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Bone mineral density in children with systemic lupus erythematosus and juvenile rheumatoid arthritis

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BACKGROUND: Although there is increasing interest in bone metabolism in patients with rheumatic disorders, few data exist on bone mineral density (BMD) in children with rheumatic disorders or on the association of BMD with disease-related variables. We determined BMD in Iranian children with systemic lupus erythematosus (SLE) and juvenile rheumatoid arthritis (JRA) to evaluate the relationship between disease-related variables and BMD.
PATIENTS AND METHODS: Twenty patients (13 girls and 7 boys) with SLE (n=15) and JRA (n=5) with a mean age of 13.10±3.29 years (range, 6-17 years), attending a pediatric rheumatology clinic and 20 healthy controls (matched for age and sex with each patient) were enrolled in a cross-sectional study between 2001 and 2003. BMD (g/cm^2) of the femoral neck (BMD-F) and lumbar vertebrae (BMD-L) were measured by dual energy X-ray absorptiometry (DEXA). The correlation between BMD and cumulative dose of steroids, daily dose of steroid, disease duration, disease activity, height, weight, and age was investigated.
RESULTS: BMD in the patients (BMD-F=0.72±0.15, BMD-L=0.70±0.19) was significantly lower than controls (BMD-F=0.95±0.17, BMD-L=0.98±0.20, P<0.001). The severity of decreased BMD was more prominent in lumbar vertebrae than the femoral neck (P= 0.04). None of the variables were consistently related to a decrease in BMD.
CONCLUSION: BMD was significantly lower in patients compared with controls. It was more prominent in lumbar vertebrae (trabecular bone). Although cumulative dose of steroids and disease duration appeared to have some influence on BMD, none were independently correlated with BMD.

Osteoporosis is characterized by loss of both bone mass and microarchitectural integrity, resulting in an increased risk of fractures with associated morbidity and mortality.[1] Increasing interest has focused on bone metabolism in patients with rheumatic disorders. In adults with rheumatic disorders a number of risk factors for development of osteoporosis have been described, including disease duration and severity, diet, level of physical activity, past corticosteroid treatment, and reduced exposure to sunlight due to photosensitivity.[2,3] Only a few such studies have addressed childhood-onset rheumatic disorders, particularly systemic lupus erythematosus (SLE) and juvenile rheumatoid arthritis (JRA).[4-8]

Dual-energy X-ray absorptiometry (DEXA) has become a standard technique for the measurement of bone mineral density (BMD) of the lumbar spine, femur, forearm, and whole body, due to its low radiation dosage, ease of use, rapidity, accuracy, precision, and reproducibility under controlled circumstances.[9,10] We studied BMD by DEXA in a cohort of Iranian children and adolescents with SLE and JRA and compared it with that in healthy age- and sex- matched controls. We also investigated the relationship between several disease-related variables and BMD.

METHODS

Twenty patients (13 girls and 7 boys) with SLE (15) and JRA (5) with mean age of 13.10±3.29 years (range, 6-17 years), attending the pediatric rheumatology clinic of Motahari clinic at Shiraz, Iran, were enrolled in a cross-sectional study between 2001 and 2003. The inclusion criteria were disease onset before the age of 17, a minimum disease duration of 6 months, and the presence of

at least four of the American College of Rheumatology (ACR) criteria for classification of SLE.[11] In 5 patients the diagnosis of JRA was based on the ACR criteria for diagnosis of JRA.[12] At the time of this study all patients had been receiving steroids, calcium and vitamin D during the past 6 months. Disease duration was defined as the period of time from the diagnosis of disease based on the appearance of initial clinical symptoms clearly attributable to the disease until the time of the study. Twenty healthy controls (matched for age and sex with each patient) were selected randomly from the schools located in Shiraz. All participants were ethnic Iranians and ate typical Iranian food. Informed consent was obtained from the patients, controls, and their parents. This study was approved by our university ethics committee.

