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Prevalent Vertebral Fractures among Children Initiating Glucocorticoid Therapy for the Treatment of Rheumatic Disorders

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Abstract

Objectives—Vertebral fractures are an under-recognized problem in children with inflammatory disorders. We studied spine health among 134 children (87 girls) with rheumatic conditions (median age 10 years) within 30 days of initiating glucocorticoid (GC) therapy.

Methods—Children were categorized as follows: juvenile dermatomyositis (juvenile DM, N=30), juvenile idiopathic arthritis (JIA; N=28), systemic lupus erythematosus (SLE) and related conditions (N=26), systemic arthritis (N=22), systemic vasculitis (N=16), and other conditions (N=12). Thoracolumbar spine radiograph and dual energy x-ray absorptiometry for lumbar spine areal bone mineral density (LS BMD) were performed within 30 days of GC initiation. Genant semi-quantitative grading was used for vertebral morphometry. Second metacarpal morphometry

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was carried out on a hand radiograph. Clinical factors including disease and physical activity, calcium and vitamin D intake, cumulative GC dose, underlying diagnosis, LS BMD Z-score and back pain were analyzed for association with vertebral fracture.

Results—Thirteen vertebral fractures were noted in 9 children (7%). Six patients had a single vertebral fracture and three patients had two to three fractures. Fractures were clustered in the mid-thoracic region (69%). Three vertebral fractures (23%) were moderate (Grade 2); the others were mild (Grade 1). For the entire cohort, mean (±SD) LS BMD Z-score was significantly different from zero (−0.55±1.2, $p<0.001$) despite a mean height Z-score that was similar to the healthy average (0.02±1.0, $p=0.825$). Back pain was highly associated with increased odds for fracture (OR 10.6, 95% CI 2.1 to 53.8, $p=0.004$).

Conclusions—In pediatric rheumatic conditions, vertebral fractures can be present prior to prolonged GC exposure.

Introduction

There is increasing recognition that juvenile-onset, inflammatory rheumatic conditions are associated with adverse effects on the developing skeleton. Reductions in lumbar spine (LS), femoral neck and distal radial bone mineral density (BMD) in children with juvenile idiopathic arthritis (JIA) have been consistently documented among those who have been treated with glucocorticoids (GCs) (1–13) and those who have not (1–6,8,9,12,14–16). Reduced LS BMD has also been shown in children with juvenile dermatomyositis (DM) (17–21) and in juvenile systemic lupus erythematosus (SLE) (3,21–27).

Vertebral and extremity fractures have also been described in pediatric rheumatic disease. An increase in extremity fractures among children with arthritis has been documented through a large, population-based retrospective study (28). Furthermore, vertebral fracture prevalence ranging from 10 to 50% has been shown in cross-sectional studies of children with prolonged rheumatic disease durations and/or GC exposure (11,25,29,30). These cross-sectional reports have been important in highlighting the extent of spine morbidity in the years following diagnosis. However, the timing of vertebral fracture onset remains unknown. In addition, many of the previously reported children with vertebral fractures were treated with GCs and other potentially osteotoxic medications, making it difficult to determine if the observed fractures and reductions in BMD were related to the underlying disease, GC therapy, or other factors.

Our goal was to document the prevalence of vertebral fractures within 30 days of GC initiation in an inception cohort of GC-treated children with rheumatic disorders. In addition, we sought to determine the relationship between vertebral fractures and relevant clinical factors including spine BMD, underlying diagnosis, disease activity, age, pubertal stage, gender, back pain, calcium and vitamin D intake and physical activity.

Subjects and Methods

Patients and Study Design

Patients were recruited through the Canadian **ST**eroid-associated **O**steoporosis in the **P**ediatric **P**opulation (**STOPP**) research initiative, a national research program that studies bone morbidity in children with chronic illnesses. Patients from one month to 17 years of age were enrolled (N = 134) between January 1 2005 and December 31 2007 in 10 participating tertiary care children's hospitals. Patients were enrolled within 30 days of first-time GC treatment for inflammatory rheumatic conditions, including juvenile DM, juvenile SLE, JIA (all sub-types), systemic pediatric vasculitides (excluding Henoch-Schonlein purpura and Kawasaki Disease), juvenile scleroderma (both systemic and localized), and overlap syndromes (including mixed connective tissue disease). Diagnoses were made by university-affiliated, pediatric rheumatologists.

Children were excluded if GCs had previously been used at any time for treatment of the underlying disease. Patients were also excluded if they had received intravenous or oral GCs for more than 14 consecutive days in the 12 months preceding study enrolment to treat any other medical condition (e.g. asthma). Patients who had received prior medication for osteoporosis were also excluded, as were those who had received previous treatment with calcium and/or vitamin D supplementation that exceeded the Dietary Reference Intake for age (31). Since this study involved radiation from DXA and skeletal radiographs, girls were excluded if they were pregnant or menstruating and unwilling to use medically approved contraception. The study was approved by the Research Ethics Board in each institution and informed consent and/or assent was obtained prior to study enrolment.

