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

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ABSTRACT. ***Objective.*** To describe the frequency of abnormal bone mineralization in a population of children with juvenile systemic lupus erythematosus (JSLE), juvenile dermatomyositis (JDM), and systemic vasculitis; and to investigate the relationship of bone mineral density (BMD) to cumulative corticosteroid dose, disease duration, Tanner stage, calcium intake, and exercise in these patients.

Methods. A retrospective chart review of children attending the pediatric rheumatology clinic at British Columbia's Children's Hospital was conducted to obtain demographic data (sex, ethnicity, disease duration, cumulative corticosteroid dose, and mean daily corticosteroid dose). All patients had at least one BMD measurement by dual energy x-ray absorptiometry (DEXA) at lumbar spine, hip, and total body. BMD was expressed as g/cm^2 and Z scores; an abnormal Z score was defined as ≤ –1.5. Daily calcium intake was calculated. Physical activity was scored using a validated 7 day physical activities questionnaire.

Results. A total of 36 patients were studied. Twenty-five patients had SLE, 7 had JDM, and 4 had systemic vasculitis. Fourteen subjects were Caucasian, 13 Asian, 6 East Indian, and 3 Canadian First Nations. An abnormal Z score at one or more sites was found in 10/25 (40%) with JSLE, and in 3/11 (27%) JDM/vasculitis patients. The mean Z scores (± SD) for lumbar spine were –1.02 (± 1.2), for hip –0.88 (± 1.3), and for total body –0.77 (± 1.5). Compared to children with normal bone densities, those with lower bone density tended to be younger (13.5 ± 2.2 vs 15.5 ± 1.7 yrs), received higher corticosteroid dosages at the time of the study (0.78 ± 0.6 vs 0.35 ± 0.2 mg/kg), and were more often prepubertal (OR for total body scores 5, 95% CI 0.7–46).

Conclusion. Decreased bone density is common in children with SLE and other systemic rheumatic diseases. Age, corticosteroid dose, and pubertal stage all appear to have some influence on bone mass in these children. (J Rheumatol 2005;32:729–33)

Key Indexing Terms:
BONE DENSITY OSTEOPOROSIS CHILD SYSTEMIC LUPUS ERYTHEMATOSUS
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Decreased bone mineral density (BMD) and an increased risk of fractures have been increasingly recognized in children with rheumatic diseases, particularly in those treated with corticosteroids[1-15]. BMD is now usually measured using dual energy x-ray absorptiometry (DEXA). In adults, BMD values are expressed as T scores, which indicate the number of standard deviations the subject's BMD is above or below the mean value for healthy adults. In children and adolescents in whom areal bone mass is still accruing, BMD cannot be related to peak bone mass in an adult, and is therefore usually expressed as a Z score, a measure of the number of standard deviations the patient is from a reference population matched for age, sex, and ethnicity[16,17].

In adults with rheumatic diseases a number of risk factors for development of osteoporosis have been described[18-22]. These include disease duration and severity, diet, level of physical activity, and past corticosteroid treatment. A more limited literature suggests that these factors may also be important in children with rheumatic diseases[7-10].

We studied BMD by DEXA in a cohort of children and

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adolescents with juvenile systemic lupus erythematosus (JSLE), juvenile dermatomyositis (JDM), and systemic vasculitis attending a single pediatric rheumatology clinic, and investigated the influence of cumulative corticosteroid dose, disease duration, puberty, diet, and exercise on BMD of those patients.

MATERIALS AND METHODS

Patients. A convenience sample of 36 patients (33 girls, 3 boys) with JSLE, JDM, and vasculitis attending the pediatric rheumatology clinic of British Columbia's Children's Hospital, who had had a DEXA scan as a part of their routine care in the clinic and who had agreed to complete 2 questionnaires on calcium intake and physical activity, were identified from a clinical database. There were no formal inclusion or exclusion criteria. All children with JSLE fulfilled the 1982 American College of Rheumatology criteria for SLE[23]. All children with JDM were diagnosed on a basis of proximal muscle weakness, rash, and abnormal muscle enzymes or/and abnormal muscle magnetic resonance image findings. In 4 children, the diagnosis of vasculitis was based on a combination of clinical features and investigations that were considered by the pediatric rheumatologists to be consistent with the diagnosis. At the time of this study no patient was taking medications to treat osteopenia, and none had any other comorbid conditions such as liver, renal, or endocrine disease. All patients had been advised to take calcium supplements at a dose of 1000 mg/day and 400 IU vitamin D per day.

