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Incident Vertebral Fractures Among Children With Rheumatic Disorders 12 Months After Glucocorticoid Initiation: A National Observational Study

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Objective. **To determine the frequency of incident vertebral fractures (IVF) 12 months after glucocorticoid (GC) initiation in children with rheumatic diseases and to identify children at higher risk.**

Methods. **Children with rheumatic diseases initiating GC were enrolled in a prospective observational study. Annual spine radiographs were evaluated using the Genant semiquantitative method. Spine areal bone mineral density (aBMD) was measured every 6 months. Clinical features, including cumulative GC dose, back pain, disease and physical activity, calcium and vitamin D intake, and spine aBMD Z scores, were analyzed for association with IVF.**

Results. **Seven (6%) of 118 children (95% confidence interval 2.9–11.7%) had IVF. Their diagnoses were: juvenile dermatomyositis (n = 2), systemic lupus erythematosus (n = 3), systemic vasculitis (n = 1), and mixed connective tissue disease (n = 1). One child was omitted from the analyses after 4 months because of osteoporosis treatment for symptomatic IVF. Children with IVF received on average 50% more GC than those without ($P = 0.030$), had a greater increase in body mass index (BMI) at 6 months ($P = 0.010$), and had greater decrements in spine aBMD Z scores in the first 6 months ($P = 0.048$). Four (67%) of 6 children with IVF and data to 12 months had spine aBMD Z scores less than −2.0 at 12 months compared to 16% of children without IVF ($P = 0.011$).**

Conclusion. **The incidence of VF 12 months following GC initiation was 6%; most children were asymptomatic. Children with IVF received more GC, had greater increases in BMI, and had greater declines in spine aBMD Z scores in the first 6 months.**

INTRODUCTION

Compromised bone strength is increasingly recognized as an important consequence of childhood rheumatic diseases. Such patients have multiple risk factors for impaired skeletal health, including the inflammatory process itself, delayed growth and development, decreased weight bearing and physical activity, muscle dysfunction, suboptimal nutritional status, and medications, especially glucocorticoids (GC) (1–3).

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Significance & Innovations

- This prospective pediatric study provides novel insights into the timing and nature of spine fragility following glucocorticoid initiation in children with rheumatic diseases.
- A subset of children with rheumatic conditions has the potential to develop incident vertebral fractures within 12 months of glucocorticoid initiation; those who did typically manifested a single asymptomatic incident vertebral fracture.
- One child developed multiple painful incident vertebral fractures 4 months following glucocorticoid initiation, prompting intervention with an intravenous bisphosphonate.
- Children with incident vertebral fractures tended to receive higher doses of glucocorticoid therapy, particularly in the first 6 months of treatment, and also had greater increases in body mass index Z scores and declines in lumbar spine areal bone mineral density Z scores.

A number of studies have documented bone mass reductions in children with rheumatic diseases (1–7). These decrements in bone mass may increase the risk of fractures in childhood, and potentially later in adulthood, as a result of suboptimal accrual of peak bone mass (3,4). More definitive evidence of bone fragility in children with rheumatic diseases is provided by studies documenting vertebral and extremity fractures. Studies have reported vertebral fracture (VF) prevalence of 10–34% (6,8–12). Although these findings help to establish the magnitude of this problem during the course of the illness, clinically relevant questions remain unanswered regarding the frequency and timing of an atraumatic incident (i.e., new) VF (IVF) in relation to GC dose and duration.

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Drs. Rodd and Lang contributed equally to this work.

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Through our national observational study of Steroid-Associated Osteoporosis in the Pediatric Population (STOPP), we have prospectively studied a cohort of children with GC-treated rheumatic diseases. We have previously documented a VF prevalence of 7% in our cohort within 30 days of GC initiation (2). The aims of the present study were to determine the frequency and characteristics of IVF 12 months after GC initiation and to identify patients at higher risk of fractures.

PATIENTS AND METHODS

Patients and study design. Patients were recruited through the STOPP research initiative. Children from age 1 month to 17 years were enrolled (n = 136) between January 1, 2005, and December 31, 2007, in 10 participating Canadian children's hospitals. Children were enrolled within 30 days of first-time GC treatment for inflammatory rheumatic disorders and grouped according to "related" disease categories, as follows: juvenile dermatomyositis (DM), systemic lupus erythematosus (SLE), and related conditions, including mixed connective tissue disease and other overlap syndromes, juvenile idiopathic arthritis (JIA; excluding systemic arthritis), systemic arthritis, systemic vasculitis (excluding Henoch-Schönlein purpura and Kawasaki disease), and "other conditions," including juvenile scleroderma (both systemic and localized).

Children were excluded from the study if GC had previously been used for treatment of the underlying disease. Patients were also excluded if they received intravenous or oral GC for more than 14 consecutive days in the 12 months preceding study enrollment to treat any other medical condition (e.g., asthma), if they received prior medication for osteoporosis, or if they had received calcium or vitamin D supplementation that exceeded the Dietary Reference Intake for age recommended at the time of the study (13,14). In addition, patients who developed symptomatic IVF during the observation period requiring osteoporosis treatment in accordance with the local standard of care were removed from the bone health natural history analyses from the time of osteoporosis intervention forward (with results presented separately). Finally, children who did not have spine radiograph data at 12 months were excluded. The clinical characteristics at study entry were compared for children with and without 12-month spine radiograph data.