Clinical Data

The decision to initiate GCs was made clinically prior to consideration for study enrollment. Demographic and anthropometric data were recorded using standard methods. Height, weight, and body mass index (weight (kg) divided by height (meters^2)) raw values were transformed into age- and gender-matched Z-scores according to the United States Centers for Disease Control National Center for Health Statistics normative database (32); for children under 2 years of age, BMI Z-scores were calculated according to the World Health Organization child growth standards (33). Pubertal staging was carried out according to the methods of Marshall and Tanner (34,35). The presence or absence of reported back pain at the time of diagnosis was recorded, and the spine was palpated for tenderness over the posterior spinous processes (T4 to L4). Time since diagnosis and symptom onset to the LS BMD assessment were recorded. Children were divided into sub-groups to facilitate characterization of the cohort, as follows: juvenile DM, juvenile JIA (excluding systemic arthritis), juvenile SLE and related conditions, systemic arthritis, systemic vasculitis and other conditions.

Assessment of Calcium and Vitamin D Intake

Calcium and vitamin D intake were assessed by a validated food frequency questionnaire (36). Intake for each nutrient was expressed as the percent of the Adequate Intake value based on the Dietary Reference Intakes (31). Calcium and vitamin D intake by

supplementation was added to the dietary intake to arrive at a total daily intake for both nutrients. The percentage scores were then classified as <50% of the age-related DRI, 50–100% of the DRI, and >100% of the DRI.

Physical Activity Assessment: The Habitual Activity Estimation Scale (HAES)

The HAES is a validated, self/proxy report that provides an estimation of the intensity and duration of physical activity over a single day (37,38). Activity was reported for both a typical weekday and weekend day in the previous three months. Activity classifications were as follows: Inactive (e.g. lying down), Somewhat Inactive (e.g. sitting), Somewhat Active (e.g. walking), and Very Active (e.g. running). Total inactive and total active times were determined by summing the two inactive and the two active categories for each of the weekend and weekday reports

Physician Global Assessment of Disease Activity According to Visual Analogue Scale

There is no assessment tool which has been shown to allow comparison of disease activity across rheumatic conditions. However, the use of visual analogue scales (VAS) completed by a physician who is expert in the assessment of pediatric rheumatic conditions has been validated in a variety of rheumatic conditions in the pediatric setting (39–41). Disease activity was scored according to a VAS by the patients' attending rheumatologists, measuring Physician Global Assessment of Disease Activity. The VAS was represented by a 10 cm scale, where 0 cm = inactive disease, and 10 cm = extremely active disease. Erythrocyte sedimentation rate (ESR) was also measured, using standard methodology from the local laboratories.

Lumbar Spine BMD by Dual-Energy X-Ray Absorptiometry (DXA)

BMD was measured in the anterior-posterior direction at the LS (L1-L4) by dual-energy x-ray absorptiometry using either Hologic machines (QDR 4500, 3 centers; Discovery, 2 centers; Delphi, 1 center; Hologic, Waltham, MA) or Lunar Prodigy (4 centers; GE Medical Systems, Madison, WI). Machines were cross-calibrated as previously described (42). The primary outcome for the study was LS BMD Z-scores; raw LS BMD results were transformed to chronological age- and gender-specific Z-scores as well as bone-age and gender-matched Z-scores using the Hologic 12.4 normative database provided by the manufacturer, which comprises the full age range of the children enrolled in the study. In vivo precision for LS BMD was available in 8 of 10 centers and ranged from 0.003 to 0.017 gm/cm^2.

Bone Age and Second Metacarpal Morphometry

Radiographs of the left hand and wrist for bone age were read independently by two pediatric radiologists (NS, MM) according to Greulich and Pyle (43). If results for the two examiners were within 12 months of each other, the average of the two readings was used. For results that differed by more than 12 months (N=10), a third reader (LMW), blinded to the results of the first two, adjudicated the discrepant reports. The intra-class correlation coefficient (ICC) was 0.99 (95% CI 0.986 to 0.993) between the two initial examiners. The radiographs were also evaluated for the possibility of rickets.

Using the same hand radiographs, a single observer measured the second metacarpal length, mid-shaft periosteal diameter, and inner diameter, as previously described (44), for derivation of the following indices: combined cortical thickness, cortical area, percent cortical area and inner diameter area. Indices were converted into age- and gender-matched Z-scores as previously described (45). The intra-observer reliability scores assessed by ICC were as follows: 1.0 (95% CI 0.999 to 1.0), 0.99 (95% CI 0.986 to 0.997) and 0.89 (95% CI 0.777 to 0.945) for metacarpal length, outer diameter and inner diameter, respectively.