Data collection. Clinical data collected from a retrospective chart review were sex, ethnicity, age at onset, disease duration in months, mean and cumulative corticosteroid dose and duration of corticosteroid therapy prior to DEXA scan, and height and weight at the time of the scan. Disease activity was based on a physician global disease activity Likert scale of inactive, mild, moderate, or severe scored at the time of the clinic visit nearest to the time of the DEXA examination.

Two questionnaires were completed by all subjects or their parents. The first determined the calcium intake by a detailed food frequency questionnaire and calcium calculator (available on The Osteoporosis Society of Canada website, www.osteoporosis.ca). The patient's calcium intake was classified as adequate or inadequate based on American Academy of Pediatrics recommendations[24]. The second questionnaire was a modified version of the Physical Activity Questionnaire for Children (PAQ-C)[25], which measures daily activity in the moderate to vigorous range over 7 days' recall. General physical activity scores ranged from 1 (low activity) to 5 (high activity).

Maturity. Tanner stage of pubertal developmental was evaluated by a validated self-assessment method using line drawings[26,27].

BMD measurement. BMD (g/cm^2) of lumbar spine (L1 to L4), hip (left, total hip), and total body were measured in all patients by DEXA. All patients were scanned by the same instrument (Hologic Delphi QDR-70312, A series; Hologic, Bedford, MA, USA) and all measurements were analyzed by the same radiologist (HN). Normative data (Z scores) were obtained from 2 sources. The Hologic densitometer software provided lumbar spine data; Z scores from all 3 sites were provided from the Stanford Bone Densitometry Applet[17].

There are no consensus criteria for defining osteopenia or osteoporosis on the basis of BMD measurements in children. For the purpose of this study, the following values were used: normal = BMD Z score > –1.4, abnormal = BMD Z score ≤ –1.5. These values are consistent with available adult data that show women with BMD > 1 SD below normal are at increased risk of fracture[28,29]. Our definitions make no assumptions about fracture risk.

Statistical analysis. Descriptive statistics were used to describe the demographic and main variables measured in the study. Patients were divided in 2 groups based on Z scores. Group 1 consisted of patients with normal BMD at all sites (Z score > –1.4), and Group 2 consisted of patients with abnormal BMD (Z score ≤ –1.5) at one or more sites. Differences between these 2 groups with respect to age at disease onset, age at DEXA scan, and disease duration were compared by independent T test.

Potential risk factors for low bone density were mean corticosteroid dose, cumulative corticosteroid dose, duration of corticosteroid treatment, calcium intake, body mass index (BMI), and age at the time of DEXA scan. These potential risk factors were first analyzed as continuous variables using the independent T test, and then by dichotomizing the risk factors as present or absent using cutoff points determined by their normal distribution and using Fisher's exact test. The potential risk factors identified by Fisher's exact test were then entered into logistic regression analysis. The relationship between BMD at any site and cumulative corticosteroid dose was evaluated using univariate linear regression analysis.

The study protocol was approved by the ethics committee of the University of British Columbia. Written informed consent was obtained from parents and from patients older than 16 years of age.

RESULTS

Twenty-five patients had JSLE, 7 had JDM, and 4 had systemic vasculitis (Takayasu's arteritis, Behçet's disease, Wegener's granulomatosis, polyarteritis nodosa). Fourteen patients were Caucasian, 13 were Asian, 6 were East Indian, and 3 were Canadian First Nations. The mean BMI for the group was 23.34 ± SD 5.8, as per BMI for age cutoff values (US Centers for Disease Control BMI for age percentiles); one patient was underweight (< 5th percentile), 16 were between 5th and 85th percentiles, 10 were considered at risk for overweight (85th to < 95th percentiles), and 9 were overweight (≥ 95th percentile). The mean age at time of study was 11.4 years (SD ± 2.9 yrs, range 8–19), mean disease duration was 2.89 years (SD ± 2.5 yrs, range 0.3–8.25), mean cumulative corticosteroid dose was 293.56 mg/kg (SD ± 182.3, range 0–861). The mean calcium intake was 2322 mg (SD ± 1714.8 mg, range 0–9825).

All patients were taking corticosteroids at the time of DEXA except one patient with mild SLE who had never received corticosteroids. Ten patients with JSLE were also taking azathioprine, 10 (9 JSLE, one Takayasu's arteritis) were taking cyclophosphamide, and 11 (7 JDM, 2 JSLE, one Takayasu's arteritis, one Wegener's granulomatosis) were taking methotrexate. Twenty patients had moderately active disease, 12 had mildly active disease, and 4 had severe disease activity at the time of DEXA scan. No patient had had a recent bone fracture at the time of the study. No patient with JDM had diffuse calcinosis that might have altered the DEXA results.