Children were studied every 3 months for 1 year to allow accurate collection of the clinical data. The 12-month visit had a ±3-month window of time in which to collect the data. Each participating institution's research ethics board approved the study, and informed consent/assent was obtained prior to enrolment.

Clinical data. Demographic and puberty data were obtained as previously described (2). Height, weight, and body mass index (BMI; weight [kg] divided by height [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 (15); for children under 2

years of age, BMI Z scores were calculated according to the World Health Organization child growth standards (16). In addition, the children were assessed every 3 months for the presence of back pain since the last visit, calcium and vitamin D intake was assessed by a validated food frequency questionnaire, and supplemental calcium and vitamin D intake was also recorded (14). Physical activity was assessed quarterly using the Habitual Activity Estimation Scale (2,17). Additionally, a physician global assessment of disease activity was determined quarterly on a 10-cm visual analog scale (VAS) by the patients' attending rheumatologists (where 0 cm = inactive disease and 10 cm = extremely active disease), as previously described (2,18–20). At 12 months, the spine was palpated for tenderness over the posterior spinous processes (T4 to L4) and history of back trauma was recorded.

Quantification of GC and methotrexate exposure. Each patient was seen quarterly to collect height and weight to determine body surface area (calculated as the average over the observation period) and records of all GC received. From this, the dose of systemic GC therapy (oral and intravenous, including pulse therapy) was converted into prednisone equivalents and results were expressed in 3 ways (21–23): 1) cumulative GC dose, defined as the total amount of GC in prednisone equivalents (mg/m^2) received during the observation period; 2) GC dose intensity, defined as the cumulative dose in prednisone equivalents (mg/m^2) divided by the number of days actually taking GC during the observation period; and 3) average GC dose, defined as the cumulative dose in prednisone equivalents (mg/m^2) divided by the total number of days in the observation period. Methotrexate exposure was expressed as whether children had received the drug or not and as a cumulative dose to the 12-month followup.

VF assessment. Lateral thoracolumbar spine radiographs were carried out at enrollment and 12 months. The Genant semiquantitative method for vertebral morphometry (24) was performed as previously described (2). 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 (anterior 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 reductions in height ratios: grade 0 = 20% or less, 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.

An IVF was defined as a new VF at 12 months in a vertebral body that was normal at study entry, or worsening of an existing VF (progression from grade 1 or more to a higher VF grade).

Lumbar spine (L-spine) bone mineral density (BMD) by dual-x-ray absorptiometry. BMD was measured in the anteroposterior direction at the L-spine (L1–L4) using either Hologic machines (QDR 4500, 3 centers; Discovery, 2 centers; Delphi, 1 center) or Lunar Prodigy (4 centers) at study enrollment and 6 and 12 months. Machines were cross-calibrated, as previously described (2). Data were converted to Hologic units and Z scores were generated using the Hologic 12.4 normative database. In vivo precision for L-spine areal BMD (aBMD) was available in 8 of 10 centers and ranged from 0.003–0.017 gm/cm^2.

Bone age and second metacarpal morphometry. Radiographs of the left hand and wrist for bone age were read independently and second metacarpal morphometry was obtained and analyzed using the methods previously described (2).

Statistical analyses. All analyses were conducted using SPSS, version 18.0. Categorical variables were summarized using the frequency and percentage. Normally distributed continuous variables were summarized using the mean ± SD. Non–normally distributed continuous variables were summarized using the median and range. The 95% confidence intervals (95% CIs) for the proportion of patients with vertebral deformities were calculated using the Wilson score method (25). Z score variables were compared against the healthy average (Z score 0.0) using 1-sample Student's *t*-test to assess whether the patient population significantly differed from the normal reference values. Results for height, weight, BMI, L-spine aBMD, and disease activity by VAS were compared using paired Student's *t*-test at the time of study enrollment and 12 months. Children with IVF were compared to those without using Wilcoxon-Mann-Whitney and Fisher's exact tests. Presented *P* values are 2-sided and a *P* value less than or equal to 0.05 was considered significant.

RESULTS

Characteristics of the natural history cohort. A total of 117 (86%) of the 136 children who were enrolled within 30 days of GC initiation completed the bone health natural history assessment through to 12 months. One additional child was included in the natural history analyses to 3 months, but was excluded thereafter because she received osteoporosis therapy (intravenous pamidronate) for symptomatic IVF at 4 months post–GC initiation; this child is described separately at the end of the Results. Eighteen other children were excluded from all analyses: 10 did not have spine radiographs at 12 months, 2 were lost to followup, and 6 withdrew consent. At study enrollment, the clinical characteristics of these 18 children did not differ significantly from the natural history cohort (data not shown).

