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Original Articles

Frequency of Low Bone Mineral Density and Its Associated Factors in Patients with Juvenile Systemic Lupus Erythematosus

MY ***So***, CC ***Mok***, KM ***Ma***, AWL ***Kwok***, PC ***Leung***, SN ***Wong***

Abstract ***Objective:*** To evaluate the frequency of low bone mineral density (BMD) in Chinese patients with juvenile systemic lupus erythematosus (JSLE) and the associated protective and risk factors. ***Methods:*** We evaluated the BMD in 21 patients with JSLE with a mean age at diagnosis of 13.6±2.1 years. All patients had at least one BMD measurement by dual-energy X-ray absorptiometry at lumbar spine (L2-4) and femoral area at or beyond the age of 18. The correlations between BMD and cumulative dose of steroids, disease duration, disease activity, disease-related damage, clinical features, body mass index and age were investigated. ***Results:*** 'Low BMD for chronological age' (Z-score ≤-2.0) at one or more sites was seen in three patients (14.3%) and 'osteopenia' (Z-score <-1.0 and >-2.0) at any site was present in 12 patients (57.1%). Multiple linear regression analyses showed that body mass index was a positive predictor for BMD at all sites. Cumulative steroid dose, disease activity or lupus nephritis were not related to low BMD. ***Conclusions:*** Low bone mineral density is a common problem among Chinese patients with JSLE. Lower body mass index was shown to be a possible risk factor for low BMD.

Key words Bone mineral density; Children; Chinese; Juvenile; Systemic lupus erythematosus

Department of Paediatrics and Adolescent Medicine, Tuen Mun Hospital, Tsing Chung Koon Road, Tuen Mun, N.T., Hong Kong, China

SN **Wong** (黃錫年) *MBBS, FHKAM(Paediatrics)*
MY **So** (蘇美如)* *MBChB, MRCPCH*

Department of Medicine and Geriatrics, Tuen Mun Hospital, Tsing Chung Koon Road, Tuen Mun, N.T., Hong Kong, China

CC **Mok** (莫志超) *MD(HK), FRCP(Lond and Edin)*

Department of Diagnostic Radiology and Nuclear Medicine, Tuen Mun Hospital, Tsing Chung Koon Road, Tuen Mun, N.T., Hong Kong, China

KM **Ma** (馬國文) *MBBS*

The Chinese University of Hong Kong Jockey Club Centre for Osteoporosis Care and Control, Shatin, N.T., Hong Kong, China

AWL **Kwok** (郭慧良) *MHealthAdmin&InfoSys, FCHSE*
PC **Leung** (梁秉中) *MBBS, FRCS(Edin), FHKCOS*

Correspondence to: Dr SN **Wong**

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*Current address of MY So: Department of Paediatrics and Adolescent Medicine, Alice Ho Miu Ling Nethersole Hospital, 11 Chuen On Road, Tai Po, N.T., Hong Kong, China

Introduction

Osteoporosis is defined as a skeletal disorder characterised by compromised bone strength predisposing to an increased risk of fracture.[1] This is a well-recognised major health problem in adult patients with systemic lupus erythematosus (SLE).[2] Evidence of reduced bone mineral density (BMD) with increased fracture risk in adult SLE patients has been consistently documented.[3-9] However, similar topic in childhood-onset or juvenile SLE (JSLE) has not yet been well studied. Despite limited evidence, majority of the related studies have demonstrated that low BMD is a common problem in JSLE patients. Frequency of osteopenia at one or more skeletal sites in patients with JSLE was found to be up to 40%.[10-13] And the rate of vertebral fracture varied from 6% to 23% as reported in two studies.[11,13]

Potential risk factors of low BMD can be related to the disease itself or the side effect of treatment. SLE-related risk factors include vitamin D deficiency due to chronic renal failure or conscious avoidance of sunshine, premature ovarian failure and the inflammatory process of the disease itself.[14] Corticosteroid use is recognised as another crucial

risk factor of osteopenia. Cumulative corticosteroid dosage was reported to be independently associated with decreased BMD in JSLE.[11,12]

Bone mass increases gradually throughout childhood and adolescence until young adulthood at which peak bone mass is achieved. Failure to accrue optimal peak bone mass has been linked to an increased risk of osteoporosis.[15,16] Obviously, patients with JSLE are being exposed to various potential risk factors of osteoporosis during their golden period of bone development. Peak bone mass in this group has been suggested to be lower than healthy adolescents or adults.[11,14] However, the impact on peak bone mass in patients with JSLE is still unclear. Also, no similar study has been done in Chinese.

