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Osteoporosis in juvenile systemic lupus erythematosus: a longitudinal study on the effect of steroids on bone mineral density

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Abstract Peak bone mass is an important determinant of future bone mass and of the risk of osteoporosis and subsequent fractures. Although some information concerning bone mineral density (BMD) in adults affected with systemic lupus erythematosus (SLE) is available, few data on children and adolescents have been reported. Many variables, such as duration and activity of the disease, reduced sun exposure, and steroid therapy have been suggested as risk factors in the pathogenesis of osteoporosis in SLE. In this study, we longitudinally evaluated, by dual energy X-ray absorptiometry (DEXA), the BMD of 20 young patients affected with juvenile SLE (JSLE), in order to establish the degree of osteoporosis and the influence of steroid treatment, among other clinical variables. At baseline, the mean BMD in JSLE patients was 0.978 g/cm^2 and in controls 1.038 g/cm^2 ($P = 0.31$). At 1 year (time 2), this value became 0.947 g/cm^2 in JSLE children; the mean individual difference was 0.28 g/cm^2 (3.4%). Only in those patients aged 19–25 years BMD was significantly lower than in controls, both at baseline and at time 2. Considering the steroid treatment, no significant difference between the two groups was found either at baseline or at time 2; however, the mean yearly BMD loss in the steroid patients was 0.031 g/cm^2 (3.5%) vs. 0.005 g/cm^2 (0.5%) in those who had not taken steroids. A significantly inverse correlation between BMD and the cumulative dosage of corticosteroids has been detected. BMD produced a significantly inverse correlation to the cumulative dosage of corticosteroids; no significant correlation has been found between BMD and disease activity or duration.

Key words Osteoporosis · Systemic lupus erythematosus · Steroid treatment · Densitometry · Children

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Introduction

Children with chronic rheumatic diseases (CRD), including juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), and juvenile dermatomyositis (JDM) can develop skeletal alterations during the course of their disease [1]. An increased incidence of osteoporosis, resulting in an increased risk of fractures, has been observed in children and adolescents, as well as in adults with CRD [1–3].

The pathogenesis of osteoporosis in patients with CRD is poorly understood. The duration of the disease, the severity of the inflammatory process, and steroid therapy have been suggested as risk factors, but it is difficult to evaluate their influence individually [1].

While many papers on the negative effects of long-term, low-dose steroid treatment in rheumatoid arthritis (RA) have already been published [4–8], few data on steroid-induced osteoporosis in other connective tissue disorders are available [9–13]. In SLE, steroids have been shown to increase the tendency to develop osteoporosis; the rate of bone loss has been correlated to daily corticosteroid dose, to the duration of treatment, and to the cumulative dose [2, 14–16]. In contrast, other studies support the independence of osteoporosis in SLE from glucocorticoids [9, 12, 17, 18]. Moreover, steroid-induced osteoporosis is still poorly studied in paediatric rheumatic diseases, in particular in JRA [19–21].

In recent years, several techniques have been developed for a non-invasive measurement of bone mineral density (BMD). Dual energy X-ray absorptiometry (DEXA), at lumbar spine, has proved to be very precise and is widely used in CRD patients since the trabecular bone of the spine appears to be most affected by corticosteroid therapy, leading to a high rate of vertebral fractures [22, 23].

The aims of our study were to determine with DEXA the BMD of children and adolescents affected with juvenile SLE (JSLE), and to establish the influence of steroid treatment, or other clinical and/or anthropometric variables during a follow-up period of 1 year.

Table 1 Demographic and clinical data at baseline

	Sex (F/M)	Puberty (pre/post)	On steroids (yes/no)	Previous steroid use (yes/no)	Other drugs (yes/no)	Disease activity (active/inactive)
Patients (*n*)	18/2	14/6	13/7	12/8	14/6	11/9

Patients and methods

Patients

A total of 20 consecutive outpatients (18 females and two males; 17 Caucasian, one Hispanic and two African-Americans; age range 5–25 years, mean 13.7±5.3 years), fulfilling the American Rheumatism Associations (ARA) revised criteria for the diagnosis of SLE [24], entered the study. Disease onset was at less than 16 years of age for all patients. All patients were regularly followed at the Paediatric Rheumatology Unit of the Paediatric Department.

A group of 31 healthy subjects, matched in age, weight, height, sex and puberty stage, was used as a control group; these controls were chosen from children and adolescents coming to our Paediatric Rheumatology Unit as a result of musculo-skeletal symptoms, but with no rheumatic disease.