Clinical features of the cohort at 12 months are shown in Table 1. The characteristics of the 12-month cohort did not differ significantly from the full cohort at study entry with respect to sex, ethnicity, concordance between bone age and chronologic age, and distribution of prepubertal to pubertal Tanner stages (data not shown). Rheumatic disease activity as measured by the 10-cm VAS showed a

Table 1. Description of children with rheumatic disorders and bone health natural history data to 12 months post–GC initiation*

Clinical characteristics at 12 months	Overall study cohort with data to 12 months (n = 117)	Juvenile DM (n = 27)	JIA (n = 22)	SLE and related conditions (n = 20)	Systemic arthritis (n = 21)	Systemic vasculitis (n = 16)	Other conditions (n = 11)
Demographic data							
Female, no. (%)	74 (63)	16 (59)	14 (64)	17 (85)	12 (57)	8 (50)	7 (64)
Age, median (range) years	11.0 (2.3–17.9)	8.3 (2.8–16.0)	13.1 (4.7–17.9)	14.5 (6.0–17.2)	6.6 (2.3–16.2)	14.1 (5.5–17.9)	9.0 (4.4–17.5)
White ethnicity, no. (%)	92 (79)	24 (89)	19 (86)	9 (45)	18 (86)	11 (69)	11 (100)
Anthropometry							
Height Z score, mean ± SD	−0.2 ± 0.9†	−0.4 ± 0.9	−0.4 ± 1.0	−0.3 ± 0.8	−0.2 ± 0.9	0.1 ± 1.0	0.2 ± 0.9
Weight Z score, mean ± SD	0.4 ± 1.3†	0.2 ± 1.4	0.1 ± 1.5	0.5 ± 1.2	0.5 ± 1.0	1.0 ± 1.4	0.4 ± 0.9
BMI Z score, mean ± SD	0.7 ± 1.2†	0.7 ± 1.2	0.3 ± 1.5	0.8 ± 1.0	0.8 ± 1.2	1.0 ± 1.3	0.5 ± 0.9
Pubertal stage, no. (%)							
Stage 1	51 (48)	15 (65)	7 (33)	3 (16)	15 (75)	5 (36)	6 (67)
Stage 2–5	55 (52)	8 (35)	14 (67)	16 (84)	5 (25)	9 (64)	3 (33)
Bone age, median (range) years	10.8 (1.8–18.0)	7.2 (1.8–16.8)	13.4 (3.8–17.0)	14.5 (5.8–17.0)	6.0 (1.8–17.0)	14.3 (4.2–18.0)	8.8 (4.0–18.0)
Rheumatic disease activity							
Disease activity (10-cm VAS), median (range)	0.5 (0.0–6.3)	0.2 (0.0–3.4)	1.3 (0.0–3.0)	0.4 (0.0–5.9)	0.2 (0.0–6.3)	0.4 (0.0–5.5)	1.1 (0.0–2.2)
Days since diagnosis, median (range)	393 (343–3,408)	386 (344–714)	413 (357–3,408)	385 (354–596)	385 (343–512)	389 (358–459)	444 (370–2,321)
L-spine aBMD							
L-spine aBMD Z score, mean ± SD	−0.8 ± 1.2†	−1.5 ± 1.1	−0.5 ± 1.2	−0.4 ± 1.1	−0.8 ± 1.2	−1.3 ± 1.2	0.0 ± 1.0
L-spine aBMD Z score less than −2.0, no. (%)	21 (19)	10 (39)	1 (5)	2 (10)	4 (20)	4 (27)	0 (0)
Vertebral fractures							
Patients with incident vertebral fracture, no. (%) (95% CI)	6 (5) (2.4–10.7)	2 (7) (2.1–23.4)	0 (0) (0–14.9)	3 (15) (5.2–36.0)	0 (0) (0–15.5)	1 (6) (1.1–28.3)	0 (0) (0–25.9)
GC treatment							
Days between GC initiation and 12-month spine radiograph, mean ± SD	389 ± 25	391 ± 26	390 ± 23	393 ± 26	386 ± 31	386 ± 19	387 ± 23
Days in receipt of GC, median (range)	342 (4–454)	368 (93–444)	129 (4–454)	378 (167–446)	362 (70–442)	367 (206–419)	75 (9–258)
Cumulative GC dose, mean ± SD mg/m^2	6,369 ± 5,146	10,258 ± 6,330	1,554 ± 1,206	6,422 ± 3,441	5,677 ± 5,213	6,824 ± 2,480	7,021 ± 4,502
Average GC dosage, mean ± SD mg/m^2/day	16 ± 13	26 ± 16	4 ± 3	16 ± 9	15 ± 14	18 ± 7	18 ± 11
GC dose intensity, median (range) mg/m^2/day	17 (1–921)	23 (8–71)	7 (1–705)	17 (6–42)	15 (3–58)	21 (9–33)	54 (8–921)
MTX treatment							
Cumulative MTX dose, median (range) mg/m^2	470 (0–2,977)	796 (0–1,426)	620 (0–1,527)	0 (0–414)	253 (0–2,977)	0 (0–565)	936 (0–1,594)
Patients who received any MTX, no. (%)	74 (63)	26 (96)	20 (91)	2 (10)	13 (62)	3 (19)	10 (91)

* GC = glucocorticoid; DM = dermatomyositis; JIA = juvenile idiopathic arthritis (excluding systemic arthritis); SLE = systemic lupus erythematosus; BMI = body mass index; VAS = visual analog scale; L-spine = lumbar spine; aBMD = areal bone mineral density; 95% CI = 95% confidence interval; MTX = methotrexate.
† Significantly different compared to normative reference data (Z score of 0).

