RESEARCH PAPER

Bone Mineral Density in Juvenile Onset Systemic Lupus Erythematosus

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Objective: To compare bone mineral density in patients with juvenile-onset Systemic lupus erythematosus and healthy controls. **Participants**: Serial bone mineral density measurements in 27 patients with juvenile-onset systemic lupus were compared to 97 healthy age-matched controls. **Results**: All patients with juvenile-onset had low bone mineral density scores at initial assessment that progressed over disease course. Low body mass index was independently associated with a decline in bone mineral density Z scores; disease activity, use of immunosuppressive agents and vitamin D levels were not risk factors. **Conclusion**: Patients with juvenile-onset systemic lupus erythematosus have low bone mineral density.

Keywords: *Bone mass, Osteopenia, Vitamin D.*

The survival of patients with Systemic lupus erythematosus (SLE) has increased over the last decade. Osteoporosis remains one of leading morbidity associated with long-term survival. Children with juvenile onset systemic lupus erythematosus (jSLE) are at even greater risk, since the disease develops even before achieving their full potential peak bone mass. Factors implicated in pathogenesis of osteoporosis in jSLE include limited physical activity, limited exposure to sunlight, severity of the inflammatory process, corticosteroid and other immunosuppressant therapy, endocrine dysfunction, inadequate dietary intake of calcium and vitamins, and renal insufficiency [1]. The objective of our study was to determine the proportion of patients with jSLE having low bone density in comparison to healthy controls, and to identify risk factors associated with low bone mineral density (BMD).

METHODS

The participants were jSLE patients less than 13 years of age who attended the Pediatric rheumatology clinics of Sultan Qaboos University Hospital, Muscat, Oman. The study protocol and procedures were approved by the Research and Ethics committee at Sultan Qaboos University, Muscat, Oman. The diagnosis was based on the 1997 revised criteria for the classification of SLE [2]. Information collected included age, gender, body mass index (BMI), age at disease onset, disease duration, clinical features, disease activity, 25-OH vitamin D levels, chronic use of medication including current and cumulative steroid dose, and the use of other immunosuppressive agents such as methotrexate, azathioprin, mycophenolate mofetil, cyclophosphamide and rituximab. We defined low, medium and high cumulative steroid doses as below 10 grams, between 10-20 grams, and over 20 grams, respectively. BMI was expressed as body weight in kilograms divided by the square of height in meters (kg/m^2). Underweight was defined as BMI <18.5, normal weight as BMI 18.5-25, overweight as BMI 25-30, and obese as BMI >30.

Disease activity in JSLE patients was assessed and scored according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). The disease was considered to be active when index score was ≥10, and inactive when index was <10. The serum concentration of 25-OH vitamin D was measured using radio-immuno-assay. Vitamin D deficiency was defined as levels <50 nmol/L, vitamin D insufficiency as levels 50-75 nmol/L, and adequate at levels 75-250 nmol/L, respectively, according to the Endocrine Society Clinical Practice Guidelines [3].

BMD was measured at diagnosis and was repeated annually. The results of first and last BMD measurements were included in the study. Evaluation of BMD was carried out by Dual energy *X*-ray absorption (DEXA) using a Lunar DPX densitometer. Whole body and lumbar spine BMD measurements were documented. Lumbar spine was measured from L2 to L4 and the mean lumbar BMD (L2–L4) was calculated. The results were expressed in g/cm^2 and in terms of *Z*-score. Osteopenia was defined as lumbar spine BMD score <-1 and >2.5, and osteoporosis as lumbar spine BMD Z

score of <-2.5 [4]. The age- and gender-matched controls were chosen from healthy children with no rheumatic disease.

At least one year follow-up on 50 patients was needed (10 on the SLE group and 40 on the control cohort; 1:4 ratio) to have 80% power to detect a difference of 0.10 gm/cm^3 (0.70 and 0.8 gm/cm^3) between the two cohorts at the 5% significance level. Differences between groups were analyzed using Pearson chi-square test or Fisher exact test, wherever appropriate. The differences in BMD scores adjusting for gender were analyzed using multiple ordinary least squares (OLS) regression. Statistical analyses were conducted using STATA version 13.1 (STATA Corporation, College Station, TX).

RESULTS

We evaluated 27 patients of jSLE and 97 controls. The mean (SD) age at diagnosis of jSLE was 6 (3) years with (SD) mean disease duration of 4 (3) years. The main clinical features of jSLE during course of disease included: fever and weight loss in 15; arthritis in 17; mucocutanous rashes in 16; nephritis in 15; pulmonary hemorrhage in 4; pericardial effusion in 2; and hematological involvement in 10 patients.

The demographic and clinical features of jSLE in comparison with the controls are shown in ***Table* I**. BMD measurements of jSLE patients are shown in ***Table* II**. The mean (SD) ages at first BMD were 7 (3) yr and 10 (3) yr, respectively. The mean (SD) disease duration at first BMD measurement was 4(2) months. All patients with JSLE had low BMD. Z scores at initial measurements. Osteopenia occurred in 85% (n=23) while osteoporosis occurred in 15% (n=4). In the last BMD measurements, BMD worsened; osteopenia occurred in 46 % (n=11) and osteoporosis in 54% (n=13). Between the first and last measurements, there was a significant decline in BMD *Z* score despite a statistical improvement in disease activity measurements.

All 27 patients with jSLE received corticosteroid and immunosuppressive medications during the course of their disease. The mean (SD) daily and cumulative steroid dose was 9 (3) and 13 (8) g, respectively. Cumulative steroid dose (low, medium and high) did not show a significant effect on BMD measurements. All patients received concomitant calcium and vitamin D supplements. The mean (SD) daily dose of vitamin D was 533 (221) IU, while none of the controls were supplemented with vitamin D. The mean vitamin D levels were significantly higher in patients with jSLE in comparison to controls (61 *versus* 46 nmol/L; P<0.001).