The objective of our study is to evaluate the frequency of low BMD in Chinese patients with JSLE and the associated protective and risk factors. BMD at their young adulthood has been studied, aiming at a better projection of the impact on the peak bone mass. As a pilot study, we have also applied local reference of BMD for calculation of Z-score, so as to give a clearer picture of bone health in Hong Kong Chinese patients with JSLE.

Methods

Patients

All the patients with JSLE who were diagnosed and had treatment at the paediatric units of Tuen Mun Hospital, Hong Kong, from January 1994 to January 2010, were identified. The inclusion criteria were the presence of at least four of the American College of Rheumatology (ACR) criteria for classification of SLE,[17] disease onset before the age of 18, minimum disease duration of 24 months and having dual-energy X-ray absorptiometry (DXA) scan done at or beyond the age of 18 within the study period.

Demographic data, age and body mass index at the time of DXA scan, clinical manifestations at diagnosis and history of fracture, current and cumulative dose of corticosteroid, including pulses of methylprednisolone (expressed as prednisolone equivalents), current and prior use of other medications, disease activity and damage index of subjects were collected through record review. Disease duration was defined as the time period from diagnosis of SLE to the time of DXA scan.

Puberty status or menarche could not be accurately evaluated by chart review and so were not included in the analysis. Evaluation of diet or physical activity was also not feasible for a retrospective study.

The study was approved by the regional clinical and research ethics committee.

Disease Activity and Damage Index

Disease activity of SLE was measured using the modified SLE Disease Activity Index (SLEDAI 2000), a validated global index including 24 weighted objective clinical and laboratory variables to assess the ongoing or change in disease activity.[18] It was measured at diagnosis and at yearly basis during the course of disease. An average yearly score was then derived.

Damage of SLE was measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index, a validated instrument with comprehensive assessment of 12 organ systems for nonreversible organ damage which is not related to inflammation and occurs since onset of disease.[19] SLICC/ACR damage index was measured at the most recent clinic visit from the time of DXA scan.

Bone Mineral Density Measurements

Lumbar spine (L2-4) and left femoral (femoral neck, trochanter and total hip) BMD in all patients were measured by the DXA technique using Delphi™ densitometer (Hologic). Analysis software version 11.2:7 was used.

Only DXA scans done at or beyond the age of 18 were evaluated because this should better reflect the peak bone mass and in turn the risk of future development of osteoporosis in adulthood.

Bone mass was expressed as bone mineral density (g/cm^2) or as Z-score in terms of the number of standard deviation (SD) above or below the age and gender-specific mean for healthy individuals. Z-scores were derived from three reference databases. The first one was the third National Health and Nutrition Examination Survey (NHAHES III) database (hip) and the second one was the device manufacturer's dataset (lumbar spine).[20] Since these two databases were collected from white population, to have a population-specific comparison, local reference of BMD obtained from the Chinese University of Hong Kong Jockey Club Centre for Osteoporosis Care and Control was applied to estimate the Z-scores.[21]

'Low bone mineral density for chronological age' was defined as Z-score ≤-2.0 according to the recent criteria established by the International Society of Clinical Densitometry in 2007.[22] 'Osteopenia' was defined as Z-score <-1.0 and >-2.0 so as to allow comparison with previous similar studies while most of them defined 'osteopenia' as Z-score <-1.

Statistical Analysis

Data are expressed as mean±SD unless otherwise stated. Comparisons between groups were made with the Student's *t*-test for continuous data and the chi-square test with Yates correction for categorical data. Analyses of clinical variables associated with BMD values at all sites were performed using linear and multiple linear regression. As BMI and body weight were interrelated, only BMI was used as a covariate in the multivariate model. Variables were entered in multivariate analyses by standard variable selection methods. Statistical significance was defined as a *P*-value of <0.05. All statistical analyses were performed using SPSS software, version 16.0 for Windows XP.