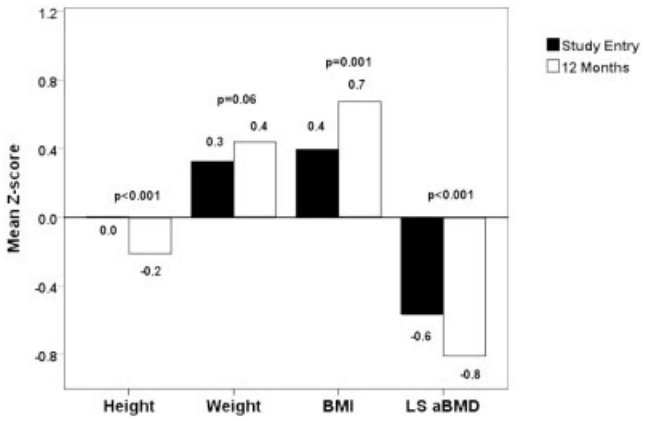

Figure 1. Mean Z scores for height, weight, body mass index (BMI), and lumbar spine (LS) areal bone mineral density (aBMD) at study entry and 12 months.

decrease at 12 months (median 0.5 cm, range 0–6.3) compared with study enrollment (median 6.3, range 0–10.0; $P < 0.001$). Compared to enrollment, height Z scores at 12 months were lower and weight Z scores were higher, resulting in increased BMI Z scores (Figure 1); these Z scores at 12 months were all significantly different compared to the normative reference data (Table 1).

IVF. Of the 117 children with natural history data to 12 months post–GC initiation, 6 (5%; 95% CI 2.4–10.7%) had a total of 7 IVF (median age 10.9 years, range 8.4–17.2 years, n = 4 girls). Five children had a single IVF and 1 had 2 IVF. All of the IVF were new fractures in previously normal vertebral bodies with no significant back trauma having occurred in any of the children. None of the children with prevalent VF at enrollment developed IVF. Only children with juvenile DM, SLE, and systemic vasculitis developed IVF (Table 1). Three children (50%) had mild (grade 1) fractures as the worst grade and 50% had moderate fractures. Five fractures (71%) were thoracic and 2 were lumbar; 6 of 7 IVF were anterior wedge fractures. Examples of IVF that were representative of those seen at 12 months are shown in Figure 2.

Comparisons of the clinical characteristics between children with and without IVF in the natural history cohort are shown in Tables 2 and 3. There was no difference between the 2 groups for age, sex, pubertal status, or disease activity. Both groups had similarly low measures of disease activity at 12 months according to the VAS ($P = 0.253$) and few had back pain by self-report or by palpation, regardless of their IVF status over the 12-month period. Specifically, 37% of those without fractures reported back pain versus 33% of children with IVF ($P = 1.00$). No differences existed in second metacarpal morphometry, physical activity, or calcium and vitamin D intake (data not shown).

Analysis of GC exposure demonstrated that those with IVF received, on average, 50% more steroids compared to those without fractures as assessed by cumulative ($P = 0.030$) or average ($P = 0.044$) GC dose, and nearly double as assessed by GC dose intensity ($P = 0.166$) (Table 2). The greater GC exposure in those with IVF occurred primarily in the first 6 months of treatment, as shown in Table 3. Those with IVF gained more weight resulting in a higher BMI, especially at 6 months ($P = 0.010$); this difference disappeared by 12 months. Additionally, children with IVF had a greater decline in L-spine aBMD Z score in the first 6 months of GC therapy ($P = 0.048$) (Table 2).

L-spine aBMD. A modest decrease in the L-spine aBMD Z score for the entire cohort at the 12-month followup is shown in Table 1 and Figure 1 ($P < 0.001$ compared to study entry and also to the healthy average). Low bone mass for chronologic age, defined as an L-spine aBMD Z score of less than −2.0 (26), was found in 19% of patients at 12 months and in 67% of those with IVF (Tables 1 and 2) compared to 16% of those without ($P = 0.011$). aBMD Z scores below 0 (the mean for chronological age) at 12 months were present in all of the children with IVF and

