Evaluation of bone mass in children and young adults with juvenile idiopathic arthritis

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Abstract

Objective

To examine bone mineral density (BMD) in the spines of patients with juvenile idiopathic arthritis (JIA), and to identify the main predictors of spine BMD.

Methods

160 patients with JIA (82 female, 78 male; median age, 8.7±3.9 years (range, 2.2–18.2 years)) who fulfilled the International League of Associations for Rheumatology (ILAR) criteria were enrolled. All subjects underwent an initial dual energy x-ray absorptiometry (DXA) scan of the lumbar spine, while 114 and 87 patients underwent a second and third scan, respectively. The data were compared with those obtained for 114 sex- and age-matched healthy controls.

Results

The DXA scans revealed that the JIA patients had a significant spine BMD deficit compared with control subjects ($p<0.001$). Longitudinal comparison of patients revealed no significant short-term improvement in the spine BMD. Spine BMD correlated with the age ($p<0.05$), subtype ($p<0.05$), and disease activity ($p<0.01$), BMI ($p=0.001$), glucocorticoid (GC) exposure ($p< 0.05$), methotrexate (MTX) therapy ($p<0.05$), and non-steroidal anti-inflammatory agents (NSAIDs) ($p<0.05$), erythrocyte sedimentation rate (ESR) ($p<0.01$), and C-reactive protein (CRP) levels ($p<0.01$).

Conclusion

Patients with JIA have low bone mass, especially those in the polyarticular group >7 years old with higher disease activity.

Key words

Juvenile idiopathic arthritis, bone mass, bone mineral density, osteopenia

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common systemic rheumatic disease in children. Reduced bone mass and an increased risk of osteoporosis and fracture, both major health problems worldwide, are well-documented in JIA patients (1). Reduced bone mass in JIA patients is related to high disease activity, the number of affected joints, early disease onset, long duration of active disease, and reduced bone formation (1-5). In addition, reduced physical activity, an unbalanced diet, and reduced muscle strength determine the overall risk for osteoporosis (4, 6-8). Although several studies have examined bone mineral density (BMD) in JIA patients, the results are contrasting and contradictory (5, 9-15), and few prospective studies examined bone mass in a large cohort of JIA patients (16-18). Also, few studies have examined bone mass in patients with enthesitis-related arthritis (ERA) (9, 16). Furthermore, the uses of drugs, particularly glucocorticoids (GC), are controversial. GC can prevent young patients from achieving optimal peak bone mass (19). A lower peak bone mass increases the risk of osteoporosis and subsequent fracture during adulthood (4, 19-21); however, a longitudinal study suggests that the risk of osteoporosis does not increase significantly in RA patients treated with low dose GC (22). Moreover, methotrexate (MTX), tumour necrosis factor-alpha (TNF-α) inhibitors, and tocilizumab (an anti-IL-6 receptor antibody) not only control inflammation but also increase bone mass in JIA patients (23-27). A long-term outcome study (1) suggests that young adults with a history of early-onset JIA are more likely to be osteopenic.

Therefore, the aims of the present cross-sectional short-term follow-up study were to evaluate spinal BMD in JIA patients and to use dual energy x-ray absorptiometry (DXA) to identify the main predictors associated with spine BMD, especially several factors are divided into subgroups when analysed.

Materials and methods

Study participants and design

Patients were recruited from the Nephrology and Immunology Department of the Children's Hospital of Chongqing Medical University between August 2013 and April 2015. The study was approved by the hospital ethics committees, and informed consent was obtained from all participants and/or parents.

One hundred and sixty consecutive JIA patients (82 female, 78 male; median age, 8.7±3.9 years (range, 2.2–18.2 years)) who fulfilled the International League of Associations for Rheumatology (ILAR) criteria (28) were evaluated, including 66 systemic JIA, 45 polyarticular JIA (comprising 9 rheumatoid factor-positive JIA), 38 oligoarticular JIA, and 11 enthesitis-related arthritis (ERA). All patients underwent a DXA scan. Of these, 6 and 12 months after the first scan, 114 patients (60 female, 54 male; median age, 10.1±3.8 years (range: 2.9–17.9 years): 52 systemic, 30 polyarticular (comprising 6 rheumatoid factor-positive), 24 oligoarticular, and 8 ERA) and 87 (48 female, 39 male; median age, 11.6±4.0 years (range: 3.2–18.1 years): 37 systemic, 23 polyarticular (comprising 6 rheumatoid factor-positive), 19 oligoarticular, and 7 ERA) underwent a second and third DXA scan respectively. The data were compared with those from 114 sex- and age-matched healthy controls.