DISCUSSION

This study demonstrated that jSLE patients had low BMD scores at initial assessment that worsened over follow-up. Low BMI at disease onset was associated with a significant decline in Z scores, however, other possible risk factors such as improvement in disease activity, use of other immunosuppressive agents and vitamin D levels were not found to have a significant effect on BMD in jSLE.

Limitations of the study include a small sample size, and relative delay in obtaining the first BMD measurement from the time of diagnosis. Another limitation was that the controls were not gender matched with equal distribution of males and females, while there were more females in the jSLE group. However, this limitation was minimized by analysis using multiple linear regression with gender as a co-variate.

In adult patients with SLE, studies on steroid-induced osteoporosis have produced conflicting results. While some studies support the increasing tendency to develop osteoporosis depending on daily steroid dose, other studies support the independence of osteoporosis from steroids [5]. There is paucity of data on steroid-induced

TABLE I COMPARISON OF DEMOGRAPHICS, BMD AND VITAMIN D BETWEEN JUVENILE SLE PATIENTS AND HEALTHY CONTROLS (N=124)

Characteristic	*jSLE (n=27)*	*Control (n=97)*	*P value*
Age, mean (SD), y	11(4)	12 (2)	0.091
Female gender, *n* (%)	20 (74%)	54 (56%)	0.095
BMI, mean (SD), Kg/m^2	16 (2)	19 (5)	0.007
BMD, mean (SD), g/cm^2	0.72 (9)	0.84 (10)	<0.001
*25-OH Vitamin D, mean (SD)	61 (17)	46 (16)	<0.001

*BMD: bone mineral density; jSLE: juvenile-onset SLE; SLE: systemic lupus erythematosus; BMI: body mass index; *Values in nmol/L.*

TABLE II BMD SCORES OF JUVENILE SLE PATIENTS AT DIAGNOSIS AND SERIAL FOLLOW-UP (N=124)

Parameter	*BMD (first)*	*BMD (last)*	*P value*
Z scores*	-2.2 (0.7)	-2.6 (0.7)	0.038
Spine scores*	0.46 (0.09)	0.53 (0.13)	0.002
All BMD scores	0.72 (0.09)	0.73 (0.09)	0.665
SLEDAI, mean (SD)	16 (7)	5 (4)	0.001

**Mean (SD), g/cm^2; BMD: bone mineral density; SD: standard deviation; SLEDAI: systemic lupus erythematosus disease activity index.*

WHAT THIS STUDY ADDS?

- The prevalence of low bone mineral density is high in juvenile-onset SLE in Oman.

osteoporosis in children with chronic rheumatic conditions, in particularly jSLE [6-10]. Lim, *et al*. [10] demonstrated high prevalence of osteoporosis, and an association of low BMD with low BMI in pediatric SLE patients. The association of vitamin D and SLE disease activity is not clear [11,12]. A recent study showed that a modest increase in vitamin D levels was associated with a modest decrease in SLE activity; however, there was no evidence of additional benefit from higher vitamin D levels [12].

We, conclude that patients with jSLE have low bone mineral density that worsens over follow-up. We recommend larger well-controlled studies with a longer duration of follow-up.

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REFERENCES

1. Sinigaglia L,Varenn Ma, Binelli L, Zucchi F, Ghiringhelli D, Fantini F. Bone mass in systemic lupus erythematosus. Clin Exp Rheumatol. 2000:18:S27-S34.
2. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40:1725.
3. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al*. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911-30.
4. Gordon CM, Bachrach LK, Carpenter TO, Crabtree N, El-Hajj Fuleihan G, Kutilek S, *et al*. Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions. J Clin Densitom. 2008;11:43-58.
5. Cunnane G, Lane NE. Steroid-induced osteoprotosis in systemic lupus erythematosus. Rheum Dis Clin North Am. 2000;26:311-29.
6. Compyrot-Lacassagne S, Tyrrell PN, Atenafu E, Doria AS, Stephens D, Gilday D, *et al*. Prevelance and etiology of low bone density in juvenile systemic lupus erythematosus. Arthritis Rheum. 2007;56:1966-73.
7. Lilleby V, Lien G, Frey Froslie K, Haugen M, Flato B, Fore O. Frequency of osteopenia in children and young adults with childhood onset systemic lupus erythematosus. Arthritis Rheum. 2005;52;2051-9.
8. Trapani S, Civinini R, Ermini M, Paci E, Falcini F. Osteoporosis in juvenile systemic lupus erythematosus: A longitudinal study on the effect of steroids on bone mineral density. Rheumatol Int. 1998;18:45-9.
9. Alsufyani KA, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Nadel H, *et al*. Bone mineral density in children and adolescents with systemic lupus erythematosus, juvenile dermatomyositis, and systemic vasculitis: Relationship to disease duration, cumulative corticosteroid dose, calcium intake, and exercise. J Rheumatol. 2005;32:729-33.
10. Lim SH, Bensler SM, Tyrrell PN, Charron M, Harvey E, Hebert D, *et al*. Low bone mineral density is present in newly diagnosed paediatric systemic lupus erythematosus patients. Ann Rheum Dis. 2011;70:1991-4.
11. Bonakdar ZS, Jahanshahifar L, Jahanshahifar F, Gholamrezaei A. Vitamin D deficiency and its association with disease activity in new cases of systemic lupus erythematosus. Lupus. 2011;20:1155-60.
12. Petri M, Bello KJ, Fang H, Magder LS. Vitamin D in systemic lupus erythematosus: Modest association with disease activity and the urine protein-to-creatinine ratio. Arthritis Rheum. 2013:65:1865-71.