1 patients and the C-HAQ (Child-HAQ) score in group 2 patients with an average value of 1.34 (0-2.56) and 0.68 (0-0.98), respectively. Twenty patients (71%) received oral corticosteroid therapy with an average dosage of 7.90 mg/day (0-40). Eight patients (30%) received corticosteroid pulses and fourteen patients (52%) received intra-articular injections. Eighteen patients (67%) were treated with NSAIDs. The anti-rheumatic treatments used were as follows: 23 patients (85%) used methotrexate for an average duration of 15.46 years (0-52), thirteen patients (48%) used biological treatment Etanercept (44%), Adalimumab (4%), and Rituximab (4%). The main characteristics of the disease were summarized in Table 1.

In our study, low bone mass was noted in 10 patients (37%). Only two patients presented a fragility fracture in adulthood represented by a hip fracture following low-energy trauma at the age of 46 and 53 years, respectively. The two patients underwent a surgical treatment for Total Hip Prosthesis.

Regarding treatment, none of the patients in our series received anti-osteoporotic treatment.

Relationship between low bone mineral density and the sociodemographic and biometric characteristics of patients:

A statistically significant association was found between low bone mass and the age of onset (p = 0.041), weight (p = 0.03), and physical activity (p = 0.05) among patients aged over 16 years. However, among patients aged under 16, low bone mass was significantly correlated to weight (p = 0.020) and to BMI (p = 0.028) (Table 2).

Table 1. Main characteristics of the disease

	N	Minimum	Maximum	Average	Standard deviation
Age of onset (years)	26	1	16	7.88	4.520
Mean disease duration (years)	26	2	54	20.23	13.006
JADAS10	19	0.00	10.31	2.2027	2.45802
CHAQ	13	0.00	3.00	.6823	1.02351
Dose of corticosteroid (mg)	26	0.0	40.0	7.904	8.1142
Duration of corticosteroid use (months)	26	0.00	30.00	6.9423	7.87347
Calcium intake (mg)	26	0	1000	580.77	360.021
Duration of méthotrexate use	24	0	52	15.46	12.169
Duration of biologic treatment use.	14	0	14	5.57	4.183

N: number, JADAS: Juvenile Arthritis disease activity score, CHAQ: Child Health assessment Questionnaire

Table 2. The relationship between low bone mineral density and the sociodemographic and biometric characteristics of patients

Patient sociodemographic and biometric characteristics	Group 1	Group 2
Age	0.231	0.130
Age of onset	0.041	0.163
Puberty age	0.067	0.222
Weight	0.030	0.020
Height	0.210	0.321
BMI	0.317	0.028
Physical activity	0.050	0.142

BMI: Body mass index

Relationship between low bone mineral mass and disease characteristics

Low bone mass was significantly associated with disease duration (p = 0.021) and functional impact of the disease as assessed by the HAQ score (p = 0.018) in patients aged over 16 years. A statistically significant association was found between low bone mineral density and disease duration (p = 0.045), ANA positivity (p = 0.050), and disease activity assessed using JADAS10 (p = 0.019) in patients aged under 16 years (Table 3).

Table 3. Relation between low bone mass and disease characteristic

Disease characteristics	Group 1	Group 2
JIA form	0.990	0.329
Disease duration	0.021	0.045
ACPA positivity	0.480	0.167
ANA positivity	0.111	0.050
RF positivity	0.512	0.356
DAS28ESR	0.261	0.019
HAQ	0.018	0.199

JIA: juvenile idiopathic arthritis, ACPA: anti-citrullinated protein antibodies, ANA: antinuclear antibodies, RF: rheumatoid factor, DAS28: Disease activity score 28 joints, HAQ: health assessment questionnaire

Relationship between bone fragility and anti-rheumatic treatments

The presence of low bone mineral density in patients aged more than 16 was significantly associated with oral corticosteroid therapy intake and the use of biologic treatment (p = 0.014 and 0.012, respectively). In the group of patients aged under 16 years, both oral corticosteroid therapy intake and the mean corticosteroid dose were significantly associated with low bone density (p = 0.043) (Table 4).

Table 4. Relationship between low bone mass and anti-rheumatic treatment received

Treatment	Group1	Group2
Oral corticosteroid intake	0.014	0.034
Mean corticosteroid dose	0.121	0.026
Average duration of corticosteroid therapy	0.190	0.382
Corticosteroid bolus	0.116	0.134
Intra-articular corticosteroid injection	0.226	0.356
NSAIDs	0.532	0.289
Methotrexate	0.333	0.149
Average duration of methotrexate use	0.274	0.306
Biologic treatment	0.012	0.043
Average duration of biologic use	0.403	0.313

NSAIDs: Non-steroidal anti-inflammatory drugs

Discussion

In our study, the frequency of low bone mineral density was 41% in children with JIA and 68% in adult patients with JIA. Fragility fracture was reported in two cases.