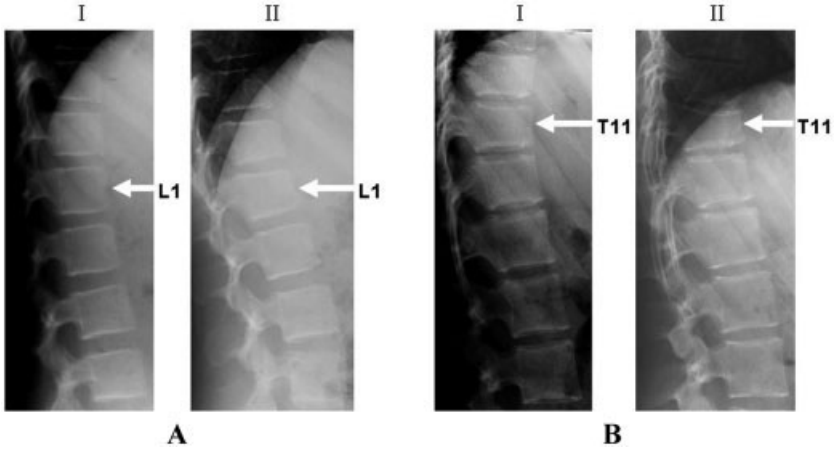

Figure 2. Examples of incident vertebral fracture at 12 months. **A** (I) shows a normal spine radiograph at study entry (within 30 days of glucocorticoid initiation) in an 11-year-old girl with systemic lupus erythematosus. At 12 months (II), this child manifested a grade 1 incident vertebral fracture at L1. **B** (I) shows a normal spine radiograph at study entry in a 16-year-old girl with systemic lupus erythematosus. At 12 months (II), this child was identified as having a grade 2 incident vertebral fracture at T11.

Table 2. Comparison of children with and without incident fractures at 12 months post–initiation of GC*

Clinical characteristics	Children without incident vertebral fractures (n = 111)	Children with incident vertebral fractures (n = 6)	*P*†
Demographic data			
Female, no. (%)	70 (63)	4 (67)	1.000‡
Age at 12 months, median (range) years	11.0 (2.3 to 17.9)	10.9 (8.4 to 17.2)	0.578
Anthropometry			
Height Z score at 12 months, mean ± SD	−0.2 ± 0.9	−0.3 ± 0.5	0.863
Δheight Z score, study entry to 6 months, mean ± SD	−0.2 ± 0.7	−0.2 ± 0.2	0.879
Δheight Z score, 6 to 12 months, mean ± SD	−0.1 ± 0.4	0.0 ± 0.3	0.949
Weight Z score at 12 months, mean ± SD	0.4 ± 1.3	0.4 ± 0.8	0.911
Δweight Z score, study entry to 6 months, mean ± SD	0.3 ± 0.6	1.1 ± 0.7	0.009§
Δweight Z score, 6 to 12 months, mean ± SD	−0.2 ± 0.4	−0.6 ± 0.6	0.056
BMI Z score at 12 months, mean ± SD	0.7 ± 1.2	0.7 ± 0.8	0.951
ΔBMI Z score, study entry to 6 months, mean ± SD	0.5 ± 0.8	1.4 ± 0.8	0.010§
ΔBMI Z score, 6 to 12 months, mean ± SD	−0.3 ± 0.5	−0.7 ± 0.7	0.205
Pubertal stage at 12 months (Tanner stage 1), no. (%)	50 (50)	1 (20)	0.365‡
Bone age, median (range) years	10.8 (1.8 to 18.0)	10.0 (7.0 to 17.0)	0.822
Rheumatic disease characteristics, median (range)			
VAS score at 12 months	0.5 (0.0 to 6.3)	0.0 (0.0 to 2.2)	0.253
ΔVAS score, study entry to 6 months	−4.4 (−9.6 to 3.0)	−2.5 (−7.6 to 1.9)	0.182
ΔVAS score, 6 to 12 months	−0.2 (−4.9 to 5.8)	−0.2 (−1.7 to 0.0)	0.978
Days since diagnosis	393 (343 to 3,408)	409 (362 to 447)	0.528
L-spine aBMD			
L-spine aBMD Z score at 12 months, mean ± SD	−0.8 ± 1.2	−1.7 ± 1.1	0.060
ΔL-spine aBMD Z score, study entry to 6 months, mean ± SD	−0.4 ± 0.5	−0.8 ± 0.5	0.048§
ΔL-spine aBMD Z score, 6 to 12 months, mean ± SD	0.1 ± 0.4	0.3 ± 0.6	0.674
L-spine aBMD Z score less than −2.0 at 12 months, no. (%)	17 (16)	4 (67)	0.011§
Vertebral fractures at study entry			
Patients with vertebral fractures at study entry, no. (%)	9 (8)	0 (0)	1.000‡
Back pain			
Back pain during 12 months of followup anytime after study entry, no. (%)	41 (37)	2 (33)	1.000‡
Patients with spine pain by palpation at 12 months, no. (%)	4 (4)	1 (20)	0.192‡
GC treatment			
Days between GC initiation and 12-month spine radiograph, mean ± SD	388 ± 25	406 ± 27	0.073
Days in receipt of steroids, median (range)	342 (4 to 454)	383 (264 to 446)	0.088
Cumulative GC dose, mean ± SD mg/m^2	6,203 ± 5,181	9,452 ± 3,447	0.030§
Average GC dosage, mean ± SD mg/m^2/day	16 ± 13	24 ± 9	0.044§
GC dose intensity, median (range) mg/m^2/day	16 (1 to 921)	30 (7 to 34)	0.166
MTX treatment			
Cumulative MTX dose, median (range) mg/m^2	503 (0 to 2,977)	158 (0 to 1,111)	0.560
Patients who received any MTX, no. (%)	71 (64)	3 (50)	0.668‡

* GC = glucocorticoid; BMI = body mass index; VAS = visual analog scale; L-spine = lumbar spine; aBMD= areal bone mineral density; MTX = methotrexate.
† Statistical significance determined by Mann-Whitney U test for independent samples.
‡ Statistical significance determined by Fisher's exact test.
§ Statistically significant at $P \leq 0.05$.