General information was obtained by means of a detailed questionnaire on dietary habits, past medical history, mobility, previous fractures, and pubertal development. The daily dietary calcium intake proved to be normal in all patients compared to the values recommended by the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN). None of our patients suffered from renal, liver, or endocrine disorders; if these had been present, such patients would have been excluded from the study, as these diseases could influence the bone metabolism and, thus, the BMD value. Regarding general mobility, all patients stated that they were capable of performing the normal activities of daily life. Two girls had previously suffered from vertebral collapses. At baseline, eight patients were prepubertal (two of them reached puberty during the follow-up), while 11 girls had already menstruated and one boy had reached puberty (adult testicular volume). The disease duration ranged from 1 to 202 months (mean 37.6 months ±45.1). Disease activity in the SLE patients was assessed and scored according to the systemic lupus erythematosus disease activity index (SLEDAI) [25]; the disease was considered active when the index score was 10 or more, and inactive when the SLEDAI was less than 10.

On the basis of the wide variation in age of our patients and the correlation between mineralization and age, the studied population was arbitrarily subdivided into three subgroups: five patients aged 5–11, ten aged 12–18, and five aged 19–25 years. The mean BMD value of each subgroup was evaluated and compared to that of the same age subgroups of controls.

The JSLE patients were divided into two further subgroups, according to steroid treatment:

Group A included 13 patients (12 females and one male, mean age 14.1±1.3 years) who, at the time of enrollment in the study, were taking or had previously received oral corticosteroids. Four of them started steroid treatment immediately before BMD measurement. Prednisone use was recorded as current daily dose (per kilogram), and as cumulative dose. Ten patients were on a daily regimen, whereas three received steroids on alternate days.

Group B included seven patients (six females and one male, mean age 13.3±2.2 years) who had never received steroids.

To determine the cumulative lifetime dose responsible for the highest rate of bone loss, we arbitrarily defined low, medium, and high cumulative doses as amounts below 10 000 mg, between 10 000 and 30 000, and over 30 000 mg, respectively; JSLE patients treated with steroids were subdivided in these three categories. Before enrollment in the study, informed consent was obtained from all patients or parents.

Table 2 Anthropometric data at time 1 and time 2; mean results (±SD) and range

	Age (years)	Weight (kg)	Height (cm)	Steroid cumulative dose (mg)
Time 1	14.5 (±5.1)	47.5 (±10.6)	151.6 (±14.2)	10 898 (±16 045)
Range	5–25	27–65	112–172	0–53 777
Time 2	16.7 (±4.9)	48.3 (±10.5)	153.2 (±11.6)	20 594 (±17 857)
Range	7–26	27–64	132–172	0–54 992

BMD measurement

Lumbar vertebral BMD was measured using a DPX densitometer unit (Lunar Radiation, Madison, WI, USA) at baseline and 12 months later. This system scans the lumbar spine on a straight line with a collimated X-ray beam which is filtered to allow emission at two energy levels (38 and 70 keV). The patients are placed in a supine position and the physiological lumbar lordosis is flattened by elevating the knees. The scan sequence progresses from midline level below the iliac crest (L5) up to the first rib (T12). The scanning time ranges from 3 to 5 min and the radiation dose varies from 2.4 mrem to 4.8 mrem. DEXA detects the bone mass value as bone mineral content (BMC), expressed in grams; the software analyses the projected area of each vertebra and calculates the BMD expressed in grams per square centimeter (g/cm^2). The results for L2 through L4 are averaged to obtain the patient's total spine bone mass. BMD was measured at baseline (time 1) in all 20 children; 15 patients repeated DEXA 1 year later (time 2).

Statistical analysis

The data are expressed as means ± SD and range. Parameters which were different at time 1 and at time 2 (daily steroid treatment dosage, cumulative dose of corticosteroids, and other variables of clinical interest such as age, weight, height, disease activity and duration) were evaluated as individual differences at baseline vs. time 2. Statistical significance was assessed using a *t*-test for paired data. All statistical analyses were performed by statistical applied software (SAS). The Pearson correlation coefficients (PCC) were considered to assess the correlations. Statistical significance was taken at $P<0.05$.

