Incident Vertebral Fractures and Risk Factors in the First Three Years Following Glucocorticoid Initiation Among Pediatric Patients With Rheumatic Disorders

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ABSTRACT

Vertebral fractures are an important yet underrecognized manifestation of osteoporosis in children with chronic, glucocorticoid-treated illnesses. Our goal was to determine the incidence and clinical predictors of vertebral fractures in the 3 years following glucocorticoid initiation among pediatric patients with rheumatic disorders. Incident vertebral fractures were evaluated according to the Genant semiquantitative method on lateral radiographs at baseline and then annually in the 3 years following glucocorticoid initiation. Extended Cox models were used to assess the association between vertebral fractures and clinical risk predictors. A total of 134 children with rheumatic disorders were enrolled in the study (mean ± standard deviation (SD) age 9.9 ± 4.4 years; 65% girls). The unadjusted vertebral fracture incidence rate was 4.4 per 100 person-years, with a 3-year incidence proportion of 12.4%. The highest annual incidence occurred in the first year (6.0%; 95% confidence interval (CI) 2.9% to 11.7%). Almost one-half of the patients with fractures were asymptomatic. Every 0.5 mg/kg increase in average daily glucocorticoid (prednisone equivalents) dose was associated with a twofold increased fracture risk (hazard ratio (HR) 2.0; 95% CI 1.1 to 3.5). Other predictors of increased vertebral fracture risk included: (1) increases in disease severity scores between baseline and 12 months; (2) increases in body mass index Z-scores in the first 6 months of each 12-month period preceding the annual fracture assessment; and (3) decreases in lumbar spine bone mineral density Z-scores in the first 6 months of glucocorticoid therapy. As such, we observed that a clinically significant number of children with rheumatic disorders developed incident vertebral fractures in the 3 years following glucocorticoid initiation. Almost one-half of the children were asymptomatic and thereby would have been undiagnosed in the absence of radiographic monitoring. In addition, discrete clinical predictors of incident vertebral fractures were evident early in the course of glucocorticoid therapy. © 2015 American Society for Bone and Mineral Research.

KEY WORDS: CHILDREN; ADOLESCENTS; RHEUMATIC DISORDERS; GLUCOCORTICOIDS; VERTEBRAL FRACTURES; BONE DENSITY
Pediatric rheumatic disorders span a broad spectrum of diseases including juvenile idiopathic arthritis (JIA), as well as systemic rheumatic disorders including juvenile dermatomyositis, systemic lupus erythematosus, and systemic vasculitides. Despite important advances in therapeutic options for pediatric patients with rheumatic disorders, glucocorticoids (GC) continue to be an important treatment for many patients. At the same time, GC therapy is associated with numerous potential side effects, including detriments to skeletal health during the critical period of bone strength development.1–6 We have shown through prospective surveillance that 7% of children will have prevalent VF in the first few weeks of GC therapy,7 and that 6% will have incident VF by 12 months following GC initiation.8 We have also shown that children with incident VF at 12 months had greater increases in body mass index (BMI) Z-scores and decreases in bone mineral density (BMD) Z-scores in the first 6 months of GC therapy,9 suggesting that early bone and body composition changes may signal which pediatric patients will develop VF following GC initiation.

At the same time, a number of questions about the natural history and clinical predictors of VF in this setting remained unanswered. For example, it is not known whether the incidence of VF continues to increase over time following GC initiation, and at what time point the VF incidence reaches its peak. Questions also remain about the severity of bone morbidity due to VF over the longer-term and whether readily measurable clinical predictors are evident that can alert clinicians to those children at greatest risk for VF in the years following GC initiation. Understanding these issues will facilitate the development of logical monitoring strategies that target at-risk patients and identify the best candidates for intervention. The purpose of this report was to determine the incidence of VF in pediatric patients with GC-treated rheumatic disorders in the 3 years following GC initiation, to describe the pattern (time point, location, symptomatology, and severity) of incident VF, and to elucidate clinical predictors of 3-year incident VF.