Vertebral Morphometry

The Genant semi-quantitative method for vertebral morphometry was performed in the following manner. Vertebral bodies were first assigned a severity score: grade 0 (normal), grade 1 (mild), grade 2 (moderate) or grade 3 (severe). The morphometric grading corresponded to the extent of the reduction in height ratios when the anterior vertebral height was compared to the posterior height (wedge fracture), the middle height to the posterior height (biconcave fracture), and the posterior height to the posterior height of the adjacent vertebral bodies (crush fracture). The scores corresponded to the following reduction in height ratios: Grade 0: 20% or less; Grade 1: >20 to 25%; Grade 2: >25 to 40%; Grade 3: >40%. Grade 0 was considered to be normal while higher grades were considered to be a fracture. Minimal physiological rounding of vertebral bodies in the mid-thoracic region of the spine, as can be seen in normal children, was assigned a grade 0 score (46).

Vertebral fracture assessment was carried out independently by two radiologists (NS, MM) from T4 to L4 (42,47). Discrepancies between the first two readers were resolved by a third expert radiologist (BL), who was blinded to the results of the other two. The inter-observer reliability for the first two readers according to Cohen's kappa was 0.44 (95% CI 0.28 to 0.59) when Genant grade 0 scores were compared to Grades 1, 2 and 3 combined. For Grades 0 and 1 combined compared to Grades 2 and 3 combined, the Cohen's kappa was 0.66 (95% CI 0.46 to 0.87).

Statistical Analyses

Analyses were conducted using SPSS 16.0 (SPSS Inc., Chicago IL). Presented *p*-values were two-sided. To account for multiple comparisons, a Bonferroni correction was applied to the univariate analyses. Categorical variables were summarized using frequency and percentage. Normally distributed continuous variables were summarized using mean and standard deviation (SD). Non-normally distributed continuous variables were summarized using median and range. Z-score variables were compared against the healthy average (Z-score = 0.0) using one-sample student's t-test to assess whether the patient population significantly differed from the normal reference values. Proportions and 95% Confidence Intervals (CI) were calculated using the Wilson score method (48). Mann-Whitney or Fisher's exact test was used to compare patients with and without fracture. The comparison of combined cortical thickness Z-score between patients with and without fracture was adjusted for metacarpal length Z-score using linear regression.

Univariate logistic regressions were performed to identify clinical parameters that were associated with the presence of vertebral fractures. Multiple logistic regression was not

performed due to the small number of vertebral fracture events. Univariate linear regressions were similarly performed to identify the factors associated with LS BMD Z-score. To adjust for bone size, height Z-score was included in all linear regression on LS BMD Z-score models (both univariate and multivariate analysis). The following variables were included in a clinically-driven, multiple linear regression model which sought to determine associations between relevant factors and age- and gender-matched LS BMD Z-score: gender, height Z-score, BMI Z-score, pubertal stage (Tanner stage 1 versus 2–5), time since symptom onset, disease activity, cumulative GC dose in prednisone equivalents, diagnosis, and vitamin D intake. The results of this model were then verified using a step-wise model selection procedure which incorporated these same factors as well as age, physical activity, calcium intake, number of days on GCs, and time since diagnosis (log transformed to reduce skewness).

Results

Patient Characteristics

Descriptions of the cohort are provided in Tables 1 a and b. Seventy-five percent of the children were White; the other 25% of children were Black (7%), Aboriginal (5%), South Asian (3%) and Other or Mixed Ethnicity (10%). Height Z-scores were comparable to the healthy average for all disease sub-groups (overall cohort, p=0.825; juvenile DM, p=0.559; JIA, p=0.252; SLE and related conditions, p=0.292, systemic arthritis, p=0.255, systemic vasculitis, p=0.174 and other conditions, p=0.248). Weight was significantly above the healthy average for the overall cohort (p=0.006), and the systemic vasculitis sub-group (p=0.045), while BMI was increased in the overall cohort (p<0.001), the SLE and related conditions sub-group (p=0.017) and in systemic vasculitis (p=0.046).

Vertebral Fracture and Second Metacarpal Morphometry Status

Nine of the 134 children (7%, 95% CI, 3.6% to 12.3%) were found to have a total of 13 vertebral fractures. These children ranged in age from 6 to 16.5 years (5 boys, 4 girls). Six children had one fracture, two children had two fractures and one child had three fractures. Nine of the fractures were thoracic (four at T6, three at T7, two at T8) and four were lumbar (two at L1 and one each at L2 and L4). Nine of the fractures were mild anterior wedge (Grade 1); three were moderate (Grade 2) wedge fractures and one was a mild (Grade 1) crush fracture. There were 3/30 children with fractures in the juvenile DM sub-group (10%, 95% CI 4% to 26%), 2/22 from the systemic arthritis category (9%, 95% CI 3% to 28%), 2/26 from the SLE and related conditions category (8%, 95% CI 2% to 24%), 1/16 from the systemic vasculitis sub-group (6%, 95% CI 1% to 28%) and 1/12 in the other conditions category (8%, 95% CI 1% to 35%). None of the children with JIA (excluding systemic) manifested vertebral fractures (95% CI 0% to 12%). The three children with moderate (Grade 2) fractures had Wegener granulomatosis, SLE and systemic JIA. The six children with mild (Grade 1) fractures had juvenile DM (N=3), systemic JIA, SLE and scleroderma. Examples of mild and moderate fractures that were representative of the fractures detected in this cohort are presented in the Figure 1. There was no prior history of trauma in any of the patients.