Results

Clinical Characteristics of the Study Subjects

The study population comprised 21 Chinese patients with JSLE who had a DXA scan performed at the mean age of 19.9 years (median 19.1 years; range 17.7-24.5 years). The demographic, anthropometric, disease characteristics and medication use in the study group were shown in Table 1. A DXA scan done at the age of 17.7 years was included in this study because the patient had low BMD and this was the only baseline scan done before the bisphophosphate therapy. This scan was done 4 years after diagnosis of JSLE and it should adequately reflect the possible impact of disease and treatment on BMD.

The mean age at disease onset was 13.6±2.1 years (median 13.8 years; range 8.8-17.3 years) with a mean SLEDAI score at diagnosis of 12.2±5.6 and 12 (57%) patients had high or very high activity (SLEDAI >10) at diagnosis. The mean disease duration was 6.3±2.7 years (median 5.8 years; range 2.3-11.9 years) and all patients had their yearly average SLEDAI score less than five which was defined as mild activity.[23] One-third of patients had SLICC/ACR damage index ≤1.

For the clinical features at diagnosis, most patients had skin or haematological manifestations. About half of them had joint or renal involvement and seven patients had renal biopsy showing Class III-IV lupus nephritis. Concerning the medication use, all patients had been taking corticosteroid and at least one steroid-sparing agent during the course of their disease. The majority of patients (95.2%) were under corticosteroid therapy at the time of DXA, with a mean daily prednisolone dose of 9.8± 3.8 mg/day and a mean cumulative dose of 22.6±12.7 g. Prednisolone was stopped in one patient (4.8%) 18 months before the DXA assessment. Her BMD Z-scores for total hip, femoral neck, trochanter and lumbar spine were -2.2, -1.3, -1.7 and -1.4, respectively. All patients were given calcium and vitamin D supplements during the whole course of steroid therapy.

Bone Mineral Density Findings

The BMD values at four sites and the corresponding Z-scores derived from Hong Kong reference were presented in Table 2. Statistically significant reduction in mean BMD at all sites was shown, as compared with the reference norms for Hong Kong Chinese at age 20. The mean Z-scores for lumbar spine and total hip BMDs were -0.76 and -0.99 respectively.

Frequency of Low Bone Mineral Density

Three (14.3%) of the patients with JSLE had 'low BMD for chronological age' (Z-score ≤-2.0) at one or more sites. 'Osteopenia' (Z-score <-1.0 and >-2.0) at any sites was detected in 12 (57.1%) of the patients. One patient had bilateral hip avascular necrosis at 6 months after SLE diagnosis. She had finished her induction phase of treatment and was on 10 mg daily when she presented with hip pain. Her mean daily prednisolone dose was 0.7 mg/kg/day and cumulative dose was 5385 mg before the development of avascular necrosis. Her hip BMD values were not available. Only BMD at lumbar spine for this patient was available and the corresponding Z-score was appropriate for chronological age.

The sites affected most frequently were the total hip and the lumbar spine. The proportions of patients having 'osteopenia' at either the total hip or the lumbar spine were the same and each accounted for 38.1% of the patients.

None of the patients suffered from osteoporotic fractures.

Relationship Between Clinical Variables and BMD

Univariate analyses were performed on the relationship of BMD at each site to all variables listed in Table 1, but only the statistically significant correlations were included in Table 3. Univariate analysis did not reveal any significant correlation between BMD at any sites and cumulative corticosteroid dose, disease activity or lupus nephritis. Multiple linear regression analyses showed that body mass index was an independent positive predictor for BMD at all sites (Table 4). Both initial presentation with serositis and ever-used-cyclosporine were shown to have significant correlation with BMD on univariate analysis but not in multivariate analysis. Such result may be a false positive as patients in each of these groups are too small.