78% of those without IVF. Two of 6 children with IVF showed an increase in L-spine aBMD Z score from baseline to 12 months; this was similar to the 34% of children without IVF who had a rise in L-spine aBMD Z scores.

Patient with multiple VF requiring bisphosphonate therapy. When the patient treated with intravenous pamidronate was considered along with the children in the natural history cohort, the IVF rate was 6% (95% CI 2.9–11.7%). This 7-year-old girl with mixed connective tissue disease developed multiple symptomatic IVF 4 months post–GC initiation (Figure 3). At enrollment her spine radiograph was normal and her L-spine aBMD Z score was −1.1. Analysis of her bone health natural history data to 3 months demonstrated GC exposure very similar to the other 6 children with IVF (cumulative GC dose to 3 months was 6,838 mg/m^2 in this patient versus 7,186 mg/m^2 [range 1,613–9,224] for the other children with IVF and 3,466 mg/m^2 [range 14.8–19,349] for patients without IVF). She did not differ significantly from the natural history cohort with respect to calcium and vitamin D intake, disease activity, or physical activity. Notable clinical features of this patient included a dramatic increase in her BMI from baseline to 3 months (ΔBMI Z score

Table 3. Distribution of glucocorticoid (GC) and methotrexate (MTX) exposure for children with and without incident vertebral fractures during the 12-month followup period

Parameters	0–6 months			6–12 months		
	Children without incident vertebral fractures	Children with incident vertebral fractures	*P**	Children without incident vertebral fractures	Children with incident vertebral fractures	*P**
GC quantification						
Days between GC initiation and 12-month spine radiograph, mean ± SD	201 ± 21	193 ± 13	0.311	187 ± 29	212 ± 21	0.024†
Days in receipt of GC, median (range)	182 (4–245)	192 (176–209)	0.233	168 (1–252)	199 (56–237)	0.226
Cumulative GC dose, median (range) mg/m^2	4,570 (15–25,525)	8,450 (2,079–10,864)	0.025†	1,156 (14–13,006)	1,291 (229–4,804)	0.904
Average GC dosage, median (range) mg/m^2/day	21 (0.1–123)	43 (10–60)	0.026†	6 (0.1–64)	6 (1–21)	0.694
GC dose intensity, median (range) mg/m^2/day	23 (1–922)	43 (10–60)	0.093	7 (1–903)	7 (2–21)	0.628
MTX quantification						
Cumulative MTX dose, median (range) mg/m^2	236 (0–1,007)	107 (0–508)	0.673	270 (0–2,608)	52 (0–611)	0.558
Patients who received any MTX, no. (%)	67 (60)	3 (50)	0.683‡	69 (62)	3 (50)	0.674‡

* Statistical significance determined by Mann-Whitney U test for independent samples.
† Statistically significant at $P \leq 0.05$.
‡ Statistical significance determined by Fisher's exact test.

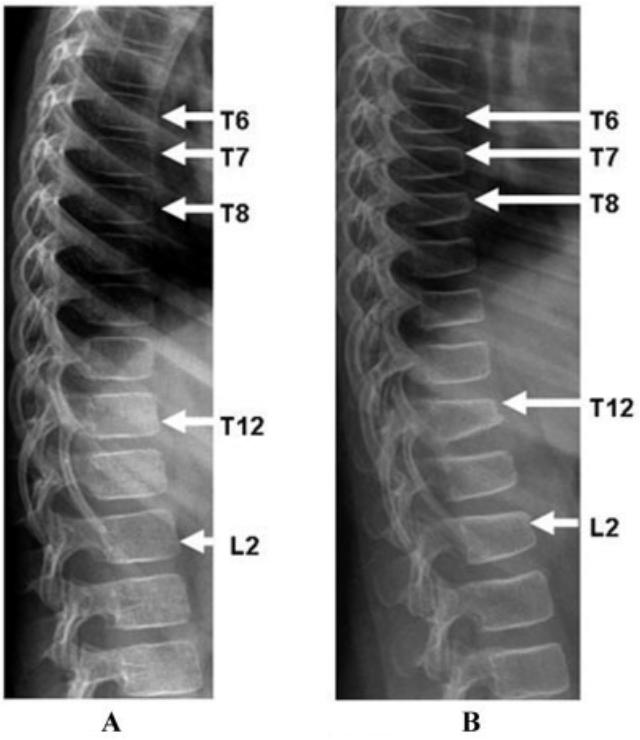

Figure 3. Spine radiographs from a 7-year-old girl with mixed connective tissue disease. At study entry (**A**), her spine radiograph showed no signs of vertebral fractures; however, she manifested multiple painful vertebral fractures during the observation period (**B**). This patient was excluded from the bone health natural history analyses because she required bisphosphonate therapy to treat the symptomatic fractures; however, a brief description of her skeletal phenotype is provided in the Results.