The time of disease onset was defined according to the date on which a paediatric rheumatologist first documented arthritis and/or systemic features. The disease subtype was defined according to reported definitions (28).

The following clinical and demographic data were obtained from medical records: age, sex, height, weight, body mass index (BMI), JIA subtype, time of disease onset, disease course, treatment, physical activity, past fracture (yes/no), and any family history of osteoporosis. Exposure to GC (duration, cumulative dose (0–100 mg/kg, low cumulative dose; 100–200 mg/kg, median cumulative dose; >200 mg/kg, high cumulative dose)) was assessed. Baseline clinical assessment of JIA, mainly focusing on disease activity and laboratory data, was performed longitudinally.

The exclusion criteria for the present study (which applied to both patients and controls) were as follows: meta-

bolic bone diseases, hyper-/hypoparathyroidism, cancer, a history of drug addiction, and osteoporosis risk factors (*e.g.* family history of osteoporosis). Any patient/control with an established diagnosis of osteoporosis and/or previous or present bisphosphonate therapy was excluded.

Healthy control subjects

The control group included 114 healthy sex- and age-matched subjects (63 female, 51 male; median age, 10.3±3.6 years (range: 3.1–17.8 years)) with non-inflammatory musculoskeletal complaints. Exclusion criteria (in addition to those listed above) included any chronic disease or medication known to affect bone mass (*e.g.* renal or hepatic disease, endocrine disorders, or a history of GC or anticonvulsant therapy). All subjects/parents provided informed consent.

Study methods and laboratory tests

Height was measured to the nearest 0.1 cm. Body weight was measured to the nearest 0.1 kg. BMI was calculated as weight divided by height (in meters) squared (kg/m^2). Age-related reference values for height and BMI were obtained from the child growth standards published by the World Health Organization (WHO) (29). Height and BMI were normalised according to chronological age by converting values to a standard deviation score (SDS). The SDS was calculated as follows: patient value – mean of age-related reference-value/standard deviation (SD) of the age-related reference value.

DXA was used to examine BMD in the lumbar spine (L1–L4). A strict protocol and the same equipment (Delphi-A System, Hologic Inc, Waltham, MA, USA) were used for each subject. BMD (g/cm^2) was calculated by the software supplied with the DXA instrument. Average BMD values for L1–L4 were used for all calculations, and data were expressed as Z scores (the patient's value-the normal value (according to age)/ the SD of the normal population).The intraobserver coefficient of variation was 1.0%.

To facilitate comparisons between JIA patients and healthy subjects, a Z score <-1 was defined as low bone mass. A phantom was used at regular intervals to check the reliability of the densitometer. All BMD measurements were performed by the same operator.

Clinical assessment of disease activity

Disease activity was assessed using the JIA Disease Activity Score 28 (DAS 28) (30-31). The DAS 28 is calculated according to the number of tender joints and swollen joints, the patient's global assessment of disease activity on a visual analogue scale (VAS) (as a part of the Childhood Health Assessment Questionnaire (CHAQ)(32)), and the ESR. A high DAS 28 score indicates high disease activity. Disease activity is scored as follows: <2.6, remission; ≥2.6 but ≤3.6, low activity; ≥3.6 but ≤5.5, moderate activity; and >5.5, high activity.

Serum markers of inflammation included the white blood cell count (cells/L), the absolute neutrophil count (cells/L), the platelet count (cells/L), the red blood cell count (cells/L), the erythrocyte sedimentation rate (ESR)(mm/h), and C-reactive protein (CRP) levels (mg/L).

