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Long-Term Bone Health in Glucocorticoid-Treated Children with Rheumatic Diseases

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Abstract Glucocorticoids (GC) are a standard treatment for pediatric rheumatic disease. Recent literature highlights skeletal vulnerability in children with rheumatic illness, including vertebral and peripheral fractures and reductions in bone mineral density in longitudinal follow-up. Annual vertebral fracture incidence of 4–6 % in those recently diagnosed and prevalence of 7–28 % in those several years post diagnosis have been reported. The fractures are often asymptomatic, often thoracic in location, and usually of mild, anterior wedge morphology. Diseases with more systemic involvement and severe inflammation (SLE, JDM) seem to be at higher risk. Neither BMD nor GC dose are ideal predictors for risk of fractures. These children also seem to have an increased incidence of long-bone fractures, particularly in the forearm and wrist; in the scant literature, long-bone fractures are not predictive of vertebral fractures. Bone mass accrual is typically suboptimum across time, although the use of potent steroid-sparing anti-inflammatory agents may counteract the effects of GC and active disease. Vitamin D insufficiency warrants ongoing monitoring. Additional targeted studies are justified to increase understanding of bone health risks in this population.

Keywords Glucocorticoids · Vertebral fractures · Fragility fractures · Osteoporosis · Low bone mass · Hypovitaminosis D · Vitamin D · BMD · DXA · Bone health · Long-term bone health · Children · Rheumatic diseases

Abbreviations

aBMD	Areal bone mineral density
BMAD	Apparent bone mineral density
BMD	Bone mineral density
BMI	Body mass index
D	Day
DMARDs	Disease-modifying antirheumatic drugs
DXA	Dual-energy X-ray absorptiometry
GC	Glucocorticoids
JIA	Juvenile idiopathic arthritis
JDM	Juvenile dermatomyositis
kg	Kilogram
L	Lumbar
MCTD	Mixed connective tissue disease
SLE	Systemic lupus erythematosus
T	Thoracic
VF	Vertebral fractures

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Introduction

Rheumatic disease in children encompasses a variety of diagnoses, including juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), systemic vasculitis, and juvenile dermatomyositis (JDM) [1]. Even with advances in therapy, glucocorticoids (GC) remain an important component of treatment regimens for many disorders [2–5]. Children with rheumatic diseases are now increasingly recognized as having impaired bone health and resulting fragility fractures [1, 6–9]. Multiple factors reduce the child's likelihood of accruing normal bone mass and/or achieving

typical adult peak bone mass. Among the risk factors are systemic inflammation and medications, including GC. Also contributing are decreased physical activity, in particular low levels of weight-bearing exercise, muscle dysfunction, delayed puberty, and modifiable factors, for example suboptimum calcium and vitamin D intake [10, 11, 12•].

Glucocorticoids can reduce bone mass or limit its accrual through several mechanisms, including increased osteoclast and reduced osteoblast activity and reduced intestinal calcium absorption [1, 13–15]. Recent literature provides insights into the range of bone health problems encountered in children with rheumatic disorders. Similar to GC-treated adults with arthritis, these children seem especially prone to vertebral fractures as common fragility fractures, although these may be asymptomatic and found only incidentally [16, 17•]. This review will focus on the latest literature describing the frequency of vertebral fractures and their predictors, the incidence of other fragility fractures, longitudinal bone mass changes, and vitamin D status in children with GC-treated rheumatic disorders.

Vertebral Fractures

It has been several decades since vertebral fractures were first recognized as a bone health threat to children with juvenile arthritis [7]. It is only recently, however, that the frequency, clinical presentation, and predictors of these fractures have been examined in detail in cross-sectional and longitudinal studies. The purpose of these studies was to determine which children would benefit from screening for fractures, to establish the best method of fracture detection, and to identify optimum grading techniques for pediatric fractures [18, 19]. Their ultimate purpose is to reduce fracture occurrence.