Patients and Methods

Data for this study were obtained from children and youth with rheumatic disorders enrolled in the Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) study. The STOPP study is part of a prospective, longitudinal observational research program involving 10 Canadian academic pediatric centers studying bone health among those with GC-treated diseases. Details of the STOPP protocol for pediatric patients with rheumatic disorders have been published.12,13

Patients enrolled in the study

The patients enrolled in this study held the following diagnoses: juvenile dermatomyositis, systemic lupus erythematosus and related conditions, JIA (excluding systemic arthritis), JIA (systemic arthritis), systemic vasculitides (excluding Henoch-Schönlein purpura and Kawasaki disease), and other conditions, including juvenile scleroderma (both systemic and localized). The eligibility criteria for enrollment in the STOPP study have been described in detail elsewhere for this cohort.12 In brief, children ≤16 years with rheumatic disorders were targeted for enrollment within 30 days of GC initiation and followed for 3 years. Patients were excluded from the study if they had previously taken GC for the treatment of their underlying disease. Patients were also excluded if they had received intravenous or oral GC for >14 consecutive days in the 12 months preceding study enrollment to treat any other medical condition (e.g. asthma), or if they had previously been treated with an osteoporosis medication (e.g. a bisphosphonate). The cohort was studied every 3 months for 3 years to allow for accurate clinical data collection. The research ethics board at each participating institution approved the study and informed consent/assent was obtained prior to enrollment.

Clinical data

Demographic and clinical data were collected as described.12 Height, weight, and BMI (weight [kg] divided by height [m] squared) were measured at baseline and every 3 months thereafter. The raw values for height, weight, and BMI were transformed into age- and gender-matched Z-scores according to the U.S. Centers for Disease Control and Prevention National Center for Health Statistics normative database.14 for children under 2 years of age, BMI Z-scores were calculated according to the World Health Organization child growth standards.15 In addition, the presence or absence of back pain as reported by the participant was recorded every 3 months, with recent back pain defined as pain reported in the 12 months preceding each annual VF assessment by lateral spine radiograph.

Dietary calcium and vitamin D intake were assessed by a validated food frequency questionnaire every 3 months.16 Calcium and vitamin D intake by supplementation was added to the dietary intake to arrive at a total daily intake for both nutrients, which were further classified as <50% of the age-related Dietary Reference Intake (DRI), 50% to 100% of the DRI, and >100% of the DRI.17 Physical activity was assessed every 3 months using the Habitual Activity Estimation Scale12,18 as described by our group.12,13 A physician global assessment of disease activity for each patient was determined every 3 months on a 10-cm visual analog scale by a pediatric rheumatologist (where 0 cm = inactive disease and 10 cm = very active disease).12,19–21 Methotrexate exposure was expressed as the average weekly dose (mg/kg) from all routes of administration.

Quantification of GC exposure

The dose of systemic GC therapy (oral and intravenous) received during the 3-year observation period was determined entirely at the discretion of the treating rheumatologist. Daily GC doses and any subsequent changes were documented quarterly by chart review, patient or parent interview, and review of home GC diaries. When a patient missed a study visit, a research assistant called the family by telephone to record GC dose changes. GC diaries. When a patient missed a study visit, a research assistant called the family by telephone to record GC dose changes. GC doses were converted to mg/kg in prednisone equivalents. GC exposure was described in separate analyses as five time-dependent variables up until the date of each child’s VF assessment, as follows: (1) average daily dose, defined as the total amount of GC in prednisone equivalents (per body weight) divided by the total number of days in the observation period; (2) duration of GC therapy, expressed as the number of days on GC since initiation; (3) GC dose intensity, defined as the total amount of GC per body weight divided by the number of days on GC during the observation period; (4) recent average daily GC dose (i.e. average daily dose in the 12 months immediately
preceding each VF X-ray assessment); and (5) recent duration of GC therapy (also in the 12 months preceding each VF X-ray assessment).