Treatments

The cross-sectional short-term follow-up evaluations included a therapy assessment to ascertain whether certain treatments affected BMD; such treatments included non-steroidal anti-inflammatory drugs (NSAIDs), GC, MTX, TNF-α and/or IL-6 inhibitors, and calcium supplementation, vitamin D supplementation. The period of exposure to any drug was also recorded. Moreover, information about the type, dose, and duration of GC therapy was obtained from clinic, hospital, or emergency department records. Data were summed to identify the cumulative dose from the time of onset to the time of the first, second, and third DXA scans. The doses of all systemic GC were converted to an equivalent dose.

Laboratory and functional tests

Haemoglobin levels and red blood cell, white blood cell, and platelet counts, and the ESR and CRP levels, were measured using standard laboratory tests.

Statistical analysis

Statistical analyses were performed using SPSS19 (SPSS19 Inc, Chicago, IL, USA). Continuous variables were expressed as the mean ± SD or as the median and range depending on whether data were normally distributed. Differences between patients and controls were analysed using the Student's *t*-test and the Mann-Whitney U-test, depending on the distribution of the analysed variable. The chi-square test and Fisher's exact test were used as appropriate to examine associations between dichotomous variables. Inter-group comparisons were performed using analysis of variance (ANOVA) or repeated-measures analysis of covariance (ANCOVA), as appropriate. Spearman's (rank) correlation tests were used to determine correlation coefficients. Multiple stepwise regression was used to identify independent variables that correlate with lumbar spine BMD SDS values. *p*-values <0.05 were considered statistically significant.

Results

The first DXA scan

The baseline characteristics of the patients and controls are listed in Tables I and II.

At the first evaluation, all JIA patients showed lower spine BMD SDS values than the controls (-1.24±1.08 *vs.* -0.35±1.05, respectively; $p<0.001$). This trend remained true after JIA was subcategorised as systemic (-0.99±0.89, $p<0.001$), polyarticular (-1.52±1.21, $p<0.001$), oligoarticular (-1.36±1.33, $p<0.001$), or ERA (-1.46±0.82, $p=0.001$) (Fig. 1).

At the time of the first DXA scan, disease duration was not significantly different among the JIA subgroups (Table I). JIA patients with disease duration >2 years had a significantly lower spine BMD SDS than those with disease for <1 year (-1.50±1.21 *vs.* -1.05±0.93, respectively; $p=0.03$).

Apart from the polyarticular and systemic onset groups (-1.52±1.21 *vs.* -0.99±0.89, respectively; $p=0.014$), there were no significant differences in the spine BMD SDS between JIA subgroups (Fig. 1).

The spine BMD SDS for JIA was sig-

Table I. Baseline characteristics of the JIA patients and controls at the first DXA evaluation.

Characteristic	JIA	Controls (n)	*p*-value
No. of patients undergoing the first DXA (F:M)	82:78	63:51	NS
Age at the time of the first DXA scan (years ± SD; median)	9.8 ± 3.9; 9.8	10.3 ± 3.6; 10.0	NS
Height SDS	-0.9 ± 2.2	-0.3 ± 1.3	< 0.001
BMI SDS	-0.2 ± 1.3	-0.3 ± 1.2	< 0.001
Past fracture (Y/N)	N	N	NS
Physical activity (H/weeks)	2.8 ± 0.7	3.1 ± 0.9	NS
Type of JIA (%)			
Systemic	66 (41)		
Polyarticular	45 (28)	–	–
Oligoarticular	38 (24)		
ERA	11 (7)		
Age at onset (years ± SD)	7.5 ± 3.9		
Systemic	7.5 ± 3.9		
Polyarticular	7.1 ± 4.1	–	–
Oligoarticular	6.9 ± 3.9		
ERA	9.7 ± 3.0		
Disease duration (years ± SD)	2.3 ± 2.5		
Systemic	2.1 ± 2.3		
Polyarticular	2.4 ± 2.7	–	–
Oligoarticular	2.8 ± 2.2		
ERA	2.6 ± 3.0		
BMD SDS (L1–L4)			
Systemic	-0.99 ± 0.89	-0.35 ± 1.05	< 0.001
Polyarticular	-1.52 ± 1.21	-0.35 ± 1.05	< 0.001
Oligoarticular	-1.36 ± 1.33	-0.35 ± 1.05	< 0.001
ERA	-1.46 ± 0.82	-0.35 ± 1.05	= 0.001
Total	-1.24 ± 1.08	-0.35 ± 1.05	< 0.001