Table 1 Demographic, anthropometric, disease characteristics and medication use in all patients, patients with low BMD Z-score at one or more sites and patients with normal BMD at all sites

	All patients* (n=21)	**Patients with BMD Z-score ≤-2.0 at one or more sites(n=3)**	**Patients with BMD Z-score >-2.0 at all sites(n=17)**
Female, no. (%)	20 (95.2)	3 (100)	16 (94.1)
Age, years	19.9±2.0	18.4±0.6	20.2±2.1
Body mass index, kg/m^2	21.7±3.9	18.6±0.9	22.4±4.0
Age at disease onset, years	13.6±2.1	13.9±1.1	13.4±2.3
Disease duration, years	6.3±2.7	4.5±0.9	6.7±2.8
SLEDAI at diagnosis	12.2±5.6	14.3±6.7	11.4±5.3
SLEDAI, yearly average	2.9±1.3	3.0±1.3	2.9±1.4
SLICC/ACR damage index	0.7±1.2	1.3±2.3	0.5±0.9
Clinical features, no. (%)			
Skin disease	14 (66.7)	2 (66.7)	11 (64.7)
Serositis	3 (14.3)	1 (33.3)	2 (11.8)
Haematological involvement	15 (71.4)	2 (66.7)	12 (70.6)
CNS involvement	3 (14.3)	0 (0)	3 (17.6)
Arthritis	10 (47.6)	2 (66.7)	8 (47.1)
Lupus nephritis	11 (52.4)	1 (33.3)	9 (52.9)
Medications used, no. (%)			
NSAID	10 (47.6)	2 (66.7)	8 (47.1)
Methotrexate	1 (4.8)	1 (33.3)	0 (0)
Azathioprine	19 (90.5)	2 (66.7)	16 (94.1)
Hydroxychloroquine	14 (66.7)	2 (66.7)	11 (64.7)
Cyclophosphamide	11(52.4)	1 (33.3)	9 (52.9)
Cyclosporine	3 (14.3)	0 (0)	3 (17.6)
Mycofenolate mofetil	6 (28.6)	0 (0)	6 (35.3)
Corticosteroid			
Current user, no. (%)	20 (95.2)	2 (66.7)	17 (100)
Methylprednisolone, no. (%)	5 (23.8)	1 (33.3)	4 (23.5)
Cumulative steroid dose, g	22.6±12.7	15.4±1.8	24.6±13.3
Duration of use, years	6.0±2.4	4.0±0.2	6.7±2.8
Prednisolone, mean daily dose, mg	9.8±3.8	9.5±1.7	10.0±4.1
Prednisolone, current dose, mg/day	7.0±8.0	4.7±4.5	7.8±8.6

BMD=bone mineral density; CNS=central nervous system; NSAID=Non-steroidal anti-inflammatory drug; SLEDAI=Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR damage index=Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index

*One patient had bilateral hip avascular necrosis and only her BMD at lumbar spine was available. The corresponding Z-score was appropriate for chronological age. Therefore, this patient was not categorised into either subgroup of 'low BMD Z-score at one or more sites' or 'normal BMD at all sites'.

Table 2 BMD and Z-scores in patients with juvenile systemic lupus erythematosus

	BMD, g/cm²	Z-score*	P†
Total hip	0.76±0.12	-0.99±1.22	0.002
Femoral neck	0.69±0.11	-0.65±1.28	0.009
Trochanter	0.57±0.10	-0.84±1.08	0.003
Lumbar spine (L2-4)	0.84±0.13	-0.77±1.20	0.006

BMD=bone mineral density

*Z-score derived from Hong Kong reference; †One-sample *t*-test comparing mean BMD with the mean BMD values suggested by Hong Kong reference.

Table 3 Univariate analysis of clinical variables and bone mineral density*

	P			
	Total hip	Femoral neck	Trochanter	Lumbar spine
Age at time of DXA	0.148	0.210	0.154	0.016
Body weight	0.015	0.006	0.007	<0.001
Body mass index	0.011	0.003	0.011	<0.001
Disease duration	0.246	0.498	0.255	0.049
SLICC/ACR damage index	0.099	0.264	0.031	0.296
Serositis	0.143	0.221	0.044	0.200
Methotrexate	0.133	0.093	0.079	0.402
Cyclosporine	0.343	0.167	0.477	0.014

DXA=dual-energy X-ray absorptiometry; SLICC/ACR damage index=Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index

*All variables listed in Table 1 were tested; only the statistically significant variables were shown.