Vertebral fracture assessment

For each patient, VF were assessed at baseline and then annually by lateral thoracolumbar spine radiographs. The spine radiographs were scored independently by two pediatric radiologists according to the modified Genant semiquantitative method \(^{(22)}\) and a third radiologist resolved any discrepancies. Vertebral bodies were graded according to the extent of the reduction in height ratios when the anterior vertebral height was compared with the posterior height (anterior wedge fracture), middle height to the posterior height (biconcave fracture), and posterior height to the posterior height of adjacent vertebral bodies (crush fracture). The scores corresponded to the following reductions in height ratios: grade 0 (normal), 20% or less; grade 1 fracture (mild), >20% to 25%; grade 2 fracture (moderate), >25% to 40%; and grade 3 fracture (severe), >40%. An incident VF was defined as a new fracture in a previously normal vertebral body or worsening of an existing VF (i.e. an increase in the Genant grade by at least 1); for simplicity, such fractures are referred to as “incident VF.”

Lumbar spine bone mineral density, bone age, and second metacarpal morphometry

Within 30 days of GC initiation, areal lumbar spine bone mineral density (LSBMD) was measured in the anterior-posterior direction at the L-spine (L1–L4) by dual-energy X-ray absorptiometry (DXA) using either Hologic (Hologic Inc. Bedford, MA, USA) (QDR 4500 3 centers, Discovery 2 centers, Delphi 1 center) or Lunar Prodigy (GE Lunar Corporation, Madison, WI, USA) (4 centers) machines at enrollment and every 6 months thereafter. Machines were cross-calibrated as described. \(^{(12)}\) The raw LSBMD results were converted to Hologic units, and Z-scores were generated using the Hologic 12.3 normative database. Radiographs of the left hand and wrist were obtained at baseline and annually to determine bone age and second metacarpal percent cortical area Z-scores as described. \(^{(12)}\)

Treatment of vertebral fractures during the course of the study

The treatment of VF that occurred during the course of the study was at the discretion of the attending physicians in the various tertiary care centers, and was not dictated by a STOPP-related treatment protocol. The age of the patient, clinical stage at which bone-targeted treatment was initiated and the name of the drug were recorded; however, a detailed analysis of the rationale for treatment and the response to bone-specific therapy in the few patients who received intervention was beyond the scope of this natural history study.

Statistical analysis

Analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA). Categorical variables were described using frequency and percentage. Normally distributed continuous variables were described using mean and standard deviation (SD). Non-normally distributed continuous variables were described using median and interquartile range (IQR). Box plots were used to describe the trajectories of average daily GC dosage, LSBMD and BMI Z-scores, and disease activity over time.

The person-years incidence rate was calculated as the number of children with incident VF divided by the sum of the follow-up time for each child. \(^{(23,24)}\) The annual incidence was calculated as the number of children with incident VF divided by the number who completed the VF assessment at the end of the annual, specified time period. In order to express the 3-year incidence as a proportion, it was assumed that the children lost to follow-up or with missing data had the same probability of developing incident VF over 3 years as observed in the rest of the cohort.