JIA: juvenile idiopathic arthritis; DXA: dual energy x-ray absorptiometry; SDS: standard deviation score; BMD: bone mineral density; BMI: body mass index; ERA: enthesitis-related arthritis; NS: not significant.

nificantly correlated with disease activity (r= -0.288, p=0.001). Those with moderate and high disease activity had a significantly lower spine BMD SDS than the those in remission (-2.16±1.26 *vs*. -1.07±1.01, respectively; p<0.001) or those with low disease activity (-2.16±1.26 *vs*. -1.24±1.00, respectively; p=0.003). In addition, the spine BMD SDS showed a significant negative correlation with age (r= -0.257, p=0.002). Patients <7 years old showed a higher spine BMD SDS than those between 7 and 11 years old (-0.86±1.02 *vs*. -1.17±1.08, respectively; p=0.017) and >11 years old (-0.86±1.02 *vs*. -1.54±1.05, respectively; p=0.013).

Moreover, the spine BMD SDS for JIA patients was significantly correlated with height SDS (r=0.498, p<0.001), BMI SDS (r=0.29, p=0.001).

There was a significant correlation between spine BMD values and exposure to NSAIDs, GC, and/or MTX. At the time of the first DXA, non-NSAIDs users had a significantly lower spine BMD SDS than those treated with drugs for between 1 and 2 years (-1.70±0.79 *vs*. -0.91±0.85, respectively; p=0.025). In general, high cumulative doses of GC resulted in a lower spine BMD SDS than low cumulative doses (-1.51±0.95 *vs*. -1.29±1.04, respectively; p=0.049). However, high cumulative doses of GC in those with systemic onset JIA resulted in a spine BMD SDS lower than that for those receiving a median cumulative dose (-1.39±0.86 *vs*. -0.69 ± 0.86, respectively; p=0.035) or a low dose (-1.39±0.86 *vs*. -0.74±0.78, respectively; p=0.036). Those taking MTX for >2 years showed significantly lower spine BMD SDS than those taking the drug for between 1 and 2 years (-1.74±1.24 *vs*. -1.00±1.23, respectively; p=0.026). The spine BMD SDS correlated with ESR levels (r= -0.217, p=0.01). JIA patients with an abnormal ESR (>20 mm/h) had a significantly lower spine BMD SDS than those with a normal ESR (-1.43±1.06 *vs*. -1.03±1.07, respectively; p=0.026).

The second DXA scan

At the time of the second and third DXA scans, patients with JIA had a lower spine BMD SDS than the respective controls (second DXA: -1.31±1.13 *vs*. -0.35±1.05, p<0.001; third DXA: -1.52±1.19 *vs*. -0.35±1.05, p<0.001); thus spine BMD SDS did not improve significantly over time (Table II and Fig. 2–3). Among all JIA subgroups, spine BMD SDS did not correlate significantly with the type of onset, and comparisons among subgroups were non-significant.

At the time of the second DXA evaluation, we found these factors correlation with spine BMD SDS, which agree with the data from the first scan, as follows: disease duration (r = -0.253, p=0.034; -1.58±1.16 *vs*. -0.73±0.96 for the >2 years *vs*. the between 1 and 2 years groups, respectively; p=0.012), disease activity (moderate and high activity groups *vs*. remission group: -3.00±0.62 *vs*. -1.07±1.01, p<0.001; moderate and high activity groups *vs*. low activity group: -3.00±0.62 *vs*. -1.57±1.15, p=0.009), age (r=-0.388, p=0.001; age <7 years *vs*. age between 7 and 11 years: -0.68±1.04 *vs*. -1.19±1.09, p=0.01; age <7 years *vs*. age >11 years: -0.68±1.04 *vs*. -1.59±1.07; p=0.012), and ESR (abnormal group *vs*. normal group: -1.75±1.19 *vs*. -0.80±0.82; p<0.001).