Table 2 shows a comparison of children with vertebral fractures and those without. Back pain was reported in seven of nine (78%) children with fractures compared to 25% (31/125) of those without (p=0.002). A sub-set of patients (131/134) also underwent palpation of the T4 to L4 posterior spinous processes; only 8 of these 131 children reported pain on palpation and none of these 8 children manifested vertebral fractures. Children with fractures had a mean ± SD LS BMD Z-score of −1.2±1.0 compared to −0.5±1.2 among those without (p=0.082). For the children with fractures, the mean combined second metacarpal cortical thickness Z-score was −0.23±0.9 compared to 0.31±1.0 among those without (p=0.061), following adjustment for metacarpal length Z-score. In Table 3, univariate logistic regression against prevalent vertebral fracture revealed that back pain was highly associated with increased odds for fracture (OR 10.6, 95% CI 2.1 to 53.8, p=0.004).

Bone Densitometry

LS BMD Z-scores for the entire cohort are presented in Table 1. There was no significant difference between bone age and chronological age (p=0.610). Similarly, LS BMD Z-scores were no different when bone age was substituted for chronological age (p=0.331). The mean LS BMD Z-scores were significantly below the healthy average for the entire cohort (p<0.001) and for the following diagnostic sub-groups: juvenile DM sub-group (p<0.001), JIA (excluding systemic JIA, p=0.015), and systemic arthritis (p=0.002). Such differences were not observed in the SLE and related conditions sub-group (p=0.768), in systemic vasculitis (p=0.089) and in the other conditions category (p=0.875). There was no significant difference in the mean (±SD) LS BMD Z-score between those without fractures (−0.51±1.23; N=125) compared to those with mild (−0.76±0.92; N=6) and moderate vertebral fractures (−2.1±0.70; N=3; p=0.079).

The following variables were significant in a clinically-driven linear regression model which sought to determine associations between relevant factors and age- and gender-matched LS BMD Z-score: gender (β 0.67; 95% CI 0.25 to 1.08; p=0.002), height Z-score (β 0.32; 95% CI 0.13 to 0.50; p=0.001) and BMI Z-score (β 0.43; 95% CI 0.26 to 0.60; p<0.001). The results of this model were confirmed using a step-wise model selection procedure, which produced the same results and explained 31% of the variability in the LS BMD Z-score.

Discussion

Our work highlights novel observations about bone morbidity in pediatric rheumatic conditions, since this prospective study evaluated vertebral fracture status early in the course of GC exposure. We have documented a prevalent vertebral fracture rate of 7% in our inception cohort, with rates of 10% in juvenile DM, 9% in systemic arthritis, 8% in SLE and related conditions, 6% in systemic vasculitis, and 8% in the other conditions sub-group. While fractures were not observed in the JIA (excluding systemic) sub-group, our data suggest the potential for up to 12% of children with JIA to manifest vertebral fracture if the results were inferred to a larger population of children with JIA. Given that agreement between the radiologists on vertebral fracture assignment was fair to moderate, the protocol used in our study to assign vertebral fractures (which required agreement by two of three radiologists before a vertebra was considered fractured) would tend to under-estimate the

prevalence of fracture; therefore, the fracture prevalence rate may have been even slightly higher in these disease groups.

The observations in this study have important clinical implications. First, children with rheumatic conditions can manifest clear evidence of bone fragility (i.e. vertebral fractures) early in their disease course and exposure to GCs. Second, back pain is a highly associated clinical feature (though not universal, since 2 of the 9 children with fractures did not report such pain). That vertebral fractures can be present in the absence of back pain has been described in women with post-menopausal osteoporosis (49), in children with long-standing histories of rheumatic conditions (11), and in childhood acute lymphoblastic leukemia (ALL) (42). Overall, these results highlight that vertebral fractures are an under-recognized problem in children who have recently initiated GC therapy for rheumatic disorders.

We found that vertebral fractures were clustered in the mid-thoracic and upper lumbar regions, similar to reports in men and women with osteoporosis (50–53), as well as recent studies in children with rheumatic conditions (29) and leukemia (42). It is suggested that this fracture pattern results from the mechanical stresses induced by the natural kyphosis-lordosis of the spine (54). The location of fractures in areas for which there is a known predilection adds credence to our method of fracture determination. The fact that wedge deformity was the most common morphological finding is further in keeping with observations in large populations of adults with vertebral fractures (54) and in children with leukemia (42).