Extended Cox regression models, which allow non-proportional hazards, recurrent events, and time-varying covariates, \(^{(25)}\) were used to determine the association between incident VF and (1) time-independent risk factors including age, bone age, pubertal stage, gender, specific diagnosis as well as prevalent VF at baseline, and (2) time-dependent risk factors including GC exposure as defined above, disease activity, BMI Z-score, LSBMD Z-score, second metacarpal percent cortical area Z-score, recent back pain (in the 12 months preceding each VF assessment), physical activity, and average calcium and vitamin D intake from diet and supplementation combined. Data were censored at the point when one of the following occurred first: the 36-month follow-up visit, the last available visit, or when bone-specific therapy (such as a bisphosphonate) was instituted for symptomatic VF in accordance with the local standard-of-care. A test for non-proportional hazards using the Schoenfeld residuals \(^{(25)}\) was performed, and smooth estimates of hazard ratios were calculated using the method of Therneau and Grambsch. \(^{(26)}\) If the proportional hazards assumption was not rejected at the 0.05 significance level, the constant hazard ratio (consistent with the proportional hazards assumption) was used to reduce the risk of overfitting bias. \(^{(26)}\) Robust variance estimators were used to account for multiple VF assessments on the same patient. Selection of VF risk factors for inclusion in the final models was guided by clinical judgment and univariate analysis, with the effects from the extended Cox models expressed as the hazard ratio (HR), corresponding 95% confidence interval (CI), and the associated p value.

Results

Clinical characteristics of the cohort

A total of 136 pediatric patients with rheumatic disorders were enrolled into the study; 2 were excluded because of failure to undergo a bone health evaluation within 30 days of GC initiation. The number of children with a valid VF assessment at the 12-month, 24-month, and 36-month follow-up visits was 118, 105, and 110, respectively. Note, one child received bisphosphonate therapy at 4 months after GC initiation because of symptomatic vertebral collapse; this child was included in the calculation of incident VF in the first 12 months following GC therapy. The reasons for lack of available data on some patients at each time point are presented in Fig. 1. The clinical profile at baseline for patients with incomplete data did not differ significantly from those with complete follow-up (data not shown).

Descriptions of this cohort at baseline and at 12 months following GC initiation have been published in two reports. \(^{(12,13)}\) In brief, among the 134 patients (mean ± SD age 9.9 ± 4.4 years; 65% girls; 75% Caucasian; 7% with prevalent VF at baseline), 30 (22%) had juvenile dermatomyositis, 28 (21%) had JIA (excluding systemic arthritis), 26 (20%) had systemic lupus erythematosus, 22 (16%) JIA (systemic
(arthritis), 16 (12%) systemic vasculitis, and 12 (9%) had other rheumatic disorders (localized scleroderma, n = 10; generalized scleroderma, n = 1; and eosinophilic fasciitis, n = 1). The baseline VF assessment occurred at a median of 18 days (IQR, 11 to 24) following GC initiation. There were no significant differences for the following studied variables in respect to race and gender: prevalent and incident VF, LSBMD Z-score, age, diagnosis, average daily GC dose, BMI Z-score, physical activity, calcium intake, and vitamin D intake. On the other hand, the disease activity score at baseline was higher for boys compared to girls (mean ± SD 6.4 ± 5.1 versus 5.1 ± 2.8, p = 0.011).

For vitamin D daily intake through supplementation and diet combined at baseline, the mean ± SD % of the DRI was 111% ± 79%. Overall, 48% of children were below the DRI at baseline. By 36 months, the mean ± SD % of the DRI increased to 138% ± 106% and the % of patients below DRI decreased to 38%. Although there was a statistically significant increase in the total vitamin D intake at 36 months compared to baseline (p = 0.018), the proportion of children with intakes less than 100% of the DRI was not different between these two time points (p = 0.136).

For daily calcium intake through supplementation and diet combined, at baseline the mean ± SD % of the DRI was 246% ± 165% and 15% of patients fell below the DRI at this time point. By the end of 36 months, the mean ± SD % of the DRI decreased to 175% ± 81%; at this time point, only 24% of the patients were below the DRI. Although there was a statistically significant decline in the total calcium intake between baseline and 36 months (p < 0.001), the proportion of children with intakes less than 100% of the DRI was not different between these two time points (p = 0.123).