In addition, the spine BMD SDS correlated with exposure to GC and MTX. JIA patients exposed to a high cumulative dose of GC had a significantly lower spine BMD SDS than those with no exposure (-1.81±0.98 *vs*. -1.16±1.26, respectively; p=0.041) or a median cumulative dose (-1.81±0.98 *vs*. -0.90±1.04, respectively; p=0.001). Patients with a course of MTX lasting >2 years resulted in a significantly lower spine BMD SDS than those with a course lasting <1 year (-1.86±1.28 *vs*. -1.19±0.96, respectively; p=0.041), a course lasting between 1 and 2 years (-1.86±1.28 *vs*. -0.9±1.15, respectively; p=0.02), or no MTX at all (-1.86±1.28 *vs*. -0.98±0.89, respectively; p=0.023). These results remained consistent when we compared the spine BMD SDS of JIA patients with abnormal CRP levels with that of patients with normal levels

(-2.04±1.14 *vs*. -1.03±1.00, respectively; p=0.001).

Moreover, the spine BMD SDS for JIA patients was significantly correlated with height SDS (r=0.651, p<0.001), sex (if female = 1, male = 2; r = -0.255, p=0.036), and duration of NSAID treatment (r = -0.247, p=0.039).

The third DXA scan

At the time of the third DXA scan, the spine BMD SDS correlated with disease activity (r = -0.49, p<0.001; moderate and high activity group *vs*. remission group: -2.92±0.64 *vs*. -1.08±0.84; p<0.001; low activity group *vs*. remission group: -1.85±1.28 *vs*. -1.08±0.84; p=0.021), age (r = -0.353, p=0.007; age <7 years *vs*. age between 7 and 11 years: -0.61±0.95 *vs*. -1.23±1.08, p=0.008; age <7 years *vs*. age >11 years: -0.61±0.95 *vs*. -1.59±1.04, p<0.001), CRP level (r = -0.362, p=0.006; abnormal group *vs*. normal group: -1.19±1.03 *vs*. -2.06±1.00; p=0.006), ESR (r= -0.636, p=0.006; abnormal group *vs*. normal group: -2.31±1.31 *vs*. -0.97±0.72; p=0.016), height SDS (r=0.636, p<0.001), and BMI SDS (r=0.453, p=0.001).

There was a correlation between BMD and exposure to GC at the time of the third DXA scan. JIA patients exposed to a high cumulative dose of GC had a significantly lower spine BMD SDS than those with a low cumulative dose (-1.92±0.89 *vs*. -1.03±0.92, respectively; p=0.031) or a median cumulative dose (-1.92±0.89 *vs*. -1.19±0.98, respectively; p=0.017).

Table II. Evaluation of JIA patients and controls at the second and third DXA evaluations.

Characteristic	JIA	Controls (n)	p-value
No. of patients undergoing a second DXA scan (F:M)	60:54	63:51	NS
Age at the time of the second DXA scan (years ± SD; median)	10.1 ± 3.8; 10.0	10.3 ± 3.6; 10.0	NS
Physical activity (H/weeks)	2.9 ± 0.8	3.1 ± 0.9	NS
Type of JIA at the second DXA scan (%)			
Systemic	52 (46)		
Polyarticular	30 (26)	–	–
Oligoarticular	24 (21)		
ERA	8 (7)		
Disease duration at time of the second DXA scan (years ± SD)	2.8 ± 2.0		
Systemic	2.7 ± 2.0		
Polyarticular	2.8 ± 2.5	–	–
Oligoarticular	3.0 ± 1.3		
ERA	3.1 ± 3.4		
BMD SDS (L1–L4) measured at the second DXA scan			
Systemic	-1.20 ± 0.89	-0.35 ± 1.05	< 0.001
Polyarticular	-1.31 ± 1.42	-0.35 ± 1.05	= 0.001
Oligoarticular	-1.49 ± 1.27	-0.35 ± 1.05	< 0.001
ERA	-1.65 ± 0.73	-0.35 ± 1.05	= 0.001
Total	-1.31 ± 1.13	-0.35 ± 1.05	< 0.001
No. of patients undergoing a third DXA scan (F:M)	48:39	63:51	NS
Age at the time of the third DXA scan (years ± SD; median)	11.6 ± 4.0; 11.5	10.3 ± 3.6; 10.0	NS
Physical activity (H/weeks)	3.0 ± 0.8	3.1 ± 0.9	NS
Type of JIA at the third DXA scan (%)			
Systemic	37 (43)		
Polyarticular	23 (27)	–	–
Oligoarticular	19 (22)		
ERA	7 (8)		
Disease duration at the time of the third DXA scan (years ± SD)	3.1 ± 1.9		
Systemic	2.8 ± 1.6		
Polyarticular	3.0 ± 1.7	–	–
Oligoarticular	3.1 ± 1.5		
ERA	3.2 ± 3.7		
BMD SDS (L1–L4) measured at the third DXA scan			
Systemic	-1.11 ± 0.86	-0.35 ± 1.05	= 0.001
Polyarticular	-1.67 ± 1.19	-0.35 ± 1.05	< 0.001
Oligoarticular	-1.50 ± 1.48	-0.35 ± 1.05	= 0.030
ERA	-1.79 ± 0.67	-0.35 ± 1.05	= 0.001
Total	-1.52 ± 1.19	-0.35 ± 1.05	< 0.001