The few studies in the literature that have assessed vertebral fractures status in children with rheumatic conditions have been conducted at time-points more distant in their disease course compared to our study. Specifically, these reports have been cross-sectional or retrospective, often in the face of long-term GC exposure, and have shown vertebral fracture prevalence rates ranging from 10 to 50% (11,25,29,30). Our study stands unique for its timing of patient evaluation, within 30 days of GC initiation. The only other study conducted early in the course of the illness was by Rouster-Stevens et al (18), who assessed spine areal BMD by DXA in 37 children with untreated juvenile DM. They found that 6 of 33 (18%) evaluable patients had LS areal BMD Z-scores less than −1.5, and that the LS BMD Z-score was related to disease duration. Vertebral fracture status was not evaluated in this cohort of patients. Interestingly, we did not find a link between disease duration and either vertebral fracture or LS BMD Z-score. Disease activity indices also showed a lack of association. These findings may reflect lack of sufficient power to detect an association, a relatively short duration from both the time since diagnosis and symptom onset for most patients, and/or confounding effects of both underlying disease and short-term exposure to GCs in our cohort.

When children with vertebral fractures in our study were compared to those without, the only variable that showed a strong relationship to fractures was back pain. Of particular note is the borderline relationship between the presence of vertebral fractures and LS BMD Z-score. In contrast, children with newly diagnosed leukemia demonstrate a strong relationship between LS BMD and vertebral fractures, with the LS BMD Z-score lower in those with fractures, and falling as the grade of fracture worsens (42). These disparate observations may

be the result of lower power due to the smaller number of fracture events in rheumatic conditions soon after GC initiation compared to leukemia (7% versus 16%); on the other hand, the more fulminate effect of the leukemic process on bone may have greater impact on LS BMD in the short term compared to the typically more insidious inflammatory state in recently diagnosed rheumatic conditions.

Our study has two limitations which merit further consideration. First, back pain by report was determined but the location of the self-reported pain and the timing of pain onset were not specified. We found that such pain was highly correlated with vertebral fracture; however, without additional information as to the precise location of the reported pain or the timing of onset, we could not further correlate such parameters with the presence of vertebral fracture or with the initiation of GC therapy. A sub-set of patients (131/134) underwent palpation of the posterior spinous processes. While only 8 of the 131 children reported pain on palpation, none of these 8 children manifested vertebral fractures. Given the small number of children with palpation tenderness, we were unable to draw further conclusions as to the relationships among spine palpation tenderness, reported back pain and vertebral fractures. At the present time, the clinical significance of back pain and vertebral fractures in the absence of localized vertebral tenderness in this population remains unclear, particularly since the underlying disorders may also be associated with back pain and tenderness.

The second limitation arises from the study design. While our overall research program is predicated upon within-subject change over time in key parameters such as vertebral morphometery, this inaugural description of an inception cohort is based on uncontrolled, cross-sectional evaluation of spine status in relation to relevant clinical parameters. The lack of a control group gives rise to two issues in data interpretation. First, our spine BMD and anthropometric Z-scores have been generated through comparison to historical, published normative data, which may serve to under-estimate such indices given the rise in secular trends (55). Secondly, the frequency of mild (Grade 1) vertebral deformity in healthy children and thereby the clinical significance of mild changes in chronic illness remains unknown. In post-menopausal women, mild prevalent vertebral fractures are associated with an increased risk of future vertebral and hip fractures (56,57), with prevalent vertebral fracture severity being the strongest independent risk factor. The relationship between prevalent Grade 1 vertebral deformity at baseline in children with rheumatic conditions and the potential for development of new or worsening fractures will be assessed through further longitudinal study of this cohort.

In conclusion, we have shown that children with a variety of GC-treated rheumatic conditions can manifest vertebral fractures around the time of GC initiation, and that back pain is a highly correlated feature. Whether the fractures will undergo reshaping or deterioration with ongoing GC treatment will be determined through longitudinal study.

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Abbreviations

BMI	Body mass index
BMD	Bone mineral density
CI	Confidence interval
DM	Dermatomyositis
DRI	Dietary reference intake
DXA	Dual-energy x-ray absorptiometry
JIA	Juvenile idiopathic arthritis
LS	Lumbar spine
SD	Standard deviation
SLE	Systemic lupus erythematosus
VAS	Visual analogue scale

