RESEARCH ARTICLE

Evaluation of Bone Mineral Density in Juvenile Systemic Lupus Erythematosus

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Abstract

Objectives: The present study aimed to determine the prevalence of low bone mineral density (BMD) and low bone mineral content (BMC) as chronic complications of juvenile systemic lupus erythematosus (JSLE) and identify the associated variables and patient characteristics to investigate the relationship between BMD and influential factors.

Methods: This cross-sectional study enrolled 54 patients with JSLE, including 38 females and 16 males. The BMD and BMC were assessed by dual-energy X-ray absorptiometry in the hip (femoral neck) and the lumbar spine. Low BMD was considered a Z-score < -2. The study investigated the association of BMC and Z-score with the current daily dose of corticosteroids, the daily dose of corticosteroids at disease onset, the duration of disease, the duration of steroid treatment, the time from the onset of symptoms to diagnosis, and renal involvement.

Results: The prevalence of low BMD in the lumbar spine and the femoral neck was 14.8% and 18.5%, respectively; the reduction of BMD was more significant in the femoral neck compared to the lumbar spine. Osteoporosis was detected in one patient. The multiple linear regression analysis found a significant association between a higher daily corticosteroid dose and lower BMC of the femoral neck and the lumbar spine. In addition, patients receiving higher doses of corticosteroids at disease onset showed better follow-up bone mineral densitometry results.

Conclusion: Based on the findings of this study, JSLE more affects the femoral neck than the lumbar spine. Patients receiving a more robust treatment with higher doses of corticosteroids at disease onset (to control the inflammatory processes) showed better spinal BMC results. A higher dose of daily corticosteroid treatment during assessment was identified as a risk factor for low BMD.

Level of evidence: IV

Keywords: Bone mineral content, Bone mineral density, Children, Juvenile systemic lupus erythematous, SLE

Introduction

Juvenile systemic lupus erythematosus (JSLE) as a chronic autoimmune disorder can be recognized by multisystem inflammation, as well as circulating autoantibodies to deal with self-antigens. The JSLE can affect almost all body organs.[1] The JSLE treatment is planned according to the patient's condition, tolerance, and specific disease manifestations. Corticosteroids are the mainstay of treatment for essential manifestations of JSLE.[1-3] However, the side effects often reduce the patient's tolerance. Some consequences of corticosteroid therapy are growth disorders, striae, weight gain, cataracts, hyperglycemia, acne development, hypertension, avascular necrosis, and osteoporosis.[3]

Osteoporosis, as one of the morbidities of JSLE, affects children's lives in the long term and is linked to a higher risk of low bone density in adults.[4,5] The diagnosis of osteoporosis in children is based on two criteria: (1) having a specific fracture history (e.g., one or more fractures in the lower limb or the vertebral column and two or more fractures in the upper limb); and (2) having bone mineral

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density (BMD) below -2 standard deviations (SDs), adjusted for age, sex, and body size.[6]

Osteoporosis in children and adolescents is divided into primary and secondary types. The primary type occurs due to heritable bone fragility due to intrinsic skeletal defects. Secondary osteoporosis happens as a result of systemic disease (such as inflammatory disorders, hematological and oncological disorders, renal disease, immobility, or muscle impairment) or medications (such as corticosteroids).[7]

Bone health monitoring is an important aspect of JSLE in follow-ups. Dual-energy X-ray absorptiometry (DEXA) is the standard and most suitable method for mineralized bone mass investigations in children. The DEXA is often performed at the spine and hip. It has low radiation intake (mrem^3), high speed, and accuracy and provides an areal mass density per area in units of g/cm2. Performing DEXA in chronic rheumatologic diseases such as JSLE and juvenile rheumatoid arthritis and patients who have been treated with steroids helps early diagnosis of osteopenia to prevent the progression of it and the possibility of fractures by starting therapeutic interventions.

Based on the International Society for Clinical Densitometry, low areal BMD or low bone mineral content (BMC) refers to a Z-score < -2.[8] Previous studies show that several factors can influence BMD in JSLE patients. These factors include high-dose corticosteroid therapy, duration of corticosteroid therapy, disease duration, renal involvement, body mass index (BMI), life habits, pubertal status, and vitamin D levels.[9-12] The present study aimed to determine the osteoporosis prevalence and low BMD in Iranian children diagnosed with JSLE and identified risk factors associated with low BMD.

Materials and Methods

All children with JSLE aged < 18 years, who were referred to the Rheumatology Department of the Children's Medical Center Hospital in Tehran, Iran, during 2016-2018, underwent BMD analysis by DEXA of the lumbar vertebrae and the femoral neck. All patients met the classification criteria of Systemic Lupus Erythematosus (SLE) International Collaborating Clinics (SLICC).[13] The Ethics Committee of Tehran University of Medical Sciences confirmed the research (IR.TUMS.MEDICINE.REC.1396.3264).

