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ORIGINAL ARTICLE

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

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Objective. **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 therapy.**

Methods. **Children were categorized as follows: juvenile dermatomyositis (n = 30), juvenile idiopathic arthritis (n = 28), systemic lupus erythematosus and related conditions (n = 26), systemic arthritis (n = 22), systemic vasculitis (n = 16), and other conditions (n = 12). Thoracolumbar spine radiograph and dual x-ray absorptiometry for lumbar spine (L-spine) areal bone mineral density (BMD) were performed within 30 days of glucocorticoid initiation. Genant semiquantitative grading was used for vertebral morphometry. Second metacarpal morphometry was carried out on a hand radiograph. Clinical factors including disease and physical activity, calcium and vitamin D intake, cumulative glucocorticoid dose, underlying diagnosis, L-spine BMD Z score, and back pain were analyzed for association with vertebral fracture.**

Results. **Thirteen vertebral fractures were noted in 9 children (7%). Of these, 6 patients had a single vertebral fracture and 3 had 2–3 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 L-spine 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 (odds ratio 10.6 [95% confidence interval 2.1–53.8], $P = 0.004$).**

Conclusion. **In pediatric rheumatic conditions, vertebral fractures can be present prior to prolonged glucocorticoid 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 (L-spine), 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 (1–13) and those who have not (1–6,8,9,12,14–16). Reduced L-spine BMD has also been shown in children with juvenile

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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 glucocorticoid 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 glucocorticoids and other potentially osteotoxic medications, making it difficult to determine whether the observed fractures and reductions in BMD were related to the underlying disease, glucocorticoid therapy, or other factors.

Our goal was to document the prevalence of vertebral fractures within 30 days of glucocorticoid initiation in an inception cohort of glucocorticoid-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, sex, back pain, calcium and vitamin D intake, and physical activity.

PATIENTS AND METHODS

Patients and study design. Patients were recruited through the Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) research initiative, a national research program that studies bone morbidity in children with chronic illnesses. Patients from 1 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 glucocorticoid treatment for inflammatory rheumatic conditions, including juvenile DM, juvenile SLE, JIA (all subtypes), systemic pediatric vasculitides (excluding Henoch-Schönlein 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 glucocorticoids had previously been used at any time for treatment of the underlying disease. Patients were also excluded if they had received intravenous or oral glucocorticoids for >14 consecutive days in the 12 months preceding study enrollment to treat any other medical condition (e.g., asthma). Patients who had received prior medication for osteoporosis (OP) were also excluded, as were those who had received previous treatment with calcium and/or vitamin D supplementation that exceeded the Dietary Reference Intake (DRI) for their age (31). Because this study involved radiation from dual x-ray absorptiometry (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 enrollment.

Clinical data. The decision to initiate glucocorticoids was made clinically prior to consideration for study enrollment. Demographic and anthropometric data were recorded using standard methods. Height, weight, and body mass index (BMI; weight in kilograms divided by height in meters squared) raw values were transformed into age- and sex-matched Z scores according to the US Centers for Disease Control and Prevention National Center for Health Statistics normative database (32); for children <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–L4). Time since diagnosis and time since symptom onset to the L-spine BMD assessment were recorded. Children were divided into subgroups to facilitate characterization of the cohort, as follows: juvenile DM, JIA (excluding systemic arthritis), juvenile SLE and related conditions, systemic arthritis, systemic vasculitis (SV), 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 DRIs (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 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 a typical weekend day in the previous 3 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 2 inactive and the 2

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active categories for each of the weekend and weekday reports.

Physician's global assessment of disease activity according to a visual analog scale (VAS). There is no assessment tool that has been shown to allow comparison of disease activity across rheumatic conditions. However, the use of a VAS completed by a physician who is an 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's global assessment of disease activity. The VAS was represented by a 10-cm scale, where 0 = inactive disease and 10 = extremely active disease. Erythrocyte sedimentation rate was also measured, using standard methodology from the local laboratories.