Initial reports placed VF prevalence at 10–34 % in children with rheumatic diseases; many of these studies were limited by small numbers of patients, restricting understanding of clinical predictors [6, 16, 20–22]. With more aggressive treatment using disease-modifying antirheumatic drugs (DMARDs), including biological therapy, these estimates had to be revised. The 2009 report by Nakhla et al. found a VF prevalence of 19 % in a comprehensive cross-sectional study of 94 children with heterogeneous rheumatic diagnoses [16] (Table 1). The median duration of disease was 4.6 years (range 0.4–15.7 years). Four recent cross-sectional studies found the prevalence of fractures was 4–28 % [17•, 23, 24•, 25•]. The number of children studied ranged from 50 to 134, the largest group being that in a natural history study entitled the Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) initiative [23]. In this study, children with newly diagnosed rheumatological conditions had spine radiographs and bone densitometry measured by dual-energy X-ray absorptiometry (DXA) within 30 days of initiating GC. They were then followed annually for six years; the prevalence of VF at recruitment was 7 % and the incidence was 6 % 12 months later. Notably, none of the children with prevalent fractures developed an incident fracture, and all incident fractures were new fractures in previously normal vertebrae.

In the second study, a cohort of 68 children with newly diagnosed SLE was monitored with three DXA scans and spine radiographs on an annual basis [25•]. There were no fractures at baseline, and the incidence of VF was 4 % at last follow-up (median 872 days). Another 3 % developed VF after the study period; all VF were asymptomatic. The remaining two recent studies describing prevalent vertebral fractures assessed 50 children with steroid-resistant JIA [17•, 24•]; evaluations of the spine were performed by use of MRI and plain radiographs. At the time of imaging, these children had a mean disease duration of 10.2 years (range 3.8–16.8 years). The VF prevalence was 28 % when assessed by MRI and 22 % assessed by use of plain radiographs. The MRI study also diagnosed disc degeneration in 46 %, protrusions in 14 %, and prolapses in 4 %; 4 % of children had mild spinal canal narrowing. The disc abnormalities were mostly located in the lower thoracic region. The clinical significance of these changes is not clear, although up to one third of healthy adolescents have been noted to have lumbar disc degeneration with subsequent early adult low back pain [26–28].

Table 1 outlines a summary of these studies. Not surprisingly there is a female predominance in all cohorts, although females did not consistently develop more VF. Not all rheumatic conditions have been evaluated for VF; the bulk of the studies examined risks in children with more severe diseases typically treated with GC, for example SLE, JDM, systemic JIA, and systemic vasculitis. Nakhla et al. reported eight VF in three steroid-naïve children with JIA, suggesting that factors other than GC use are also involved in the development of VF [16]. Moreover, these reported cohorts vary in both duration of disease and in the methods used for fracture detection (MRI vs. plain radiographs). The different VF scoring systems used (Genant semi-quantitative vs. Makitie's pediatric) also impede study comparisons [18, 19].

What is consistent across all reports is the observation that not all children experience pain with the fractures. The thoracic region seems to be particularly prone to fractures, particularly the mid region. Fractures are typically mild in their degree of collapse and have primarily anterior wedge morphology. Unfortunately, there is no consistent BMD or cumulative GC threshold that strongly predicts VF [21]. Increased BMI, likely to be a marker of higher GC dose with systemic effects, is identified as a predictor in some studies [16, 17•]. Notably, in at least two studies where the details are provided some children seem to be particularly sensitive to GC, experiencing large numbers of VF; Nakhla reported one child with systemic JIA and 11 fractures, and Rodd described another with five fractures within months of initiation of GC after diagnosis [16, 29•].