The medical information of the patients was collected, including age, sex, disease duration, duration of corticosteroid use, a daily dose of corticosteroids, corticosteroid dose at disease onset (primary dose), the interval between the onset of symptoms and diagnosis, renal involvement, and BMI. The patients' BMD was statistically analyzed, and the prevalence of decreased bone density was determined in this study.

All patients had received calcium supplements and vitamin D. Bisphosphonate was administered after bone densitometry if needed.

Statistical descriptive tests were performed in SPSS (version 25) for data analysis. First, descriptive analysis was performed for all variables (age, sex, disease duration, duration of corticosteroid use, a daily dose of corticosteroids, corticosteroid dose at disease onset (primary dose), the interval between the onset of symptoms and diagnosis, renal involvement, and BMI. The results of the DEXA method, including the femoral neck BMD, BMC, Z score, and lumbar spine BMD, BMC, Z score, were subjected to descriptive analysis. Low BMD prevalence (Z score<-2) was calculated in the femoral neck and lumbar spine. The relationship between possible influential factors (e.g., age, sex, disease duration, duration of corticosteroid use, a daily dose of corticosteroids, corticosteroid dose at disease onset (primary dose), the interval between the onset of symptoms and diagnosis, renal involvement, and BMI) with BMC and Z-score was investigated. A linear regression analysis was performed for data analysis. A *P*-value < 0.2 was regarded significant. Variables with a *P*-value < 0.2 were entered in a multiple linear regression analysis, and a *P*-value ≤ 0.05 was considered statistically significant.

Results

Fifty-four pediatrics SLE patients were studied. Table 1 presents the demographic characteristics of SLE patients [Table 1]. Table 2 shows the results of BMD according to DEXA in our patients [Table 2]. The mean BMD and BMC of the femoral neck were 0.71 and 17.7, respectively. Additionally, the mean Z-score of the femoral neck was -1.3, and the prevalence of low BMD in the femoral neck was estimated at 18.5%. Based on the obtained results, the mean BMD of the spine was 0.65, and the mean corresponding BMC was 26.3. The mean Z-score of the lumbar vertebrae was also -0.4. Moreover, the prevalence of low BMD was estimated at 14.8%.

One (1.8%) patient had a fracture in the lumbar spine and met the osteoporosis criteria. The association of possible contributing factors with BMC and Z-score was evaluated in the patients using multiple linear regression analysis [Table 3]. Factors such as disease duration and corticosteroid treatment were significantly correlated in the primary analysis. However, when included in the multiple linear regression model, they were not considered independent contributing factors. Furthermore, renal involvement was not significantly associated with BMC or Z-score.

Overall, older patients and those with higher BMI had higher spinal BMC results. Patients receiving a higher dose of corticosteroids at disease onset had better spinal BMC results. A higher daily dose of corticosteroids during BMD decreased spinal BMC and Z-score. There was a borderline association between low hip BMC and the daily dose of corticosteroid treatment (P=0.08). According to the results, patients with higher BMI and older patients had higher hip BMC (P=0.05 and P<0.001, respectively).

Treatment with corticosteroids was identified as a risk factor for low BMD. The duration of disease, the duration of corticosteroid treatment, the time from the onset of symptoms to diagnosis, and renal involvement were not related to BMD in JSLE patients [Table 3]. All patients in the study received calcium and vitamin D supplements. This variable was excluded from the analysis because all patients were taking vitamin D and calcium supplements.

Table 1. Demographics and characteristics of systemic lupus erythematosus patients (N=54)

Sex: Female / Male	38 patients/16 patients
Age (year)	11.4 (±3.08)
Renal involvement	18.5% involvement
Disease duration (months)	30 (±30.7)
Duration of corticosteroid use (months)	32.4 (±31.04)
Corticosteroid daily dose (mg/kg/day)	0.17 (±0.16) mg/kg/day
Corticosteroid dose at the onset of disease (initial dose) (mg/kg/ day)	0.63 (±0.39) mg/kg/day
Interval between onset of symptoms and diagnosis (months)	5.09 (±6.8)
Body mass index	19.2 (±5.7)

Table 2. Results of bone mineral densitometry by DEXA

Variable	Spine	Hip
BMD (gr/cm2)	0.65 (±0.18)	0.71 (±0.17)
BMC (gr)	26.3 (±13.07)	17.7 (±9.4)
Z score	-0.4 (±1.7)	-1.3 (±0.97)
Low BMD prevalence (*Z* score<-2)	14.8%	18.5%

BMC: bone mineral content; BMD: bone mineral density; DEXA: dual-energy X-ray absorptiometry