L-spine BMD by DXA. BMD was measured in the anteroposterior direction at the L-spine (L1–L4) by DXA using either Hologic machines (QDR 4500 at 3 centers, Discovery at 2 centers, and Delphi at 1 center; Hologic, Waltham, MA) or Lunar Prodigy (4 centers; GE Medical Systems, Madison, WI). The machines were cross-calibrated as previously described (42). The primary outcome for the study was L-spine BMD Z score; raw L-spine BMD results were transformed to 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 L-spine 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 2 pediatric radiologists (NS, MM) according to Greulich and Pyle (43). If results for the 2 examiners were within 12 months of each other, the average of the 2 readings was used. For results that differed by >12 months (n = 10), a third reader (LMW) who was blinded to the results of the first 2 adjudicated the discrepant reports. The intraclass correlation coefficient (ICC) was 0.99 (95% confidence interval [95% CI] 0.986–0.993) between the 2 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, midshaft periosteal diameter, and inner diameter, as previously described (44), for derivation of the following indices: combined cortical thickness, cortical area, percentage cortical area, and inner diameter area. Indices were converted into age- and sex-matched Z scores as previously described (45). The intraobserver reliability scores assessed by ICC were 1.0 (95% CI 0.999–1.0), 0.99 (95% CI 0.986–0.997), and 0.89 (95% CI 0.777–0.945) for the metacarpal length, outer diameter, and inner diameter, respectively.

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

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

Statistical analyses. Analyses were conducted using SPSS, version 16.0 (SPSS, Chicago, IL). The presented *P* values were 2-sided. To account for multiple comparisons, a Bonferroni correction was applied to the univariate analyses. Categorical variables were summarized using frequencies and percentages. Normally distributed continuous variables were summarized using means and SDs. Non-normally distributed continuous variables were summarized using medians and ranges. Z score variables were compared against the healthy average (Z score = 0.0) using a 1-sample Student's *t*-test to assess whether the patient population significantly differed from the normal reference values. Proportions and 95% CIs were calculated using the Wilson score method (48). The Mann-Whitney test 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 L-spine BMD Z score. To adjust for bone size, height Z score was included in all linear regression on L-spine BMD Z score models (both univariate and multivariate analysis). The following variables were included in a clinically-driven, multiple linear regression model that sought to determine associations between relevant factors and L-spine BMD Z score: sex, height Z score, BMI Z score, pubertal stage (Tanner stage 1 versus 2–5), time since symptom onset, disease activity, cumulative glucocorticoid dose in prednisone equivalents, diagnosis, and vitamin D intake. The

Table 1. Description of an inception cohort of children recently initiating GC 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							
Girls, no. (%)	87 (65)	18 (60)	18 (64)	22 (85)	13 (59)	8 (50)	8 (67)
Age, years	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, no. (%)†							
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, years	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 condition characteristics							
Disease activity, mean ± SD 10-cm VAS score	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/hour	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)
Days since diagnosis	22 (1–4,900)	19 (1–357)	32 (1–4,900)	16 (1–235)	22 (1–64)	21 (1–132)	61 (8–1,984)
Days since symptom onset	145 (17–5,110)	124 (27–742)	353 (30–5,110)	67 (17–765)	50 (18–225)	138 (24–975)	298 (155–2,349)
Physical activity level, HAES							
Relative physical activity, % of waking hours	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	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)
GC treatment, mean ± SD							
Cumulative GC dose (mg/m^2)‡	1,404 ± 1,690	2,334 ± 2,184	460 ± 797	1,647 ± 1,643	762 ± 1,159	1,680 ± 1,693	1,477 ± 1,417
Days taking GC, no.	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
Days between initial GC dose and DXA assessment	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
L-spine BMD, mean ± SD							
Z score	−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
Z score for bone age	−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

* Values are the median (min–max) unless otherwise indicated. GC = glucocorticoids; DM = dermatomyositis; JIA = juvenile idiopathic arthritis; SLE = systemic lupus erythematosus; BMI = body mass index; VAS = visual analog scale; ESR = erythrocyte sedimentation rate; HAES = Habitual Activity Estimation Scale; DXA = dual x-ray absorptiometry; L-spine = lumbar spine; BMD = bone mineral density.
† Data available in 131 children.
‡ Reported in prednisone equivalents.

results of this model were then verified using a stepwise model selection procedure that incorporated these same factors as well as age, physical activity, calcium intake, number of days on glucocorticoids, and time since diagnosis (log-transformed to reduce skewness).