3.1 versus mean ± SD 1.1 ± 0.4 for IVF patients and 0.6 ± 0.7 for children without IVF), as well as the development of marked cushingoid features.

DISCUSSION

Prospective longitudinal data on bone health outcomes in children with rheumatic diseases are scant, although cross-sectional studies have demonstrated reduced bone mass as well as fragility fractures in this population (4–6,8–12,27). Our study provides novel insights into the pace and nature of spine fragility in children with rheumatic disorders treated with GC. The 6% VF incidence was calculated using the standard adult definition of an IVF, with the patient as the study unit, not the individual vertebrae (28). This definition established a priori included both de novo as well as worsening of existing VF, since prior VF has been associated with the risk for IVF (29); however, it is not known whether this is the case in children. Incidentally, all of the IVF detected in our cohort were de novo fractures, whereas none were worsening of existing fractures and so this particular risk factor could not be explored. Ongoing followup of our cohort will allow us to assess whether the number of children with IVF will indeed increase over time and whether previous fractures will predict future fractures in children.

There was an excellent retention rate (86%) of children in this cohort. When we examined disease subgroups, we found IVF rates of 7% (95% CI 2.1–23.4) in juvenile DM, 15% (95% CI 5.2–36.0) in SLE, and 6% (95% CI 1.0–28.3) in systemic vasculitis. Several other reports concur that children with fractures typically have more severe under-

lying diagnoses such as SLE, juvenile DM, systemic JIA, or systemic vasculitis (8,9). The relative contributions of systemic inflammation severity, the need for high-dose GC, and other potential risk factors for poor bone health remain undetermined in these disease groups (1,7–10).

Other publications, based largely on cross-sectional analyses, cite pediatric VF rates ranging from 10–34% in rheumatic disorders (6,8–12). These studies had higher VF rates than we found in our cohort, likely because of their longer period of followup, usually approximately 5 years, as well as selection bias with continued followup of children with more severe disease and evaluation of symptomatic children. Previous studies have also reported higher rates of fracture per child, one study with an average of 2.9 fractures per child (8) and one with an average of 3.3 fractures per child (9). Varonos et al (9) conducted a retrospective study of 23 children with GC-treated JIA (including 19 with systemic arthritis) who had at least 1 VF and compared these patients to similar-aged children with JIA also treated with GC but who had no history of VF. In this study, the mean time from starting GC to vertebral collapse, as documented on routine yearly spine radiographs, was 2.7 years (range 8 months to 5.5 years). Only one-quarter of children who developed VF did so within 1 year of starting GC. This suggests that our study of the IVF rate at 12 months may have detected only those patients with the greatest predisposition to bone fragility, manifesting as IVF early in the course of disease treatment.

The child who received bisphosphonate treatment during our study was the exception and demonstrated numerous painful IVF early in her disease course. A few similarly affected children, each with 10 fractures, have been reported (8,9). Our patient with multiple IVF received a similar cumulative GC dose compared to the other 6 children with 1–2 fractures each; however, she had a greater increase in BMI in the first 3 months of GC treatment compared with the other 6 children with IVF. Her early marked Cushingoid features raise the possibility of individual genetic susceptibility to GC.

The location and severity of IVF were consistent with findings from other pediatric studies, with a bimodal midthoracic and thoracolumbar junction distribution (2,6,8,9). Typically, most of the burden was in the midthoracic spine and the majority of the fractures were mild to moderate with anterior wedge morphology (2,6,8,9). A proposed explanation for this location relates to different mechanical forces along the spine associated with its normal kyphosis (30).

Despite the robust size of our cohort and the acquisition of prospective longitudinal data, our ability to derive predictors of fracture risk was limited by the small number of patients with IVF. Those with IVF received more GC in the first 6 months of treatment (i.e., higher GC intensity early on), had a somewhat higher ΔBMI at 6 months, and also had worsening of their L-spine aBMD Z score over the same time period. We were not able to delineate the relative contributions of disease severity or cumulative GC dose to IVF. This is made challenging by the fact that GC dose may be a marker of an underlying disease variable such as the degree of systemic inflammation. The cumulative GC dose was strongly associated with prevalent VF in a study of 94 children with a variety of rheumatic diseases followed at a single center (8). There are, however, conflicting reports in the literature on the correlation of GC dose with the prevalence of VF and reduced bone mass in children with rheumatic diseases (6,8). This may, in part, reflect the heterogeneity of the disease populations studied, as well as the varied duration of diseases and their treatment in the various reports.