Table 3. Relationship between disease variables and BMC, Z score

Variable	**Spine BMC**	**Spine Z score**	**Hip BMC**	**Hip Z score**
Age	direct relation (*P*<0.001)	No relation	direct relation (*P*<0.001)	No relation
Duration of disease	No relation	No relation	No relation	No relation
Duration of steroid treatment	No relation	No relation	No relation	No relation
Daily dose of steroid at BMD time	inverse relation (*P*<0.001)	inverse relation (*P*=0.02)	Inverse relation (*P*=0.008)	No relation
Daily dose of steroids at onset of disease	direct relation (*P*=0.05)	No relation	No relation	No relation
Renal involvement	No relation	No relation	No relation	No relation
Interval between the onset of symptoms and the diagnosis	No relation	No relation	No relation	No relation
body mass index	direct relation (*P*=0.001)	No relation	direct relation (*P*=0.05)	No relation

BMC: bone mineral content; BMD: bone mineral density

Discussion

We evaluated the prevalence of low BMD and its risk factors in Iranian children diagnosed with JSLE. In this study, the mean Z-score was lower for examining the femoral neck compared to the lumbar vertebrae. Additionally, the prevalence of low BMD was higher in the femur (18.5%) than in the lumbar vertebrae (14.8%). Compared to a study on healthy Iranian children, the prevalence of low bone mass was higher in the femoral neck in JSLE patients (18%) compared to healthy children (10%). In comparison, it was lower in the lumbar region in the patients than in healthy children (14%).[14] These results may be attributed to close follow-up, inflammation control, and calcium and vitamin D supplements intake in JSLE patients. The femoral neck was more affected by JSLE in this study, contrasting the results of other studies.[15,16]

Patients with JSLE have several risk factors for osteoporosis, including biochemical abnormalities, active inflammation, low physical activity due to musculoskeletal involvement, and corticosteroid use.[9-12] Low physical activity is a critical factor for decreased BMD in rheumatologic disorders. In our previous study, more than 90% of patients had musculoskeletal involvement.[17] In glucocorticoid-related osteoporosis, there is a decrease in bone turnover and a disproportionate decline in the formation of bone in the bone resorption phase.[18] Steroids affect bone metabolism through suppression of osteoblast generation and function, reduced lifespan of the osteoblast, and stimulating osteoclast generation.[19]

Active inflammation and corticosteroid use affect bone health.[9,20-23] Low BMD in recently diagnosed JSLE patients indicates systemic inflammation has more critical detrimental effects on BMD than corticosteroid therapy during systemic disease.[23] Vitamin D deficiency can intensify such problems in bone metabolism due to a lack of sun exposure and diminished physical activity because of SLE.[20-,24] In contrast, a previous study in Iran[15] showed that a higher dose of corticosteroid therapy during BMD had an inverse relationship with spinal BMC, spinal Z-score, and hip BMC. The reduction in the BMC of patients receiving a higher dose of steroids at the time of DEXA can be due to the active inflammatory process during JSLE or the destructive effects of steroids on the bone.

Statistical analysis revealed that patients who received higher doses of corticosteroids at disease onset had higher spinal BMC during BMD examination. Therefore, patients who received more potent treatments to control inflammatory processes at disease onset had better spinal BMC results. This finding supports the destructive effects of the inflammatory nature of JSLE on bone metabolism. It shows that better control and more substantial treatment at disease onset can improve the patient's bone density in the future.

Based on the obtained results, the presence or absence of renal involvement did not affect the patient's BMD outcomes. Some studies describe a lack of vitamin D supplementation as a risk factor for low BMD.[24] Prophylactic treatment with bisphosphonates has been suggested to be effective in improving bone health in JSLE patients receiving steroid treatment.[25] In a longitudinal study of 250 SLE patients, Garelick et al. reported that glucocorticoid treatment did not significantly affect bone fractures during 28 years.[26] However, the cumulative steroid dose (and disease duration) had a negative effect on bone health and densitometry.[27,28] It seems that corticosteroids alone do not affect BMD in SLE patients, and other factors such as single nucleotide polymorphism and serum nuclear factor κ B ligand (RANKL)/osteoprotegerin (OPG) ratio may be possible predictors of decreased BMD in SLE.[29] Recent studies demonstrate higher serum RANKL and lower OPG and 25(OH)VitD3 concentration in children with JSLE compared to healthy children.[30]

Long disease duration and higher activity levels are other predictors indicating the multifactorial nature of osteoporosis in SLE.

There are a few limitations in this study. The first one is that our study did not evaluate disease activity scores. Delayed puberty is common in juvenile SLE due to endocrine disorders and corticosteroid therapy. Endocrine disorders were serially assessed in our patients; however, our study did not consider the evaluation of the puberty stage in children older than 11 years.

Conclusion

Although corticosteroids are considered a significant risk factor for reducing BMD in various diseases, this research showed that the disease activity and its inflammatory nature play a more critical role in reducing BMD and that better disease control can prevent its destructive effects. Therefore, in addition to reducing the daily dose of corticosteroids as soon as possible, more robust treatments at onset of the disease are recommended to control the disease.

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