The frequency and pattern of incident vertebral fractures

Twenty-nine incident VF (26 thoracic, 3 lumbar) were identified in 14 children during the 3 years following GC initiation. Children with incident VF held the following diagnoses: 6 had juvenile dermatomyositis, 4 had systemic lupus erythematosus, 2 had systemic vasculitis, 1 child had JIA (systemic arthritis), and 1 had
JIA (excluding systemic arthritis). Of those with incident VF, 57% reported back pain in the preceding 12 months whereas 43% were asymptomatic. Twenty-eight of the 29 incident VF (97%) were in previously normal vertebral bodies, whereas only one was worsening of an existing fracture. Eight of 14 children (57%) with incident VF had a single fracture; the other 6 children (43%) had 2 incident VF \((n = 3)\), 3 VF \((n = 1)\), 5 VF \((n = 1)\) or 7 VF \((n = 1)\). Nine children (64%) had mild VF as the worst grade, 5 (36%) had moderate fractures, and none had severe fractures. Interestingly, two patients had one incident VF each after GC cessation (1.1 and 2.8 years following the discontinuation of GC therapy). All other VF occurred while on GC therapy (Fig. 2A, B).

The unadjusted VF incidence rate was 4.4 per 100 person-years, with a 3-year incidence proportion of 12.4%. Seven children had VF in the first year for an annual incidence of 6.0% (95% CI 2.9% to 11.7%), 5 children had VF during the second year (annual incidence 4.8%; 95% CI 2.1% to 10.7%), and 4 children had VF during the third year (annual incidence 3.6%; 95% CI 1.4% to 9.0%). Two children had incident VF at two different time points (i.e. a recurrence of incident VF), whereas the other 12 children had incident VF at a single time point (i.e. at 12, 24, or 36 months). One patient with recurrent VF was an 8-year-old girl with lupus. This patient had her first VF at 12 months (grade 2, T12) and the second at 24 months (grade 2, T11). The other child with recurrent VF was one of the most severely affected in the cohort. This 9-year-old girl with systemic vasculitis had her first incident VF at 12 months (grade 1, T9) and then additional VF at 24 months (grade 2 at T8, grade 2 at T6, grade 1 at T11, and grade 1 at T12). In addition, the 12-month grade 1 VF at T8 progressed to a grade 2 VF at 24 months.

The mean LSBMD Z-score was low compared to the healthy average at baseline \((-0.56 \pm 1.18; p < 0.001)\) and reached its nadir at 6 months (mean \(\pm\) SD LSBMD Z-score \(-0.93 \pm 1.21\)). The LSBMD Z-score increased gradually thereafter with a mean \(\pm\) SD of \(-0.66 \pm 1.18\) at 36 months. Disease activity was high at baseline (mean \(\pm\) SD disease activity score 5.56 \pm 2.75) but dropped after the initiation of GC therapy. In contrast, the BMI Z-score increased in the first 6 months after GC therapy and then fell gradually.

### Risk factors for incident vertebral fractures

The results of the multivariate extended Cox models to identify factors associated with the risk of incident VF are presented in Table 1. The multivariate models showed that every 0.5 mg/kg
increase in average daily GC dose was associated with a 95% increased VF risk (Model 1, HR 1.95; 95% CI 1.08 to 3.51; \( p = 0.026 \)). In addition, every 1-month increase in recent duration of GC treatment was associated with a 22% increased VF risk (Model 5, HR 1.22; 95% CI 1.08 to 1.36; \( p = 0.001 \)). GC intensity, duration of GC therapy, and recent average daily GC were not significantly associated with increased VF risk. All multivariate models showed that increases in disease activity between baseline and 12 months, increases in BMI Z-scores in the first 6 of the 12 months preceding each annual VF assessment, and decreases in BMD Z-scores in the first 6 months of GC therapy were significantly associated with an increased incident VF risk. All multivariate models were adjusted for specific underlying diagnosis, as well as age and height Z-scores at baseline given their importance as potential confounders. On the other hand, the following variables were excluded from our final, reported models given their lack of significance in the multivariate regression modeling: calcium and vitamin D intake, pubertal stage, gender, prevalent VF at baseline, second metacarpal percent cortical area Z-score, recent back pain, methotrexate exposure, and physical activity.