Table 4 Multivariate analysis of clinical variables and BMD

	Adjusted R^2*	*Slope (SE)*	Beta†	P
Total hip BMD	36%			
Body mass index		0.017 (0.006)	0.53	0.010
SLICC/ACR damage index		-0.036 (0.019)	-0.34	0.079
Femoral neck BMD	42%			
Body mass index		0.017 (0.005)	0.59	0.004
Methotrexate		-0.144 (0.090)	-0.28	0.129
Trochanter BMD	38%			
Body mass index		0.013 (0.005)	0.51	0.015
SLICC/ACR damage index		-0.032 (0.026)	-0.38	0.234
Serositis		-0.022 (0.073)	-0.08	0.768
Methotrexate		-0.007 (0.109)	-0.02	0.951
Lumbar spine BMD	63%			
Body mass index		0.028 (0.007)	0.81	0.002
Age at the time of DXA		-0.002 (0.014)	-0.03	0.895
Disease duration		0.011 (0.009)	0.21	0.244
Cyclosporine		-0.026 (0.071)	-0.07	0.720

BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; SE=standard error; SLICC/ACR damage index=Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index

*Total explained variance of the model; †Unstandardized regression coefficient

Comparison Between Z-scores Derived from Hong Kong and Caucasian Reference

Mean Z-scores at all sites derived from Hong Kong reference were shown to be significantly different from those derived from Caucasian reference (Table 5). The frequency of 'low BMD at one or more sites' in our Chinese JSLE patients using the Caucasian reference was 47.6%, which is three-fold higher than that by Hong Kong reference (14.3%).

Discussion

Osteoporosis is a well-known complication in adult patients with SLE.[2,3-9] However, few studies on bone mineral density in JSLE have been done and most of them have focused on Caucasian population. To our knowledge, this study is the first to describe the frequency of low BMD and the associated factors in Chinese patients with JSLE.

This is a cross-sectional study and our results confirm that low BMD is a notable problem in Chinese patients with JSLE. Their mean BMD at all sites were shown to be significantly lower than the reference norms for Hong Kong Chinese at age 20.[21] It seems that the frequency of low BMD in the patients we investigated is lower than those reported in the previous studies.[10-13] However, these findings may not be easily comparable due to the diversity in the definition of 'abnormal' bone density and the selection of sites on evaluation. Despite the fact that only small proportions (14%) of our patients had 'low BMD for chronological age' (Z-score ≤-2.0), up to 57% of them were having 'osteopenia' (Z-score < -1.0 and >-2.0) at their young adulthood. This implies that low BMD in Chinese patients with JSLE is common but may not be severe in degree at their young adulthood. However, these patients are at high risk of failure of attaining the optimal peak bone mass and in long-term, they are subject to higher risk of developing osteoporosis in later life.[1]

Potential risk factors for low BMD included cumulative corticosteroid dose, disease duration, body weight, body mass index (BMI) and lean mass.[12,13,24-27] Body weight or BMI has been shown to be positive predictor for bone mass in four studies.[24-27] Our present study also supported that BMI was an independent determinant for BMD, though the findings may be limited by our small sample size. In fact, those patients with 'low BMD for chronological age' did have lower BMI than those with appropriate BMD (18.6±0.9 versus 22.4±4.0 kg/m^2, p=0.124). The association between BMI and BMD in patients with JSLE are to be confirmed in future studies with larger sample size.

The correlation between corticosteroid and BMD is still controversial. Cumulative corticosteroid dosage was reported to be an independent determinant for BMD by Lilleby et al[11] and Compeyrot-Lacassagne et al[12] and this was corroborated by the finding of inverse correlation between cumulative steroid dose and BMD by Trapani et al,[14] while no correlation was found in four other studies of bone density in childhood-onset SLE.[10,13,28,29] In our present study, univariate analysis did not demonstrate any correlation between cumulative steroid dose and BMD in our patients, nor was there any correlation of BMD with duration of steroid use. We were not able to directly study the correlation of BMD with steroid use per kilogram as the body weight varied greatly for each patient over the observation period of several years. To study the impact of steroid dosage per kilogram body weight, we repeated the multivariate analysis by including the variables shown to have significant correlation in univariate analysis, together with the cumulative steroid dose and duration of steroid use (although they were not significantly correlated). We found that BMI is still the only independent positive predictor for BMD at all sites. Interestingly for the lumbar spine BMD, duration of steroid use was also an independent negative predictor [slope (SE) -0.048 (0.017), beta = -0.87, p=0.013], and disease duration was an independent positive predictor [slope (SE) 0.069 (0.019), beta = +1.38, p=0.003]. This may suggest the deleteriously effect of steroid use and the beneficial effect of later periods of