Table 1 Incidence and prevalence of vertebral fractures and their determinants

Authors (year)	Patients, *n* (age range) Gender F, M (%)	Diagnoses of children evaluated	Number with VF (F/M) # of VF	VF prevalence (P) or incidence (I) (%)	Method of detection and VF assessment	Location of fractures	Severity and type of fracture	L-spine BMD *z*-score ± SD (for those with VF)	Mean cumulative GC dose (for those with VF)	Predictors of fractures
Nakhla (2009)	94 (4.3–18.0) 76, 24	**JIA**, **MCTD**, **SLE**, **DM**, **SV**	17 (7/10) 50 VF	19 P	RadGenant [18]	39 T (55 % T4–T8) 11 L	88 % mild, 8 % moderate, 4 % severe; 68 % anterior wedge, 18 % crush, 14 % biconcave	−1.40 (95 %CI: −2.01; −0.31),	258.1 $mgkg^{-1}$ [a]	Male gender Mean cumulative GC dose BMI z-score
Huber (2010)	134 (1.4–16.99) 65, 35	**JIA- systemic**, **JDM**, **SLE**, **SV**, **JS**, **OS**	9 (4/5) 13 VF	7 P	RadGenant [18]	9 T (69 % T6–T8) 4 L	77 % mild, 23 % moderate; 92 % anterior wedge, 8 % crush	−1.2±1.0	1,320±2,755 mg m^{-2} [a]	Back pain
Rodd (2012) (same as Huber (2010) 12 months later)	117 (2.3–17.9) 63, 37	JIA, **JDM**, **SLE**, **SV**, JS, **OS**	6 (4/2) 7 VF	6 I	RadGenant [18]	5 T 2 L	50 % mild, 50 % moderate; 86 % anterior wedge	−1.7±1.1	9452±3447 mg m^{-2} [a]	Cumulative GC dose Average GC dose
Markula-Patjas (2012)	50 (7.0–18.7) 82, 18	**JIA**	11 (7/4) 54 VF	22 P	RadMäkitie [19]	38 T (52 % T4 –T10) 16 L	15 % mild wedge, 50 % mild biconcave/crush, 2 % severe wedge, 33 % severe biconcave /crush	−0.7±1.6	292±323 mg kg^{-1} [b] (recent cumulative)	Recent cumulative GC dose BMI
Toiviainen-Salo (2012) (Identical with Markula-Patjas 2012)	50 (7.0–18.7) 82, 18	**JIA**	14 (8/6) 66 VF	28 P	MRIMäkitie [19]	52 T (58 % T4–T10) 14 L	73 % mild wedge or biconcave/ crush, 27 % severe wedge or biconcave/crush	−0.9±1.2	189±311 $mgkg^{-1}$ [b]	
Lim (2012)	68 (11–14.3)[c] 84, 16	**SLE**	3 (NA) 3 VF	4 I	Rad NA	NA	NA	NA	NA	NA

GC, glucocorticoid; JDM, juvenile dermatomyositis; SLE, systemic lupus erythematosus; SV, systemic vasculitis; JS, juvenile scleroderma; OS, overlap syndrome; MCTD, mixed connective tissue disease; F, female; M, male; vBMD, volumetric bone mineral density; BA, bone age; Rad, radiograph; VF, vertebral fracture; T, thoracic; L, lumbar

Bold indicates all diagnostic groups with VF

[a] Prednisone equivalent

[b] Prednisolone equivalent

[c] Interquartile range

Clearly, a lack of consistent findings is in part because of the different study designs, different populations, duration of follow-up, and individual sensitivity. At this point, we cannot provide recommendations for predicting VF on the basis of back pain or tenderness, cumulative GC dose, absolute BMD or BMI values, or changes over time. Clinical caution is required, particularly in those disease groups that seem to be at higher risk; these include SLE, JDM, systemic JIA and vasculitis. Ongoing follow-up of these cohorts and evaluation of larger cohorts, ideally with a control group and harmonized assessment techniques, will provide improved insight into the development of fragility fractures in this population.

To understand why these children are at particular risk of this type of fragility fracture, one must or we must study adults, and other pediatric diseases in which technological innovation has clarified the pathophysiology. Across all ages, trabecular bone—the major constituent of vertebrae—is metabolically very active and, compared with cortical bone, it is more vulnerable to insults such as GC [30, 31]. Analyses of adult vertebrae have elegantly revealed trabecular thinning and loss of vertical trabecular plates, both of which seem to reduce strength. This altered architecture is not apparent when standard DXA is used, which accounts for some of the difficulty in predicting patients who will fracture.