Results

The demographic, clinical, and anthropometric characteristics of JSLE children at baseline and at time 2 are reported in Tables 1 and 2. At baseline, the mean value of BMD in the JSLE group, as a whole, was 0.978 g/cm^2 (±0.165 SD), ranging from 0.646 to 1.198 g/cm^2; the mean value of BMD in the control group was 1.038 g/cm^2 (±0.225 SD), ranging from 0.653 to 1.339g/cm^2 ($P=0.31$). At time 2, the mean value of BMD in the patients was 0.947g/cm^2 (±0.184 SD) ranging from 0.612 to 1.231 g/cm^2. Again, no statistical difference was observed between the

Table 3 Mean BMD values in JSLE and healthy children as total groups, and selected by age, at baseline

Age (years)	SLE BMD	Controls BMD	Z score (JSLE)	T (JSLE)	*P*
Whole groups	0.978 (±0.16)	1.038 (±0.22)	–0.36	1.01	0.31
5–11	0.774 (±0.11)	0.775 (±0.11)	–0.009	0.02	0.98
12–18	1.048 (±0.11)	1.124 (±0.16)	–0.69	1.26	0.22
19–25	1.043 (±0.15)	1.216 (±0.07)	–1.15	2.74	0.01*

* Significant

Table 4 Mean BMD values of JSLE patients at time 1 vs. time 2, as whole group and selected by age

	Time 1 BMD	Time 2 BMD	Mean difference BMD	*P*
Whole JSLE group	0.978	0.947	–0.031	0.1
5–11	0.774	0.675	–0.019	0.13
12–18	1.048	1.008	–0.039	0.31
19–25	1.043	1.030	–0.012	0.66

BMD values of patients at time 2 and controls. The individual difference between BMD values at time 2 vs. baseline was calculated; its mean value was 0.28 g/cm^2 (3.4%). At baseline, BMD values of JSLE patients were significantly lower than values of controls ($P = 0.01$) in only the third age subgroup (19–25 years) (Table 3); their mean BMD at time 2 was still significantly lower than that of their healthy peers.

The comparison between BMD values of the patients at baseline and at time 2 showed a decrease in all three age subgroups (–0.019 g/cm^2, –0.039 g/cm^2, and –0.012 g/cm^2, respectively). The highest loss occurred in the 12–18 age group (Table 4). None of these comparisons, however, proved to be significant.

Regarding steroid treatment, groups A and B did not significantly differ with respect to age, anthropometric indices, or disease activity. At baseline, the mean baseline BMD value of group A was 0.973 g/cm^2 and of group B 0.987 g/cm^2; no significant difference between the two groups was found ($P = 0.86$). At time 2, the mean BMD values of the two groups were 0.942 g/cm^2 and 0.980 g/cm^2, respectively; again, no significant difference was recorded ($P = 0.80$). The mean yearly BMD loss in group A was 0.031 g/cm^2 (3.5%), while in group B it was 0.005 g/cm^2 (0.5%).

The correlation analysis of the anthropometric variables in the whole population at baseline indicated that age, height, and weight were directly related to BMD, with a significant Pearson coefficient (PCC = 0.4, $P = 0.09$ for age; PCC = 0.7, $P = 0.0008$ for height; PCC = 0.3, $P = 0.05$ for weight). Moreover, BMD was inversely related to the cumulative dose of steroids (PCC = –0.4, $P = 0.05$). In contrast, no significant correlation between BMD and disease activity (PCC = –0.1, P = ns), or disease duration (PCC = 0.3, $P = 0.01$) was found.

Table 5 BMD loss in the cumulative steroid dose subgroups after 1 year of follow-up

Cumulative steroid dose	Subjects (*n*)	BMD loss (g/cm^2)
Low (<10,000 mg)	4	–0.67
Medium (10,000–30,000 mg)	5	–0.02
High (>30,000 mg)	4	–0.50

The same analysis, performed at time 2, confirmed the same previous positive correlations between BMD and age (PCC = 0.4, $P = 0.1$), height (PCC = 0.7, $P = 0.0005$), weight (PCC = 0.5, $P = 0.06$), and the negative correlation between BMD and cumulative dose of steroids (PCC = –0.5, $P = 0.04$).

The evaluation of the mean loss of BMD in the three categories of patients, based on cumulative steroid dose, showed that the highest rate of bone loss is recorded in those patients with a cumulative dose of less than 10 000 mg (Table 5).

Discussion

Osteoporosis in SLE and, in particular, the role of steroids in the development of this complication, are not yet fully understood, especially in childhood. To our knowledge, this is the first longitudinal study of BMD in a group of children and adolescents affected with JSLE and compared with healthy, age-matched children.

Our results show a reduction of BMD in JSLE patients compared to the controls, with a significant difference in the oldest group of subjects (aged 19–25 years). This result suggests that patients with JSLE are not able to reach the same peak bone mass as healthy adolescents or adults. Thus, our study confirms that children with JSLE have a high risk of developing osteopenia.