RESULTS

Patient characteristics. Descriptions of the cohort are provided in Tables 1 and 2. Of the children, 75% were white; the other 25% were black (7%), aboriginal (5%), South Asian (3%), and of other or mixed ethnicity (10%). Height Z scores were comparable with the healthy average for all disease subgroups (for the overall cohort $P = 0.825$, for juvenile DM $P = 0.559$, for JIA $P = 0.252$, for SLE and related conditions $P = 0.292$, for systemic arthritis $P = 0.255$, for SV $P = 0.174$, and for other conditions $P = 0.248$). Weight was significantly above the healthy average for the overall cohort ($P = 0.006$) and the SV subgroup ($P = 0.045$), and BMI was increased in the overall cohort ($P < 0.001$), the SLE and related conditions subgroup ($P = 0.017$), and the SV subgroup ($P = 0.046$).

Vertebral fracture and second metacarpal morphometry status. Of the 134 children, 9 (7% [95% CI 3.6–12.3%]) were found to have a total of 13 vertebral fractures. The children with fractures (5 boys, 4 girls) ranged in age from 6 to 16.5 years. Of these children, 6 had 1 fracture, 2 children had 2 fractures, and 1 child had 3 fractures. Of the fractures, 9 were thoracic (4 at T6, 3 at T7, and 2 at T8) and 4 were lumbar (2 at L1 and one each at L2 and L4). Nine of the fractures were mild (grade 1) anterior wedge fractures, 3 were moderate (grade 2) wedge fractures, and 1 was a mild (grade 1) crush fracture. In the juvenile DM subgroup (n = 30) there were 3 children with fractures (10% [95% CI 4–26%]), in the systemic arthritis category (n = 22) there were 2 (9% [95% CI 3–28%]), in the SLE and related conditions category (n = 26) there were 2 (8% [95% CI 2–24%]), in the SV subgroup (n = 16) there was 1 (6% [95% CI 1–28%]), and in the other conditions category (n = 12) there was 1 (8% [95% CI 1–35%]). None of the children with JIA (excluding systemic) manifested vertebral fractures (95% CI 0–12%). The 3 children with moderate (grade 2) fractures had Wegener's granulomatosis, SLE, and systemic JIA. The 6 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 Figure 1. There was no prior history of trauma in any of the patients.

A comparison of children with vertebral fractures and those without is shown in Table 3. Back pain was reported in 7 (78%) of the 9 children with fractures compared with 31 (25%) of the 125 children without ($P = 0.002$). A subset of patients (131 of 134) also underwent palpation of the T4–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 L-spine BMD Z score of −1.2 ± 1.0 compared with −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 with 0.31 ± 1.0 among those without ($P = 0.061$), following adjustment for metacarpal length Z score. Univariate logistic regression against prevalent vertebral fracture revealed that back pain was highly associated with increased odds for fracture (odds ratio 10.6 [95% CI 2.1–53.8], $P = 0.004$) (Table 4).

Table 2. Specific diseases within diagnostic subgroups of the total cohort (n = 134)*

Diagnostic subgroups	No. (%)
Juvenile DM	30 (22)
JIA (excluding systemic arthritis)	28 (21)
Polyarticular RF-positive arthritis	5 (18)
Polyarticular RF-negative arthritis	8 (29)
PsA	2 (7)
Enthesitis-related arthritis	5 (18)
Oligoarticular arthritis	4 (14)
Unclassified	4 (14)
SLE and related conditions	26 (20)
SLE	21 (81)
Overlap syndromes: mixed connective tissue disease	5 (19)
JIA (systemic arthritis)	22 (16)
SV (excluding KD and HSP)	16 (12)
Takayasu arteritis	4 (25)
Wegener's granulomatosis	7 (44)
Microscopic polyangiitis	1 (6)
Other vasculitis†	4 (25)
Other conditions	12 (9)
Generalized scleroderma	1 (8)
Localized scleroderma	10 (84)
Eosinophilic fasciitis	1 (8)