Based on observations in adults with VF, there is a suggestion of a threshold for lower BMD predisposing to fractures (31). Similarly, in children with rheumatic diseases, a threshold Z score was observed for volumetric L-spine BMD of −1.8 predicting fractures (11). In our study, we noted that 67% of those with IVF had a BMD Z score of less than −2.0 compared to 16% of those without IVF. Given the small number of children with IVF in this study, we were unable to determine if a precise spine BMD threshold exists.

On average we found a modest decrease in the L-spine aBMD Z score over 12 months post–GC initiation. Data from most longitudinal studies are not directly comparable to ours because the commencement of their followup occurred on average 2 years following GC initiation (5,7,32). Within the entire cohort, 19% had L-spine aBMD Z scores of less than −2.0, which has been referred to as "low bone mass for chronologic age" in the literature (10,26). In particular, approximately one-quarter of children with juvenile DM and systemic vasculitis had an L-spine aBMD Z score of less than −2.0 at 12 months, as did approximately 20% of those with systemic JIA. Ongoing longitudinal followup of our cohort is essential to help understand the significance of these spine BMD findings, particularly in relation to IVF.

Within the IVF group, only a small number experienced back pain or tenderness, which is consistent with previous studies reporting that many children who experience IVF are asymptomatic, or if symptoms are present they are mild and may be transient (6,12). This is in direct contrast to our cohort at enrollment, when back pain was found to be highly associated with prevalent VF (2). Sex was not associated with IVF, nor was the use of methotrexate. The role of methotrexate as osteotoxic or osteoprotective has not been determined, as there are conflicting reports regarding its association with IVF (8,11).

There are limitations to our study that deserve consideration. First, since back pain was only assessed on a 3-month basis, it is possible that the frequency of transient pain may have been underestimated. Second, daily divided GC dosing was not captured, and therefore we could not determine if the frequency of the dosing in a 24-hour period played a role in the development of IVF (9). Moreover, we did not ascertain precise data on ancillary medications such as disease-modifying antirheumatic drugs other than methotrexate that might have provided additional proxy data on the severity of the underlying illness. It is also possible that the use of potent biologic agents may have significantly reduced the risks of IVF by the inhibition of cytokines known to promote bone resorption (33). This cohort of children is quite heterogeneous in regard to underlying diagnoses, potentially limiting our power to see differences. Finally, serum 25-hydroxyvitamin D lev-

els were not available; the deliberate rationale for excluding this parameter has been outlined previously (2).

In summary, the incidence of VF at 12 months post–GC initiation in children with rheumatic diseases was 6% and most children were asymptomatic. One child was more severely affected with multiple painful fractures. Overall, there was a suggestion that children with IVF received more GC during the observation period and had greater increases in BMI and declines in L-spine aBMD Z scores in the first 6 months of GC treatment. The longitudinal nature of this study with further followup should provide much-needed insights into the future risk for VF in this context.

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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 published. 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.

Study conception and design. Rodd, Lang, Alos, Huber, Cabral, Miettunen, Atkinson, Couch, Ellsworth, Hay, LeBlanc, Stephure, Matzinger, Shenouda, Moher, Rauch, Siminoski, Ward.

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Analysis and interpretation of data. Rodd, Lang, Ramsay, Alos, Huber, Couch, Ellsworth, Stephure, Lentle, Matzinger, Shenouda, Moher, Siminoski, Ward.

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APPENDIX A: MEMBERS OF THE CANADIAN STEROID-ASSOCIATED OSTEOPOROSIS IN THE PEDIATRIC POPULATION (STOPP) CONSORTIUM

Members of the Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) Consortium (a Pan-Canadian, Pediatric Bone Health Working Group), in addition to the authors, are as follows: Janusz Feber, Jacqueline Halton (Children's Hospital of Eastern Ontario, Ottawa, Ontario); Reinhard Kloiber, Victor Lewis, Julian Midgley (Alberta Children's Hospital, Calgary, Alberta); David B. Dix, Helen R. Nadel (British Columbia Children's Hospital, Vancouver, British Columbia); Elizabeth Cairney, Cheril Clarson, Guido Filler, Joanne Grimmer, Keith Sparrow (Children's Hospital, London Health Sciences Centre, University of Western Ontario, London, Ontario); Conrad Fernandez, Kathy O'Brien (IWK Health Center, Halifax, Nova Scotia); Steve Arora, Ronald Barr, Craig Coblentz, Colin Webber (McMaster Children's Hospital, Hamilton, Ontario); Sharon Abish, Lorraine Bell (Montreal Children's Hospital, Montreal, Quebec); Francis Glorieux (Shriners Hospital for Children, Montreal, Quebec); Josée Dubois, Caroline Laverdière, Véronique Phan (Ste. Justine Hospital, Montreal, Quebec); Maury Pinsk, Beverly Wilson (Stollery Children's Hospital, Edmonton, Alberta); Ronald Grant, Martin Charron, Diane Hebert (Toronto Hospital for Sick Children, Toronto, Ontario); Isabelle Gaboury (University of Sherbrooke, Sherbrooke, Quebec); Tom Blydt-Hansen, Sara Israels, Martin Reed (Winnipeg Children's Hospital, Winnipeg, Manitoba, Canada).