DEXA measurements. The mean Z scores for each disease group are summarized in Table 1. An abnormal Z score at one or more sites was found in 10/25 (40%) JSLE patients and in 3/11 (27%) JDM/vasculitis patients.

Relationship between BMD loss and putative risk factors. Patients with abnormal BMD (Group 2) were significantly younger at the time of the study (13.5 ± 2.2 yrs) than patients with normal BMD (Group 1) (15.5 ± 1.7 yrs; p = 0.009). Patients in Group 2 were receiving higher doses of corticosteroids at the time of study than those in Group 1:

Table 1. Z scores at different sites for each clinical group.

	Lumbar Spine, mean Z score (± SD)	Hip, mean Z score (± SD)	Total Body, mean Z score (± SD)
JSLE	–0.90 (1.2)	–0.89 (1.28)	–0.56 (1.37)
JDM	–1.14 (0.69)	–0.33 (1.23)	–0.95 (1.78)
Vasculitis	–1.65 (1.55)	–1.19 (1.22)	–1.92 (2.21)
Total	–1.02 (1.2)	–0.88 (1.24)	–0.77 (1.53)

0.78 ± 0.6 vs 0.35 ± 0.2 mg/kg, respectively (p = 0.05). However, there were no differences between patients in Groups 1 and 2 with respect to cumulative corticosteroid dose, disease duration, calcium intake, BMI, or physical activity.

Patients with Tanner stage < 4 tended to have low bone density for total body Z scores (OR 5, 95% CI 0.7–46), hip Z scores (OR 4, 95% CI 0.7–27.5), and lumbar spine Z scores (OR 3.6, 95% CI 0.6–23) (p = 0.07, 0.08, 0.09, respectively; Table 2). There was no significant correlation between BMD at any site and cumulative corticosteroid dose using univariate linear regression analysis.

Age at DEXA scan < 12 years, mean corticosteroid dose ≤ 0.5 mg/kg, and Tanner stage < 4 were entered into multiple logistic regression analysis. No association with low bone density was found.

There was no relationship between disease activity at the time of study and BMD.

Due to the small number of boys in the study, this variable could not be analyzed as a putative risk factor.

DISCUSSION

A relatively small number of studies have suggested that children with rheumatic diseases are at high risk of developing localized and generalized low bone mass[3-10]. Our results confirm that decreased bone density is a common problem in this population. The prevalence of abnormal BMD in our study was about 40% in patients with JSLE, similar to that described by Falcini and colleagues for Italian patients with JSLE[5,15].

Of 11 patients with JDM or a systemic vasculitis, 3 (27%) had a decrease in BMD; one patient from the JDM group had a decrease in BMD at the lumbar spine and 2 patients from the systemic vasculitis group had abnormal BMD at total body and hip, respectively.

We found no factors that were consistently related to a decrease in BMD. Many studies have investigated the role of such factors as disease activity, diet, physical activity, and corticosteroid use in the pathogenesis of osteoporosis in adult patients with SLE[19,21,22,30,31], but the results are controversial. Dhillon, *et al* performed DEXA scans on 22 patients with SLE (12 taking corticosteroids, 10 not on corticosteroids, 14 corticosteroid-dependent patients without SLE, and 10 healthy controls) and found no significant differences among the 3 groups, but BMD measurements were low compared to controls[32]. Formiga, *et al* found a significant reduction of BMD in 74 adult female SLE patients, but were unable to determine any association between a decreased BMD and cumulative or baseline doses of corticosteroids[33].

We are aware of only 2 reports describing potential risk factors on bone density in JSLE using DEXA[5,6]. Castro, *et al* studied BMD of 16 patients with JSLE and found no significant correlation between reduced bone mass and cumulative corticosteroid doses[6]. Trapani, *et al* studied 20 patients with JSLE and found BMD had a significant inverse correlation with cumulative corticosteroid dose; no significant correlation was found between BMD and disease activity or disease duration[5].

Table 2. Dichotomized risk factors and BMD.