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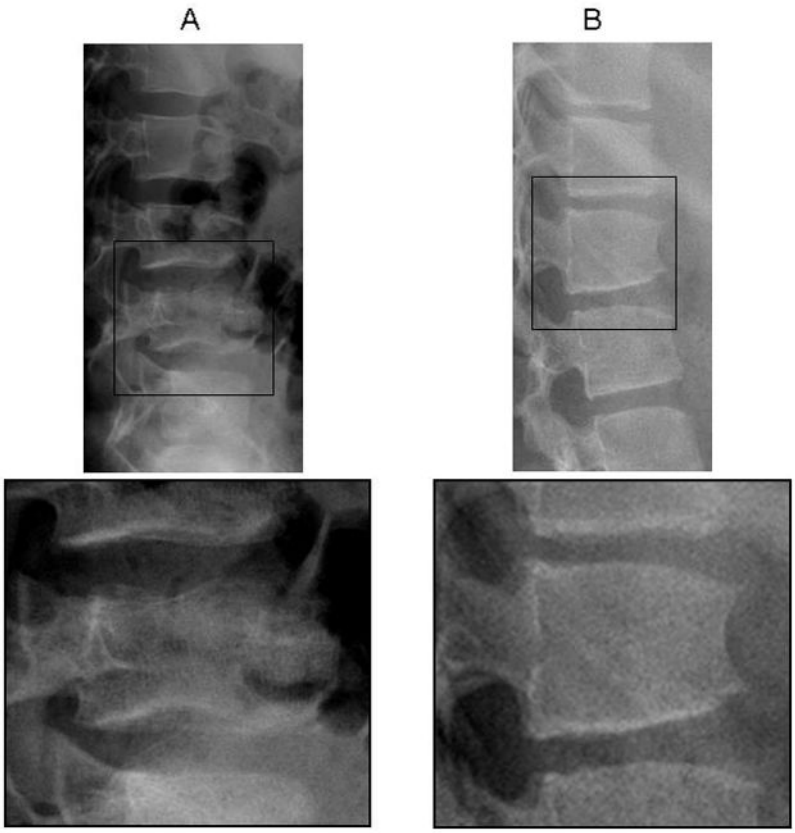

Figure 1.

A, 12-year-old boy with systemic juvenile idiopathic arthritis. Shown is a grade 1 crush fracture at L4, plus loss of endplate parallelism and endplate interruption. The lumbar spine bone mineral density (BMD) Z score was _1.4. **B**, 15-year-old girl with systemic lupus erythematosus. Shown is a grade 2 wedge fracture at L1, plus loss of endplate parallelism and anterior cortical buckling. The lumbar spine BMD Z score was _1.7.

Table 1a

Description of an Inception Cohort of Children Recently Initiating Glucocorticoids for the Treatment of Rheumatic Disorders

Clinical Characteristics	Overall Cohort N=134	Juvenile DM N=30	JIA N=28	SLE and Related Conditions N=26	Systemic Arthritis N=22	Systemic Vasculitis N=16	Other Conditions N=12
Demographic Data							
Female, N (%)	87 (65)	18 (60)	18 (64)	22 (85)	13 (59)	8 (50)	8 (67)
Age, median (min, max)	10.0 (1.4, 16.9)	7.3 (1.9, 15.1)	12.2 (3.7, 16.9)	13.6 (5.0, 16.1)	6.0 (1.4, 16.4)	12.6 (4.7, 16.9)	7.7 (3.3, 16.5)
Anthropometry							
Height Z-score, mean±SD	0.02±1.0	−0.11±1.0	−0.23±1.1	−0.17±0.8	0.28±1.1	0.42±1.2	0.36±1.0
Weight Z-score, mean±SD	0.28±1.2	0.03±1.2	0.07±1.2	0.28±1.0	0.29±1.0	0.77±1.4	0.76±1.2
BMI Z-score, mean±SD	0.37±1.2	0.19±1.2	0.23±1.1	0.46±0.9	0.23±1.3	0.69±1.3	0.76±1.3
Pubertal stage, N (%)							
Stage 1	69 (53)	24 (80)	9 (35)	7 (27)	15 (68)	7 (44)	7 (64)
Stage 2–5	62 (47)	6 (20)	17 (65)	19 (73)	7 (32)	9 (56)	4 (36)
Bone age, median (min, max)	10.0 (1.1, 17.5)	6.8 (1.4, 15.5)	12.9 (3.0, 16.0)	14.5 (4.6, 16.5)	5.9 (1.1, 17.0)	13.8 (3.3, 17.0)	7.7 (3.3, 17.5)
Age to bone age difference, mean±SD	−0.05±1.0	0.07±1.0	0.19±1.3	−0.50±1.0	0.06±0.5	−0.01±1.4	−0.14±0.8
Rheumatic Conditions Characteristics							
Disease activity (10 cm VAS), mean±SD	5.6±2.8	6.2±2.8	5.3±2.6	4.7±2.9	6.3±2.0	6.1±3.7	4.7±2.4
ESR (mm/hr), median (min, max)	33.0 (0, 133)	17.0 (2, 109)	36.0 (5, 106)	47.5 (7, 116)	58.5 (10, 133)	47.0 (1, 109)	9.5 (0, 40)
Number of days since diagnosis, median (min, max)	22 (1, 4900)	19 (1, 357)	32 (1, 4900)	16 (1, 235)	22 (1, 64)	21 (1, 132)	61 (8, 1984)
Number of days since symptom onset, median (min, max)	145 (17, 5110)	124 (27, 742)	353 (30, 5110)	67 (17, 765)	50 (18, 225)	138 (24, 975)	298 (155, 2349)
Physical Activity Level (the HAES Questionnaire)							
Relative physical activity (% of waking hrs), median (min, max)	46 (0, 97)	42 (0, 86)	51 (0, 91)	38 (0, 97)	52 (0, 83)	36 (0, 78)	67 (29, 90)
Very active weekend hours, median (min, max)	1.0 (0, 17)	0 (0, 7)	1.4 (0, 11)	0 (0, 17)	0.9 (0, 8)	0.4 (0, 5)	4.7 (0, 12)
Glucocorticoid Treatment							
Cumulative GC dose (mg/m^2), mean±SD **	1404±1690	2334±2184	460±797	1647±1643	762±1159	1680±1693	1477±1417
Number of days on GC, mean±SD	16.5±8.6	17.0±9.5	17.9±7.4	17.5±9.0	16.5±7.7	18.4±7.8	7.7±6.6
Number of days between initial GC dose and DXA assessment, mean±SD	16.7±8.7	15.8±10.0	18.6±7.1	16.0±9.4	15.5±8.7	17.1±7.5	19.3±9.5
Lumbar Spine (LS) BMD							