* RF = rheumatoid factor; PsA = psoriatic arthritis; SV = systemic vasculitis; KD = Kawasaki disease; HSP = Henoch-Schönlein purpura. See Table 1 for additional definitions.
† Includes perinuclear antineutrophil cytoplasmic antibody (pANCA)–positive vasculitis with recurrent pericarditis (n = 1), pANCA-positive vasculitis with Goodpasture's syndrome (n = 1), central nervous system vasculitis (n = 1), and pANCA-positive renal-limited vasculitis (n = 1).

Bone densitometry. L-spine 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, L-spine BMD Z scores were no different when bone age was substituted for chronological age ($P = 0.331$). The mean L-spine BMD Z scores were significantly below the healthy average for the entire cohort ($P < 0.001$) and for the following diagnostic subgroups: juvenile DM ($P < 0.001$), JIA excluding systemic JIA ($P = 0.015$), and systemic arthritis ($P = 0.002$). Such differences were not observed in the SLE and related conditions subgroup ($P = 0.768$), the SV subgroup ($P = 0.089$), or the other conditions subgroup ($P = 0.875$). There was no significant difference in the mean ± SD L-spine BMD Z score between those without fractures (−0.51 ± 1.23; n = 125) compared with 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 that sought to determine

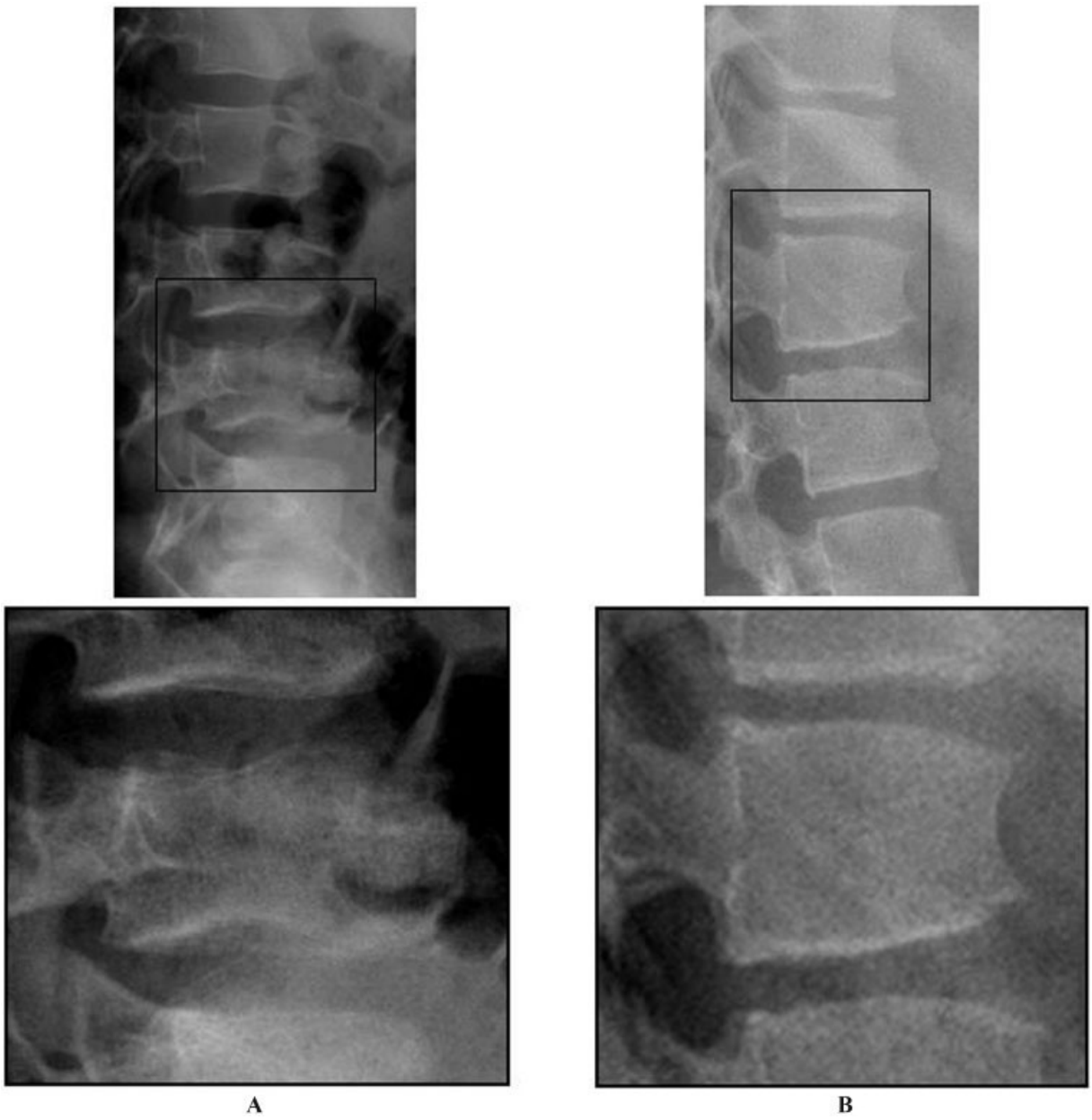

Figure 1. A, 12-year-old boy with systemic juvenile idiopathic arthritis. Shown is a grade 1 crush fracture at L4, plus loss of endplate parallelism and endplate interruption. The lumbar spine bone mineral density (BMD) Z score was −1.4. **B**, 15-year-old girl with systemic lupus erythematosus. Shown 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.