Discussion

This study provides novel data on the VF incidence in a cohort of pediatric patients with GC-treated rheumatic disorders captured through prospective, annual VF surveillance with a systematic VF

Fig. 3. Description of the 3-year trajectories for glucocorticoid exposure, lumbar spine bone mineral density Z-scores, body mass index Z-scores, and disease activity.
We found that a higher daily average dose and longer duration of GC therapy in the 12 months preceding each annual VF assessment were associated with an increased risk of incident VF. As well, readily measurable changes in patients’ clinical profiles also independently predicted increased VF risk, including increases in BMI Z-scores in the first 6 months of GC therapy (and in the first 6 months leading up to the annual VF assessment), decreases in LSBMD Z-scores from baseline to 6 months, and increases in disease activity scores from baseline to 12 months. These findings are in line with those from other studies investigating bone health outcomes in GC-treated children with rheumatic disorders with different study designs. Varonos and colleagues conducted a retrospective study of 23 GC-treated patients with JIA (including 19 with systemic arthritis) who had at least one VF and compared these patients to similar-aged children with JIA treated with GC but without a history of VF. They found children with VF received a daily GC dose that was 2.3 times higher than those without. Markula-Patjas and colleagues conducted a cross-sectional study of 50 adolescents with a history of treatment-resistant polyarticular JIA for ≥5 years or systemic arthritis for ≥3 years. Results showed that high disease activity, high BMI, and high cumulative GC dose in the 3 (retrospective) years preceding the cross-sectional VF assessment were associated with a significant VF risk. In another cross-sectional study of 94 children with a variety of rheumatic diseases, Nakhla and colleagues documented that cumulative GC dose and higher BMI Z-scores were associated with the prevalent VF after variable durations of GC exposure.

The fact that high disease activity is a consistent predictor of bone morbidity is not surprising, given the deleterious skeletal effect of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) as well as interleukin-1 and interleukin-6. These cytokines are known to impact the differentiation and function of osteoblasts and osteoclasts, uncoupling the tightly regulated bone remodeling cycle causing excessive skeletal resorption, and by promoting osteoclastogenesis through action on the osteoclast lineage including RANKL. The other

Table 1. Multivariate Cox Regression Models Assessing the Association Between Potential Risk Factors and Incident Vertebral Fracture

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
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<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Average daily GC dose (0.5 mg/kg)</td>
<td>1.95 (1.08–3.51)</td>
<td>0.03</td>
<td>0.97 (0.91–1.02)</td>
<td>0.22</td>
<td>1.36 (0.80–2.33)</td>
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<tr>
<td>VAS score, baseline to 12 months</td>
<td>1.38 (1.14–1.66)</td>
<td>0.02</td>
<td>1.32 (1.10–1.59)</td>
<td>&lt;0.01</td>
<td>1.31 (1.08–1.58)</td>
</tr>
<tr>
<td>BMI Z-score, in the first 6 months preceding each annual VF assessment</td>
<td>3.21 (1.60–6.45)</td>
<td>&lt;0.01</td>
<td>4.05 (2.13–7.69)</td>
<td>&lt;0.01</td>
<td>3.94 (2.05–7.55)</td>
</tr>
<tr>
<td>LSBMD score, baseline to 6 months</td>
<td>2.98 (1.10–8.07)</td>
<td>0.03</td>
<td>4.17 (1.48–11.77)</td>
<td>0.01</td>
<td>4.29 (1.46–12.60)</td>
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</table>

In the 12 months preceding the annual VF assessment.