Risk Factor	Bone Mineral Density (> –1.5 Z score) Total Body OR (95% CI) p	Hip Z score OR (95% CI) p	Lumbar Z score OR (95% CI) p
Age at onset of CS ≤ 10 yrs	0.69 (0.12–3.96) 0.45	0.7 (0.1–3.5) 0.6	0.7 (0.1–3.5) 0.6
CS dose ≥ 0.5 mg/kg/day	2.7 (0.8–36.2) 0.05	0.93 (0.16–5.4) 0.61	1.5 (0.3–7.6) 0.6
Duration of CS treatment ≥ 12 mo	0.2 (0.03–1.25) 0.05	2 (0.33–13.2) 0.3	0.84 (0.15–4.9) 0.55
Cumulative CS dose > 180 mg	0.47 (0.08–2.74) 0.27	1.33 (0.2–7.7) 0.5	1.9 (0.33–12.07) 0.3
Tanner stage < 4	5.06 (0.7–46.1) 0.07	4 (0.65–27.5) 0.08	3.6 (0.62–23.1) 0.09
Exercise, low and mild intensity	0.06 (0.01–0.82) 0.017	1.14 (0.17–7.94) 0.60	1.38 (0.26–7.75) 0.47
Calcium intake inadequate*	0.43 (0.02–5.15) 0.42	0.89 (0.09–7.7) 0.64	1.13 (0.16–7.57) 0.59

* Per US Food and Drug Administration recommendation. CS: corticosteroid.

Adequate calcium and vitamin D intake during childhood is critical for optimal mineralization of the skeleton. Johnston, *et al* showed that calcium supplement (1000 mg/day) enhances the rate of increase in BMD in normal prepubertal children[34]. Warady, *et al* found a significant improvement in spinal bone density of children with rheumatic diseases when they received a minimum daily intake of 1 g calcium and 400 IU vitamin D[35]. Reed, *et al* supplemented 13 children with juvenile rheumatoid arthritis with 25OH- vitamin D for 1 year, but noted no significant increase in BMD over that time[36].

Of interest, 8 of our patients had poor calcium intake as judged by the diet questionnaire. This information suggests that recommending routine calcium supplement to children with rheumatic diseases is likely necessary, as many children and adolescents will not have adequate intake in their regular diet.

Several investigators have shown that regular exercise results in increased BMD in healthy children[37-39]. Twenty-two patients in our study had low levels of physical activity as assessed by the activity questionnaire, but the study failed to observe any relationship between activity and bone density.

In this study, there was a trend that suggests some influence of pubertal stage on BMD; however, the results were statistically not significant. We are not aware of any study of the effect of puberty on BMD in patients with JSLE. We know from a previous study evaluating the effect of puberty on BMD in healthy children and adolescents that Tanner stage was significantly associated with all 3 areas of BMD measured in girls and with lumbar spine BMD in boys[40]. Compared to patients with normal bone densities, those children with lower bone density tended to be younger, were more often prepubertal, and had received higher corticosteroid dosages at the time of the study; however, due to the sample size the study was underpowered to estimate the individual effect of each of these variables. It is of interest that there was a trend for lower bone densities at the spine than at the hip (Table 1). The reason for this is not clear, and it is also uncertain if these differences are clinically important. This issue warrants further study.

It is perhaps surprising that we found no consistent relationship between bone density and disease activity, duration of corticosteroid use, calcium intake, and physical activity. The most probable explanation is that these several factors together are important in determining bone density, and that the relatively small number of patients in the study provided inadequate power to reveal the relationship of any individual factor with bone density. It is also possible that the questionnaires failed to adequately estimate either calcium intake or exercise levels in these children, as there was a time lag between answering questionnaires and the time the DEXA was performed. It should also be noted that Z scores are values that relate bone density scores to normal values matched for age, sex, and ethnicity. Only limited amounts of normative data are available for children and we were unable to match for ethnicity for the children under 9 years of age, thus it may be that the normative data used were not completely accurate.

Disease activity might be expected to influence bone density. Our failure to find any such effect may be because we measured disease activity only at the time of study, as there is no satisfactory way of measuring disease activity over time. Also, it is possible that the physician global assessment of disease activity we used is less accurate as a measure of disease activity than other global indices such as the SLE Disease Activity Index (SLEDAI). However, as these indices were originally validated using various physician global assessments of disease activity measures, we feel that the method we used is an acceptable measure of disease activity in clinical practice[41].

We have confirmed the results of other studies that decreased BMD are a common and potentially serious problem in children with JSLE, JDM, and systemic vasculitides. A large number of children in this population have decreased BMD, although we encourage every child to take calcium supplements and added vitamin D.

Even if these children do not develop complications of low bone mass during childhood or adolescence, it seems possible that many of them will fail to reach a normal peak bone mass in early adult life and will therefore be at increased risk of developing hip and spine fractures in later life.

Longitudinal studies are needed to evaluate the longer-term effects of childhood rheumatic diseases on bone density, but given the prevalence of osteoporosis in this population, and the apparent inefficacy of advice to increase calcium and vitamin D intake, intervention studies using bisphosphonates would seem to be justified[42]. It is interesting that some children with rheumatic disease maintain normal bone densities. Whether there are factors, genetic or other, that are protective against bone loss is an issue that warrants further investigation.

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