It is well known that bone mass is accumulated progressively from infancy through young adulthood and that it generally parallels linear growth. The annual rate of increase is approximately 8%, and complete skeletal maturation is reached during the middle part of the third decade of life [26]. Our data did not confirm this expected age-related yearly increase; the bone mass of the children studied decreased by about 3.4% during the 12 months of the study. Furthermore, when the three age categories are evaluated, the greatest bone loss rate takes place between the ages of 12 and 18, when BMD growth should be at its highest (see Table 4).

Some general risk factors for osteopenia, such as immobility, inadequate dietary intake of calcium or of Vitamin D, low body mass, and insufficient sunlight exposure may increase the incidence and severity of this complication in CRD, especially in SLE. In order to detect their influence on osteopenia, we investigated these variables in our JSLE population: diet, daily physical activity and weight all proved normal, while sun exposure was limited, because of the potential worsening of the disease. Lack of sunshine

exposure certainly represents an important risk factor for the development of osteoporosis in SLE and in JSLE.

Of the specific risk factors implicated in the pathogenesis of osteoporosis in SLE, disease duration and activity, as well as pharmacological treatment, have already been investigated [9–18]. From our results, BMD does not seem to be significantly related to disease duration or to disease activity, even if a weak correlation with the SLEDAI score was found. As regards corticosteroids, our data could not exhaustively clarify their role in the pathogenesis of bone loss in SLE.

At baseline, those children who were taking corticosteroids showed just a slightly lower, but not significant, BMD than patients not on steroids. This data, however, could be explained partially by the fact that some patients were enrolled in the study at the onset of their disease.

On the other hand, the mean BMD values of the whole JSLE population showed an inverse correlation to cumulative steroid dosage, at both baseline and time 2. Moreover, in the steroid-treated group, a yearly bone loss of approximately 3.5% was detected, while in the non-steroid group a slight increase of BMD was observed.

We found that the highest bone loss, after 1 year of follow-up, occurred in those patients with the lowest cumulative dose of steroids. This apparently surprising result could be explained by several considerations. First of all, most of these patients began steroid treatment in the year corresponding to the period of observation, with a low cumulative dose at time 2, due to the recent onset of their disease. Second, the demineralizing effect of steroids is far more evident at the beginning of steroid treatment, within the first 6 months. Thus, the low cumulative dose is only apparently responsible for severe bone loss. Indeed, previous longitudinal studies on osteoporosis in RA have already shown that the predominant loss of bone mass occurs early (within the first year) after disease onset [27, 28]. Our data are in agreement with many previous papers on steroid-induced osteoporosis in RA and JRA [4–7, 19–21].

Very few studies on other connective tissue diseases have been performed; these studies were cross-sectional evaluations of patients in the late phase of the disease, when disability and prolonged steroid therapy overlap. To our knowledge, only a few studies have investigated the effect of oral corticosteroids on BMD in SLE, with discordant results [2, 9, 10, 12, 17]. Dykman, in a study on BMD in 33 patients with SLE, demonstrated that cumulative dosage of prednisone (over 30 mg) was the most important factor determining corticosteroid osteopenia [2]. Kalla et al. evaluated trabecular BMD in 46 SLE patients, 22 of them on steroid treatment; they found a prevalence of osteopenia in 25% of SLE patients, with no differences between patients treated with and without corticosteroids [9].

Dhillon et al. performed DEXA on 22 SLE patients (12 on steroids, ten not on steroids), 14 steroid-dependent patients without lupus, and ten controls. No difference was noted among the three groups; mean steroid dose and duration were not stated [10]. Formiga et al. found a significantly reduced BMD in 74 female SLE patients, but was not able to demonstrate any association between BMD and cumulative or baseline doses of corticosteroids [12]. Sels et al. analyzed all the SLE patients (61 cases) reported in the literature, who had never received corticosteroid treatment; he found a modest loss of BMD at spine, hip and forearm, suggesting that osteopenia might be disease-related [17]. All these studies, however, were performed on adults and gave no prospective evaluation of mineralization during steroid therapy.

Our preliminary results confirm that osteopenia should be considered as a serious complication of JSLE; its pathogenesis is probably multifactorial, whereby the disease itself, a lack of sunshine, and long-term corticosteroid therapy represent mechanisms promoting bone loss. Although our population is too small to allow a definitive statement on the exact role of steroids in osteoporosis in JSLE, this study supports the theory of corticosteroid influence on BMD. Therefore, efforts should be made to reduce medication to the lowest possible maintenance dose, and to stimulate bone formation in prepubertal JSLE children and adolescents, encouraging a calcium-rich diet, and using Vitamin D supplements [29].

Too reach a definitive conclusion about the effects of oral corticosteroids on BMD in children with JSLE, more long-term epidemiological studies on larger populations are needed.

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