It has been demonstrated that all types of JIA can present with decreased bone mineral density. However, this complication is more frequently encountered in systemic and polyarticular forms of JIA [11, 12, 13].

In a randomized controlled study conducted by Stagi et al., it was shown that the 245 included patients had lower bone mineral density compared to healthy control subjects [14].

Furthermore, two other studies have demonstrated that bone mineral density in patients with JIA was low at all measurement sites [12-15]. Thornton et al. found that adult women with JIA had a significantly lower mean Z score than women in the general population ($P < 0.02$) [16], which is consistent with the results of our study. Several risk factors for bone fragility have been identified in patients with JIA, including systemic inflammation, mainly glucocorticoid use, reduced physical activity, muscle dysfunction, delayed puberty, and inadequate vitamin and calcium intake [3, 4,17,18].

In our study, the presence of low bone density was significantly associated with disease duration and disease activity measured using JADAS10 and DAS28 ESR, which is consistent with the results of other studies. In fact, the main determinant of bone loss in JIA is the underlying inflammatory process [19]. Nakhla and al. reported eight cases of vertebral fractures in three children with JIA who had never been treated with steroids [19]. Indeed, synovitis in arthritis is a source of inflammatory cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor alpha (TNF-α), receptor activator of nuclear factor kappa-B ligand (RANKL), and IL-17, creating an environment conducive to accelerated bone remodeling and reduced bone mineral density [1, 19]. Pereira et al. suggested that low bone mass in patients with JIA was more marked at the femoral neck and radius compared to the lumbar vertebral site [21], which is consistent with the results of our study where the fracture complications were femoral neck fractures in both cases.

Low bone mass and treatment of JIA

Low-dose methotrexate, commonly used in chronic rheumatic diseases, has not been associated with an increased risk of low bone mass, which is consistent with the results of our study. In our study, 13 patients were treated by biologic treatment. A significant association was found between the use of biologic treatment and low bone mass in adult patients with JIA.

Brabnikova Maresova et al. reported that after one year of anti-TNF treatment (infliximab, etanercept, or adalimumab), 19 young adults (aged 18 to 33 years) with active JIA showed a significant increase in BMD at the lumbar spine and whole body sites, as well as an increase in serum levels of type I procollagen N-terminal propeptide (PINP) (a marker of bone formation) [22].

Another study was conducted on 20 children with polyarticular JIA, aged 5.2 to 11 years, who were treated with Etanercept for one year. The patient's bone status was determined by broadband ultrasound attenuation (BUA) at the left heel. A significant increase in BUA ($p < 0.001$) and Z score ($p < 0.002$) was observed in those whose arthritis responded to Etanercept (15/20), but not in non-responders [23].

Low bone mass and delayed puberty

In our study, no association between the age of puberty and low bone density was found. Eight patients had a delayed puberty. Delayed puberty is often reported in children with chronic diseases, including JIA [24], which is consistent with the results of our study. A greater delay in puberty is correlated with higher disease activity [25, 26]. Indeed, bone acquisition during childhood and adolescence determines up to 90% of peak bone mass [27]. Therefore, puberty is crucial for the acquisition of peak bone mass [25]. Therefore, delayed puberty is considered an important factor in reducing bone density and decreasing muscle mass [26, 27].

Low bone mass and reduced physical activity

In our study, a significant correlation between physical activity and osteoporosis in adult patients with JIA was found. A Moroccan study including 33 children with JIA (aged 4-16 years) showed a significant correlation between BMD and lean tissue mass, but no correlation between BMD and adipose tissue mass [28]. However, children with chronic rheumatic diseases often have high adipose tissue mass and body mass index (BMI), which increases their risk of fractures [29].

Our study has some limitations: the retrospective nature, the non-homogeneous population, the small sample size and the measurement at different time intervals of the BMD.

In the present study we highlighted the frequency of low bone mineral density in patients with JIA, which is a subject that has not been extensively studied.

Recognizing bone fragility as an important comorbidity in the pediatric population with JIA and subsequently implementing an adequate strategy for managing or preventing osteoporosis would optimize the care of these patients and improve their quality of life and help to reduce the economic burden of this disease and its complications [30]

Conclusion

Several factors contribute to the impairment of bone health and the decrease in bone mineral density in patients with JIA. Bone comorbidities expose these patients to fragility fractures in both childhood and adulthood.

Low bone mineral density and even fragility fractures may go unnoticed, highlighting the importance of screening for low bone density in these patients. Proper disease activity control, appropriate treatment management, adequate calcium and vitamin D supplementation, as well as regular physical activity, all contribute to preserving bone health in patients with JIA.

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