Clinical Characteristics	Overall Cohort N=134	Juvenile DM N=30	JIA N=28	SLE and Related Conditions N=26	Systemic Arthritis N=22	Systemic Vasculitis N=16	Other Conditions N=12
LS BMD Z-score, mean±SD	−0.55±1.2	−1.06±1.0	−0.71±1.4	0.06±1.1	−0.63±0.8	−0.70±1.5	0.04±0.8
LS BMD Z-score for bone age, mean±SD	−0.60±1.0	−1.01±0.8	−0.70±1.2	−0.22±0.9	−0.57±1.0	−0.76±1.3	−0.02±0.85

SD=Standard deviation, BMI=Body mass index, VAS=Visual analogue scale, ESR=Erythrocyte sedimentation rate, BMD= Bone mineral density, GC=Glucocorticoids, JIA = Juvenile Idiopathic Arthritis, DM = Dermatomyositis, SLE = Systemic Lupus Erythematosis

** Cumulative GC dose is reported in prednisone equivalents

Table 1b

Specific Diseases within Diagnostic Sub-Groups

Diagnosis	n (%)
Rheumatic Conditions: Total Cohort	**134**
Diagnostic Sub-Groups	
Juvenile Dermatomyositis	**30 (22)**
JIA (Excluding Systemic Arthritis)	**28 (21)**
Polyarticular Rheumatoid Factor positive arthritis	5 (18)
Polyarticular Rheumatoid Factor negative arthritis	8 (29)
Psoriatic arthritis	2 (7)
Enthesitis-related arthritis	5 (18)
Oligoarticular arthritis	4 (14)
Unclassified	4 (14)
Systemic Lupus Erythematosus and related conditions	**26 (20)**
Systemic Lupus Erythematosus	21 (81)
Overlap syndromes: mixed connective tissue disease	5 (19)
JIA (Systemic Arthritis)	**22 (16)**
Systemic Vasculitis (excluding Kawasaki's disease and Henoch-Schonlein Purpura (HSP))	**16 (12)**
Takayasu arteritis	4 (25)
Wegener granulomatosis	7 (44)
Microscopic polyangiitis	1 (6)
Other vasculitis, including:	4 (25)
P-ANCA positive vasculitis with recurrent pericarditis (N=1)	
P-ANCA positive vasculitis with Goodpasture syndrome (N=1)	
CNS vasculitis (N=1)	
P-ANCA positive renal-limited vasculitis (N=1)	
Other conditions	**12 (9)**
Scleroderma - Generalized	1 (8)
Scleroderma - Localized	10 (84)
Eosinophilic Fasciitis	1 (8)