JIA: juvenile idiopathic arthritis; DXA: dual energy x-ray absorptiometry; SDS: standard deviation score; BMD: bone mineral density; BMI: body mass index; ERA: enthesitis-related arthritis; NS: not significant.

Discussion

Although some studies have examined BMD in JIA (5, 9-15), prospective data in adolescents and young adults are scarce (16-18), and study on the BMD comparison between JIA subtype or multivariate subgroups is rare.

Our study shows that children and young adults with JIA had significantly less bone mass than healthy subjects at baseline. Longitudinal follow-up showed that this trend continued for up to 6 months. Furthermore, we found that age, sex, disease duration, type of onset, age at onset, disease activity, chronic inflammation, and drug treatments may play crucial roles in the bone mass deficit in JIA patients. We found that >7 years old JIA patients have significantly lower bone mass than <7 years old patients, which may due to >7 years group had longer disease durations.

Bone mass is relative to body size (1). We found that JIA patients were shorter and had a lower BMI than control subjects, and that bone mass was positively correlated with both height and BMI. Indeed, studies show that growth retardation contributes to osteopenia (1). We also found a negative correlation between disease duration and BMD in JIA patients. These results can be explained by continuing alterations in the physiological interaction between muscle and bone after disease remission (2).

We also found greater bone loss in those with polyarticular JIA than in those with systemic onset JIA. According to several authors, reduced muscle mass could explain 75% of the varia-

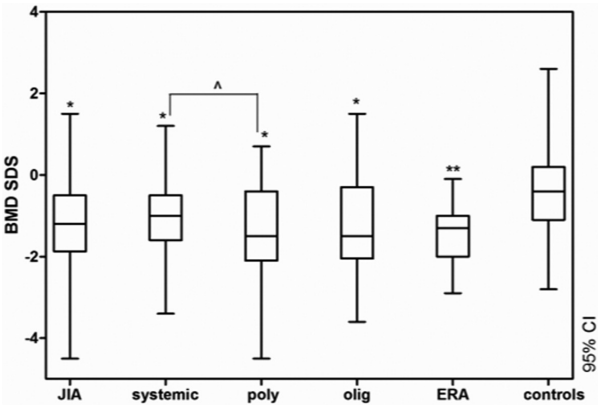

Fig. 1. The spine BMD SDS inpatients with systemic JIA, polyarticular JIA, oligoarticular JIA, and ERA vs. controls, and between JIA subgroups, at the first DXA scan. Bars represent mean and 95% CI. *p<0.001 and **p=0.001 compared with controls. ^p<0.05, pairwise contrast between JIA subgroups.

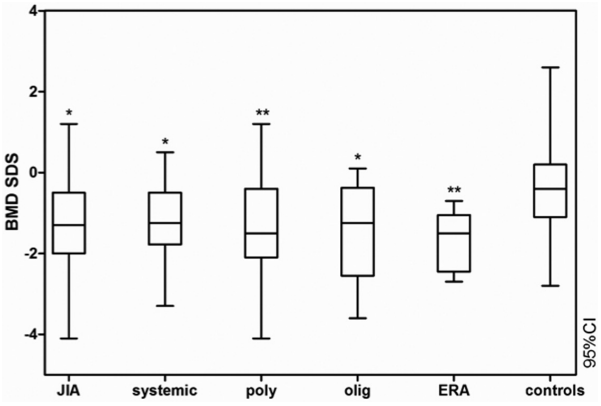

Fig. 2. The spine BMD SDS in patients with systemic JIA, polyarticular JIA, oligoarticular JIA, and ERA vs. controls, and between JIA subgroups, at the time of the second DXA scan. Bars represent the mean and 95% CI. *p<0.001 and **p=0.001 compared with controls. Pairwise contrast between JIA subgroups was non-significant.