associations between relevant factors and age- and sex-matched L-spine BMD Z score: sex (β 0.67 [95% CI 0.25–1.08], $P = 0.002$), height Z score (β 0.32 [95% CI 0.13–0.50], $P = 0.001$), and BMI Z score (β 0.43 [95% CI 0.26–0.60], $P < 0.001$). The results of this model were confirmed using a stepwise model selection procedure, which produced the same results and explained 31% of the variability in the L-spine BMD Z score.

DISCUSSION

Our work highlights novel observations about bone morbidity in pediatric rheumatic conditions, because this prospective study evaluated vertebral fracture status early in the course of glucocorticoid 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 SV, and 8% in the other conditions subgroup. Although fractures were not observed in the JIA (excluding systemic) subgroup, 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

Table 3. Comparison of children with and without vertebral fractures*

Clinical characteristics	Without fractures (n = 125)	With fractures (n = 9)	*P*†
Demographic data			
Girls, no. (%)‡	83 (66)	4 (44)	0.277
Age, years	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
Pubertal stage, no. (%)§			1.000
Stage 1	65 (53)	4 (50)	
Stage 2–5	58 (47)	4 (50)	
Bone age, years	10.0 (1.1–17.5)	13.5 (6–16)	0.103
Second metacarpal morphometry, mean ± SD Z scores			
Metacarpal length	0.35 ± 1.1	0.50 ± 0.9	0.553
Percent cortical area	0.21 ± 0.9	0.15 ± 0.6	0.628
Combined cortical thickness	0.31 ± 1.0	−0.23 ± 0.9	0.061¶
Rheumatic conditions characteristics			
Disease activity (10-cm VAS), mean ± SD	5.6 ± 2.7	5.5 ± 3.4	0.887
ESR, mean ± SD mm/hour	40.5 ± 31.2	27.9 ± 24.5	0.234
Days since diagnosis, no.	23 (1–4,900)	22 (3–1,902)	0.407
Days since symptom onset, no.	146 (17–5,110)	93 (19–2,268)	0.771
Back pain, no. (%) yes‡	31 (25)	7 (77.8)	0.002#
L-spine BMD Z score, mean ± SD	−0.51 ± 1.2	−1.2 ± 1.0	0.082
Cumulative GC treatment			
Dose in prednisone equivalents, mean ± SD mg/m^2	1,410 ± 1,600	1,320 ± 2,755	0.244
Days taking GC, mean ± SD	16.7 ± 8.5	14.1 ± 10.4	0.376
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	1.1 (0–17)	0 (0–4)	0.046