A clinical examination was performed on all of the patients and controls. A questionnaire was completed based on the information obtained from the patients' medical records and by interviewing all of the participants or their parents. Collected data included age, sex, height, weight, food and nutrient intake, cumulative corticosteroid dose, mean daily corticosteroid dose at the time of study, and disease duration. A self-reported health status questionnaire of physical activity and pain perception was also completed by the patients. In patients with SLE and JRA, disease activity was measured by the SLE Disease Activity Index (SLEDAI)[13] and ACR core set.[14]

BMD (g/cm^2) of the femoral neck (BMD-F) and the second through fourth lumbar vertebrae (BMD-L) were measured with DEXA equipment (Lunar DPX-IQ, USA). At present, Iranian reference values for bone mass measurement in children are not available. We therefore chose to compare BMD of our patients with the control group.

The Wilcoxon Signed Ranks Test was used to compare the BMD of patients and controls and to compare BMD-F with BMD-L. Correlation between reduction in BMD (BMD in controls – BMD in patients) at femoral neck and lumbar vertebrae and disease duration, amount of steroid, disease activity, and weight and height of patients, was determined by Spearman's method, and then potential risk factors were entered into multiple linear regression analysis. Data are expressed as mean±SD unless otherwise stated. *P*-values less than or equal to 0.05 were considered significant. All statistical analysis was performed using SPSS software.

RESULTS

The study population consisted of 15 patients with childhood-onset SLE and 5 patients with JRA, and 20 healthy controls, who were individually matched for age and sex (Table 1). Mean height and weight of patients was significantly lower than controls. BMD of the patients (BMD-F=0.72±0.15 g/cm^2, BMD-L=0.70±0.19 g/cm^2) was significantly lower than controls (BMD-F=0.95±0.17 g/cm^2, BMD-L= 0.98±0.20 g/cm^2, $P<0.001$). The severity of decreased BMD was more prominent in lumbar vertebrae than the femoral neck ($P= 0.04$). The mean disease activity index for SLE patients (SLEDAI) was 9±6.98 and for JRA patients was 93.8±55.47 at time of examination.

On the basis of SLEDAI scores, five patients had mild disease activity (SLEDAI=1-5), five patients had moderate activity (SLEDAI=6-10), four patients had high activity (SLEDAI=11-19), and one patient had very high activity (SLEDA= or >20) (Table 2).[15] Active

Table 1. Characteristics of patients and healthy controls.

Characteristic	Patients (n=20)	Controls (n=20)	*P* value
Female/male	13/7	13/7	>0.05
Age, years	13.10±3.29	13.10±3.29	>0.05
Weight, kg	38.35±15.63	49.2±14.37	<0.01
Height, cm	143±17.59	156.5±15.09	<0.01
Disease duration, years	2.65±2.18	-	NA
Cumulative dose of steroids, mg/kg	273±379.40	-	NA
Daily corticosteroid dose, mg	6.62±3.17	-	NA
BMD, Spine, g/cm^2	0.70±0.19	0.98±0.20	<0.001
BMD, Femoral neck, g/cm^2	0.72±0.15	0.95±0.17	<0.001

NA: Not Applicable

JRA was defined in all of our JRA patients as their score was greater than 20 based on ACR core set.[14] There was no relationship between disease activity and BMD.

Potential risk factors for low BMD were cumulative dose of steroid, disease duration, disease activity, daily dose of steroid at the time of BMD evaluation, height, weight, and age. Although cumulative dose of steroids and disease duration were considered correlated (Spearman's method) with the decrease in BMD, using multiple linear regression analysis, this association did not reach significance. Therefore no disease-related variables were identified as independent predictors of BMD.

DISCUSSION

The relationship between chronic childhood rheumatic disorders and BMD has been investigated in a relatively small number of studies.[4-8] Our results confirm that decreased bone density is a common problem in these patients. To our knowledge, the present study is the first to report BMD in Iranian children with rheumatic disorders and to describe the risk factors associated with decreased bone density in this population.

In the current study we found no factors that were consistently related to the decrease in BMD. Although several researchers investigated the role of such factors as disease activity, disease duration, and corticosteroid use in the pathogenesis of osteoporosis in adult patients with rheumatic disorders,[2,3,16] similar investigations have led to still more controversial results in children.