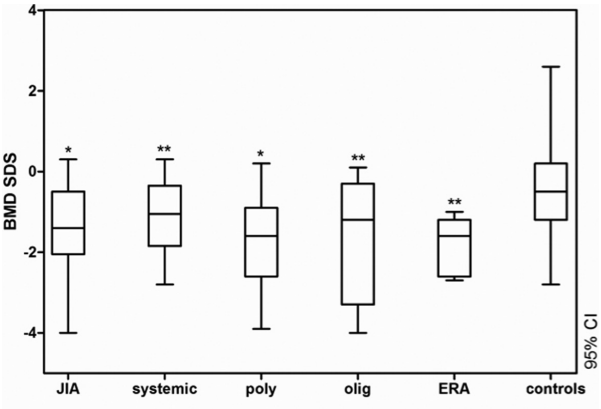

Fig. 3. The spine BMD SDS in patients with systemic JIA, polyarticular JIA, oligoarticular JIA, and ERA vs. that in controls, and between JIA subgroups, at the time of the third DXA scan. Bars represent mean and 95% CI. *p<0.001 and **p<0.05 compared with controls. Pairwise contrast between JIA subgroups was non-significant.

tion in bone mass (10, 33). The fact that 33% of patients have no active inflammation at the time of DXA supports this hypothesis (10, 33). Thus, limited physical activity and/or reduced muscle mass may be crucial determinants of bone mass (9).

BMD data with ERA patients are very rare. The results of the present study agree with those of others (2, 3, 9) showing that children and adolescents with ERA have significantly less bone mass than control subjects. These patients may show reduced physical activity, poorer physical health, and experience more pain than controls (34). Reductions in BMD may also be the result of inflammation (23-24).

Here, we showed that disease activity and ESR, both markers of inflammation, play critical negative roles in determining bone mass in JIA patients.

GC play very important roles in the therapeutic regime for JIA. Previous cross-sectional studies show that GC treatment results in reduced bone mass in the spine (19, 35). GC can cause growth retardation (35). The data presented here in reveale correlation between total GC dose and BMD values. GC deplete the osteoblastic cell population and inhibit the function of mature cells (19) and are, therefore, associated with the development of osteoporosis and bone fractures. Our data confirm that, notwithstanding the development of new therapeutic approaches, GC remain an important determinant of reduced bone accrual in these patients.

MTX increases bone mass in JIA patients by controlling joint inflammation (36). However, we observed a negative correlation between MTX treatment and BMD. Long-term exposure to MTX is associated with a high prevalence of osteopenia and osteoporosis (and an increased risk of fracture) in JIA patients (37-38).

Previous studies show that JIA patients treated with biological agents achieve clinical remission and show improved BMD (9, 16, 23); however, we did not find a correlation between TNF-α and/or IL-6 inhibitor therapy and BMD in JIA patients. This may be due to the small sample size and the short follow-up period.

In addition, our longitudinal assessment seems to suggest that JIA patients experienced no significant improvement in bone mass after 6 months of follow-up. These data show that bone mass deficits remains a concern for children, adolescents, and young adults with JIA, even though calcium supplementation improves BMD in JIA (35). In addition to routine calcium supplementation, other therapies that increase BMD values in JIA, such as physical activity, are also advocated.

Both ourselves and others found that BMD in JIA does not improve over time (17, 37); thus JIA patients may achieve unsatisfactory peak bone mass in early adulthood, leading to an increased risk of fracture.

In conclusion, patients with JIA have low bone mass, especially those in polyarticular group >7 years old with higher disease activity. Thus, JIA patients have a high risk of osteoporosis and fracture during early adulthood. To reduce these risks, close monitoring of BMD, early treatment, better control of inflammation, increased physical activity, and calcium supplementation are recommended.

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