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Table 2

Comparison of Children With and Without Vertebral Fractures

Clinical Characteristics	Children Without Vertebral Fracture N = 125	Children With Vertebral Fractures N = 9	*p*
Demographic Data			
[A] Girls, N (%)	83 (66)	4 (44)	0.277
Age, median (min, max)	10.0 (1.4, 16.9)	14.3 (6.4, 16.5)	0.043
Anthropometry			
Height Z-score, mean±SD	0.04±1.0	−0.29±0.9	0.267
Weight Z-score, mean±SD	0.31±1.2	−0.20±0.9	0.154
BMI Z-score, mean±SD	0.40±1.2	−0.13±1.1	0.213
[A] Pubertal stage, N (%)			
Stage 1	65 (53)	4 (50)	1.000
Stage 2 – 5	58 (47)	4 (50)	
Bone age, median (min, max)	10.0 (1.1, 17.5)	13.5 (6, 16)	0.103
Second Metacarpal Morphometry			
Metacarpal length Z-score, mean±SD	0.35±1.1	0.50±0.9	0.553
Percent cortical area Z-score, mean±SD	0.21±0.9	0.15±0.6	0.628
Combined cortical thickness Z-score, mean±SD	0.31±1.0	−0.23±0.9	[B] 0.061
Rheumatic Conditions Characteristics			
Disease activity (10 cm VAS), mean±SD	5.6±2.7	5.5±3.4	0.887
ESR (mm/hr), median (min, max)	40.5 (31.2)	27.9 (24.5)	0.234
Number of days since diagnosis, median (min, max)	23 (1, 4900)	22 (3, 1902)	0.407
Number of days since symptom onset, median (min, max)	146 (17, 5110)	93 (19, 2268)	0.771
Back Pain			
[A] Yes, N (%)	31 (25)	7 (77.8)	**0.002**[≠]
Lumbar Spine BMD			
Lumbar spine BMD Z-score, mean±SD	−0.51±1.2	−1.2±1.0	0.082
Glucocorticoid Treatment			
Cumulative GC dose (mg/m^2), mean±SD	1410±1600	1320±2755	0.244
Number of days on GC, mean±SD	16.7±8.5	14.1±10.4	0.376

Clinical Characteristics	Children Without Vertebral Fracture N = 125	Children With Vertebral Fractures N = 9	*p ¥
[C] ***Total Calcium and Vitamin D Intake (Diet & Supplement)***			
Total calcium daily intake, mean± SD % of the DRI			
< 50 (N = 4 with fractures, N = 0 without)	31±19	NA	NA
50 – 100 (N = 12 with fractures, N = 1 without)	68±13	70 (NA)	0.923
>= 100 (N = 104 with fractures, N = 8 without)	273±164	178±60	0.042
Total vitamin D daily intake, mean± SD % of the DRI			
< 50 (N = 30 with fractures, N = 2 without)	24±15	30±25	0.734
50 – 100 (N = 18 with fractures, N = 1 without)	74±14	74 (NA)	0.737
>= 100 (N = 73 with fractures, N = 6 without)	170±65	163±57	0.868
HAES Activity Levels			
Very active weekend hours, median (min, max)	1.1 (0, 17)	0 (0, 4)	0.046

SD=Standard deviation, BMI=Body mass index, VAS=Visual analogue scale, ESR=Erythrocyte sedimentation rate, BMD= Bone mineral density, GC=Glucocorticoids, DRI=Dietary Reference Intake

Cumulative glucocorticoid dose is reported in prednisone equivalents

[*] Statistical significance determined by non-parametric test (Mann-Whitney U with 2 independent samples)

[A] Statistical significance determined by Chi-squared test or Fisher's Exact Test

[B] *p*-value with adjustment for metacarpal length Z-score by linear regression

[C] Intake grouped into three groups based on the percent relative to the Dietary Recommended Intake for age

[¥] Level of significance after Bonferroni correction = 0.002

[#] Significant at $P \leq 0.002$

Table 3

Univariate Logistic Regression Analysis of Factors Potentially Associated with the Presence of Vertebral Fractures

Clinical Parameter	Children with Rheumatic Disorders N=134	
	Odds Ratio (95% CI)	p^{Ψ}
Age	1.2 (1.0, 1.4)	0.062
Gender (girls vs. boys)	0.4 (0.1, 1.6)	0.195
Height Z-score	0.7 (0.4, 1.4)	0.334
BMI Z-score	0.7 (0.4, 1.2)	0.185
Back pain	10.6 (2.1, 53.8)	**0.004**‡
Disease activity (10 cm VAS)	1.0 (0.8, 1.3)	0.887
Diagnosis (Juvenile DM vs. Other Diagnoses)	1.8 (0.4, 7.7)	0.420
Number of days since diagnosis (log transformed)	0.9 (0.6, 1.5)	0.693
Total vitamin D daily intake (≥ 100% of DRI vs. < 100% of DRI)	1.3 (0.3, 5.5)	0.708
Total calcium daily intake (≥ 100% of DRI vs. < 100% of DRI)	1.3 (0.2, 11.1)	0.806
Cumulative GC dose (g/m^2)	1.0 (0.6, 1.5)	0.876
Lumbar spine BMD Z-score	0.6 (0.4,1.1)	0.090

CI=Confidence interval, BMI=Body mass index, BMD=Bone mineral density, VAS=Visual analogue scale, GC=Glucocorticoids, DM=Dermatomyositis, DRI=Dietary Reference Intake

$^{\Psi}$Level of significance after Bonferroni correction = 0.004

‡Significant at $P \leq 0.004$