Alsufyani et al[5] in a study conducted on 36 child patients (25 SLE) found a reduced bone density in patients with rheumatic disorders but no factors were associated with this decrease in BMD. We reached the same results. Head et al[7] reported normal BMD in African-American children with JRA who had not previously been treated with corticosteroids. A positive correlation was suggested between severity of osteopenia and total amount of steroid used by patients with JRA in the course of their illness,[17] also osteopenia was more common in more prolonged JRA.[18]

Lilleby et al[6] in a survey carried out on 70 Norwegian children with SLE and 70 healthy controls found cumulative dose of corticosteroids to be an important variable in explaining decreased bone mass, also male sex was related to the decrease in lumbar spine bone mass. Comparing the values of BMD, it is notable that values in our children are significantly lower compared with Norwegian children, probably based on nutritional and ethnic variations (Table 3). Both studies are comparable regarding age range, corticosteroid dose, and DEXA equipment.

Table 2. BMD of femoral neck and spine, disease activity index, and Tanner stage of children with systemic lupus erythematosus and juvenile rheumatoid arthritis.

	Femoral neck (g/cm²)	Spine (g/cm²)	Disease activity index	Tanner stage
SLE patients				
1	0.653	0.602	1	IV
2	0.796	0.801	1	IV
3	1.015	0.953	1	IV
4	0.986	1.063	1	III
5	0.723	0.844	2	IV
6	0.541	0.574	8	I
7	0.694	0.588	8	III
8	0.896	0.893	8	IV
9	0.858	1.037	8	III
10	0.77	0.604	10	II
11	0.753	0.714	15	III
12	0.792	0.827	15	III
13	0.715	0.693	18	I
14	0.833	0.856	19	III
15	0.733	0.699	20	II
JRA patients				
1	0.568	0.492	21	I
2	0.593	0.581	63	II
3	0.709	0.452	89	I
4	0.525	0.44	139	III
5	0.423	0.375	157	I

The impact of puberty on BMD is described in healthy boys and girls.[19,20] De Schepper et al[20] proposed that the total increase in BMD during puberty was higher than that during the proceeding 10 years, representing a 40% increase in BMD during puberty. They also reported that pubertal stage IV is responsible for the most important increase in lumbar spine BMD in both sexes. Van Coeverden et al[21] reported an increase of up to 60% in bone mass at all skeletal sites between Tanner stages II and IV. Our results do not support the association between BMD and pubertal stage in children with SLE and JRA; similar results were obtained in another study carried out on children with SLE.[5]

It is perhaps interesting that we found no consistent relationship between BMD and disease related variables; the most probable explanation is that the relatively small number of patients provided inadequate power

Table 3. BMD comparison between Iranian and Norwegian children.

BMD, g/cm²	Patients			Controls		
	Iranian	Norwegian	*P* value	Iranian	Norwegian	*P* value
Spine	0.70±0.19	1.03±0.20	< 0.001	0.98±0.20	1.16±0.19	0.005
Femoral neck	0.72±0.15	0.95±0.18	< 0.001	0.95±0.17	1.05±0.16	0.06

to reveal the association of any individual factor with bone density.

It is postulated that obtaining the bone density value without some means of comparing it to a reference or normal range is of limited use.[10] Z scores are values that relate bone density scores to normal values matched for age, sex, and ethnicity.[5] According to the literature,[22] a Z score derived from the manufacturer's normal data are probably not appropriate for use in other populations. As no normative data were available for Iranian children to match for ethnicity, we did not calculate Z scores in our study. We showed that decreased BMD in chronic rheumatologic patients is more prominent in trabecular bones such as vertebra. The same results were achieved by other researchers.[23]

In conclusion, we observed lower bone mass in the lumbar spine and femoral neck in patients with childhood-onset SLE and JRA compared with healthy controls. These results should alert clinicians to the potentially high risk for the development of osteoporosis later in life in these patients. It is important to highlight that whereas weight and height may normalize over time with disease control, impaired peak bone mass may never be corrected.[24] Therefore, efforts should be made to reduce steroid to the lowest possible maintenance dose, and to stimulate bone formation in prepubertal patients, encouraging a calcium-rich diet, and using vitamin D supplements.[25] Besides, chronically ill children should be advised to engage in weight-bearing physical activity since decreased physical activity is reported to negatively affect bone mass accrual.[26]

Considering the limited sample size in the current study and the flaws that may accompany studies of this kind, further long-term investigations are required to evaluate the precise relationship between osteoporosis in these patients and disease-related variables.

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