Table 5 Comparison between mean Z-scores derived from Hong Kong and Caucasian reference

	Mean Z-score using Hong Kong reference	Mean Z-score using Caucasian reference	Difference in mean Z-scores (Hong Kong – Caucasian)	P*
Total hip	-0.99	-1.51	0.52	<0.001
Femoral neck	-0.65	-1.49	0.84	<0.001
Trochanter	-0.84	-1.29	0.45	<0.001
Lumbar spine (L2-4)	-0.77	-1.59	0.82	<0.001

*Paired-samples *t*-test.

non- or low steroid use. As the sample size of our study was small, our findings need to be confirmed by further studies.

Indeed we observed that one of our patients had normal BMD (Z-score >0) at all sites despite the fact that she had been on a high cumulative steroid dose up to 49.3 grams over twelve years of disease course. She had been taking the usual calcium and vitamin D supplements without any bisphosphates therapy. There were two distinct features observed from this patient. One was that she was obese with her BMI at 32.7 kg/m^2, and another was that she had a 6.5-year steroid-free period before the DXA scan was done at the age of 24 years. However, there was no baseline DXA scan for comparison so we could not show if there was any reduction in BMD during her early course of disease. Corroborating with our above suggestion of the association between BMI and BMD, this case supports that high BMI may be a protective factor against bone loss. We also postulate that there may be catch-up in BMD during the steroid-free period.

A few studies in adult patients with SLE have evaluated the correlation between daily prednisolone dose and bone loss.[6,30] Kipen et al performed a longitudinal study of BMD change in premenopausal women with SLE with mean age of 35 years.[6] Their results showed that there was a gain in BMD in those patients receiving a daily dose of prednisolone of <7.5 mg/day. The observation of having catch-up in BMD during steroid-free periods in our case is compatible with the findings of these studies. Actually, bone growth in children and adolescents can be more dynamic while they are in their growing phase of bone mass. The catch-up growth in bone mass can be even more dramatic than in adults. Further prospective studies are needed to determine the effect of corticosteroids on bone growth.

It is well-known that there are ethnic variations in BMD. The reference ranges supplied by the manufacturers of bone densitometers are unlikely to be applicable across all populations.[31] In order to have a population-specific comparison, our study has used local reference of BMD to give a clearer picture of bone health in Hong Kong Chinese patients with JSLE. The reference norm was established from a cohort of 4274 subjects from the community and nonparametric additive regression models were used to estimate the mean BMD values from aged 10 to 85 for both men and women.[21] The same reference values are applied in clinical and research use by the Chinese University of Hong Kong Jockey Club Centre for Osteoporosis Care and Control. Our results showed that there was significant difference in Z-scores for BMD estimated using the Hong Kong and Caucasian reference. Applying the Caucasian reference in calculating the frequency of reduced bone mass in our Chinese JSLE patients may lead to over-estimation of the problem, as shown by the marked discrepancy in frequency of 'low BMD at one or more sites' estimated using the two different references.

A limitation of our study was the small sample size. There was also a lack of data on puberty, menarche, diet and physical activity due to the retrospective design of the study. The Z-scores for BMD reported in our study were estimated using the mean and SD reported in the publication.[21] This may serve as a rough estimation and ideally the Z-scores should be reported using the manufacturer's software.

Our preliminary results confirm that low BMD is a common problem among Chinese patients with JSLE. Though the degree of reduction in BMD seems not severe to an extent of causing immediate impact during their childhood or even young adulthood, this insidious reduction in BMD potentially subjects patients with JSLE to higher risk of osteoporosis in later life. There is still much controversy on the risk factors of causing poor gain in bone density. We suggest that, while pending further concrete evidence from future studies, clinicians should address the potential risks and emphasize more on the general measures in prevention of osteoporosis like encouraging weight bearing exercise and calcium-rich diet, using Vitamin D supplements and prescribing the lowest possible maintenance dose of corticosteroid. Long-term studies of larger populations from different ethnic groups are needed to evaluate the associated factors, role of prophylactic therapy and long-term morbidity of reduced bone mass in patients with JSLE.

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