assessment protocol. The fact that 14 out of 136 children sustained at least 1 incident VF (on average, 2.1 VF per child) and 2 children had recurrent, incident VF (including 1 child with a total of 7 incident VF) highlights the potential for significant bone morbidity in this context. This fact is underscored by our observation that about one-third of the children with VF had moderate vertebral collapse. Importantly, the peak annual VF incidence in our cohort occurred at 12 months following GC initiation, an outcome which is not surprising given that GC exposure was highest in the first year of therapy, as well as the known rapidity with which GC exert their deleterious effects. A key finding was that 43% of patients with incident VF were asymptomatic (and would have thereby gone undetected in the absence of routine surveillance), consistent with other VF surveillance reports in children with GC-treated leukemia and nephrotic syndrome. The potential for VF to be asymptomatic appears a robust observation with considerable implications for routine monitoring.

Apart from our earlier study describing this cohort to 12 months following GC initiation, there are no other prospective, longitudinal studies describing the incidence of VF captured through routine surveillance in pediatric rheumatic disorders. We previously showed a 6% VF incidence in this context at 12 months, and noted that symptomatic VF were present as early as 4 months following GC initiation. A recent, prospective study by Lim and colleagues (with spine BMD Z-score as the main outcome) reported that 3 of 68 children (4%) with lupus had asymptomatic VF (VF assessment method not specified) over a 2-year observation period when the criteria for performing a spine radiograph was a LSBMD Z-score < −2 SD and/or back pain. In our present study, 4 of 26 children with GC-treated lupus (15%) had incident VF in the first 2 years when all children were routinely monitored, and in our overall cohort, 3 of 14 children had incident VF despite LSBMD Z-scores better than −2 SD and an absence of back pain. Our results highlight the importance of routine VF surveillance in at-risk children, even among those with LSBMD Z-scores better than −2 SD and an absence of back pain.
consistent predictor of VF (an early predictor) is an increase in BMI Z-score. Studies of weight gain as a risk factor for fractures in healthy children have been inconsistent to date; however, none of these studies assessed the relationship between weight and VF. Our results suggest the predictive increase in BMI Z-scores in the first 6 months of GC therapy may be a marker of sensitivity to GC therapy.

Our study highlights the need for a bone health assessment in at-risk patients that includes not only a DXA-based BMD but also a lateral thoracolumbar spine radiograph. Having previously described a baseline VF prevalence of 7% in this context and because the earliest report of incident VF has been at 4 months following GC initiation, it seems reasonable to recommend a baseline spine radiograph at the time of GC initiation for any child anticipated to be on GC therapy for 3 months or more. In addition, a follow-up radiograph at 12 months also appears justified given this is the time point of the highest annual VF incidence, particularly in patients with increases in disease activity and BMI and decreases in LS BMD Z-scores (the latter two variables, in the first 6 months of GC therapy). These data also support additional spine radiograph at intervals beyond the first year in those with ongoing need for GC therapy or further increases in BMI Z-scores.

Given that our data suggest a spine radiograph should be a key component of the bone health evaluation in at-risk children and adolescents, it is interesting that the International Society for Clinical Densitometry recently revised its position statement on the diagnosis of osteoporosis in children, stating that for those with a low-trauma VF, BMD-based criteria are no longer supported for this recommendation, because 8% of children in our study with at least one incident VF over the 3 year study period had a LS BMD Z-score > -2 SD. We have also made this observation in children with leukemia (48% of children with leukemia and VF at diagnosis had LS BMD Z-scores > -2 SD). Identifying children with both symptomatic and asymptomatic vertebral collapse is important, because it provides the clinician with the opportunity to institute appropriate monitoring and treatment strategies.

In summary, we have shown the VF incidence is 4.4 per 100 person-years in the 3 years following GC initiation, that the highest annual incidence of VF is at 12 months, and that discrete clinical predictors are evident early in the disease and GC treatment course. These natural history observations provide important data to support inclusion of a spine radiograph as part of the routine bone health assessment in at-risk children.

Disclosures

All authors state that they have no conflicts of interest.

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