* Values are the median (min–max) unless otherwise indicated. DRI = Dietary Reference Intake; NA = not applicable. See Table 1 for additional definitions.
† Statistical significance determined by nonparametric test (Mann-Whitney U test with 2 independent samples). Level of significance after Bonferroni correction = 0.002.
‡ Statistical significance determined by chi-square test or Fisher's exact test.
§ Data available in 122 children. Statistical significance determined by chi-square test or Fisher's exact test.
¶ *P* value with adjustment for metacarpal length Z score by linear regression.
# Significant at $P \leq 0.002$.
** By diet and supplement. Intake grouped into 3 groups based on the percentage relative to the DRI for age.

(which required agreement by 2 of 3 radiologists before a vertebra was considered fractured) would tend to underestimate 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 glucocorticoids. Second, back pain is a highly associated clinical feature (though not universal, because 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 postmenopausal OP (49), in children with long-standing histories of rheumatic conditions (11), and in childhood acute lymphoblastic leukemia (42). Overall, these results highlight that vertebral fractures are an under-recognized problem in children who have recently initiated glucocorticoid 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 OP (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 mor-

Table 4. Univariate logistic regression analysis of factors potentially associated with the presence of vertebral fractures*

Clinical parameter	Children with rheumatic disorders (n = 134)	
	OR (95% CI)	*P*†
Age	1.2 (1.0–1.4)	0.062
Sex, 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. others	1.8 (0.4–7.7)	0.420
Number of days since diagnosis, log-transformed	0.9 (0.6–1.5)	0.693
Total daily intake, ≥100% vs. <100% of the DRI		
Vitamin D	1.3 (0.3–5.5)	0.708
Calcium	1.3 (0.2–11.1)	0.806
Cumulative GC dose, g/m^2	1.0 (0.6–1.5)	0.876
L-spine BMD Z score	0.6 (0.4–1.1)	0.090

* OR = odds ratio; 95% CI = 95% confidence interval; DRI = Dietary Reference Intake. See Table 1 for additional definitions.
† Level of significance after Bonferroni correction = 0.004.
‡ Significant at $P \leq 0.004$.

phologic 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 the status of vertebral fractures in children with rheumatic conditions have been conducted at time points more distant in their disease course compared with our study. Specifically, these reports have been cross-sectional or retrospective, often in the face of long-term glucocorticoid 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 glucocorticoid 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 (18%) of 33 evaluable patients had L-spine areal BMD Z scores less than −1.5, and that the L-spine 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 L-spine BMD Z score. Disease activity indices also showed a lack of association. These findings may reflect a 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 glucocorticoids in our cohort.

When children with vertebral fractures in our study were compared with 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 L-spine BMD Z score. In contrast, children with newly diagnosed leukemia demonstrated a strong relationship between L-spine BMD and vertebral fractures, with the L-spine 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 glucocorticoid initiation compared with leukemia (7% versus 16%); on the other hand, the more fulminate effect of the leukemic process on bone may have greater impact on L-spine BMD in the short term compared with the typically more insidious inflammatory state in recently diagnosed rheumatic conditions.

Our study had 2 limitations that 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 glucocorticoid therapy. A subset of patients (131 of 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. Although our overall research program is predicated upon within-subject change over time in key parameters such as vertebral morphometry, 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 2 issues in data interpretation. First, our spine BMD and anthropometric Z scores have been generated through comparison with historical, published normative data, which may serve to underestimate such indices given the rise in secular trends (55). Second, 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 postmenopausal 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 glucocorticoid-treated rheumatic conditions can manifest vertebral fractures around the time of glucocorticoid initiation, and that back pain is a highly correlated feature. Whether the fractures will undergo reshaping or deterioration with ongoing glucocorticoid treatment will be determined through longitudinal study.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ward had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDIX A: MEMBERS OF THE CANADIAN STEROID-ASSOCIATED OSTEOPOROSIS IN THE PEDIATRIC POPULATION (STOPP) CONSORTIUM (A PAN-CANADIAN PEDIATRIC BONE HEALTH WORKING GROUP)

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