Differences in the anatomical location of VF have been reported for GC-treated children compared with adults. In a recent attempt to clarify these differences, Siminoski et al. [32] compared 44 children with 94 VF from the STOPP initiative with 221 osteoporotic adults with 545 VF, using the Genant semi-quantitative method. The STOPP initiative comprises three pediatric cohorts: children with leukemia, with rheumatic conditions and with nephrotic syndrome. By combining data on VF detected in all three groups within 30 days of GC initiation, these investigators were able to more clearly assess anatomical distribution in children. Adults and children had biphasic VF distributions, but they differed in location. Adults had peaks of fractures at T7/T8 and T12/L1 whereas children had peaks both higher in the spine at T6/T7 and also lower at L1/L2. When the 44 children were divided into two groups, those who were younger (mean age 4.1 years) had a fracture distribution more similar to that of adults. These differences have been ascribed to the different shape of the child's spine, which is straighter and has less thoracic kyphosis and lumbar lordosis [33].

Long-Bone Fractures

Several publications over the past decade have examined whether children with rheumatic conditions experience, as adults do, higher incidence of non-VF fragility fractures [8]. One such study used the UK General Practice Research Database, a longitudinal population database spanning the period 1987–2002. Prevalent and incident fractures were assessed in 1,939 children with diagnostic codes consistent with arthritis (onset between the ages of one and 19 years, 51.4 % female). Outcomes were compared with 207,072 age, gender and physician-practice-matched control subjects (53.1 % female) [8]. During follow-up (median 3.9 years), the rates of first fractures were 6.7 % and 3.3 %, in the arthritis and control groups respectively ($p<0.001$). The incidence rate ratio was significantly elevated in those aged 10–20 years with arthritis compared with control subjects. The most common sites of fractures were the forearm and the wrist, with fractures in 1.86 % of the arthritis group vs. 0.81 % of controls ($p<0.001$). Interestingly, GC were not found to be associated with increased incidence of fractures; however, only a small percentage of these children had received prescriptions for GC (4.9 %). This led the authors to propose that reduced coordination and increased sedentary habits secondary to the illness may have contributed to an increased risk of injury because of abnormal gait and reduced balance. This study was hampered by its broad definition of arthritis, by the absence of details regarding use of DMARDs, and by the lack of recent data.

The study by Markula-Patjas evaluating VF in 50 children with steroid-resistant JIA also reported a high incidence of low-impact long-bone fractures; 15 children had 24 fractures [17•]. No predictors were found; in particular, GC exposure, BMD values, age, BMI, disease duration, and disease activity were not identified as predictors. Moreover, long-bone fractures were not found to be predictive of vertebral compression fractures. Together, these two studies [8, 17•] suggest that children with rheumatic conditions are at increased peripheral fracture risk. However the effect of GC, if any, is unknown. Prospective longitudinal data are required to better understand if long bones are particularly prone to fractures in children with rheumatic conditions, and to identify potential predictors.

Longitudinal Bone Mass Changes

Accumulating evidence suggests that children with chronic rheumatic diseases may have reduced bone mass as young adults, possibly predisposing them to fragility fractures as both children and adults [12•, 34]. The recent publications outlined in Table 2 indicate that cohorts followed longitudinally for up to three years have BMD deficits, and that these persist or worsen over time [12•, 25•, 29•]. Analyses of the 89 children with JIA followed for ~3 years by Stagi et al. found that, at recruitment, patients with JIA had lower bone mineral apparent density (BMAD) than controls [35]. BMAD was inversely correlated with disease activity, systemic glucocorticoids dosage ($r=-0.45$), and number of intraarticular GC injections. There was a positive correlation

Table 2 Longitudinal assessment of bone mineral density in children with rheumatic diseases

Authors (year)	Patients, *n* (age; range in years)	Gender F, M (%)	Diagnoses of children evaluated	Baseline		Follow-up		Predictors of deterioration in BMD
				Disease duration	LS aBMD/ BMAD	Disease duration	LS aBMD/ BMAD	
Rodd (2012)	117 (2.3–17.9)	63, 37	JIA, DM, SLE, SV, JS, OS	22 days (1–4900) (median + range)	−0.6±1.0 (aBMD)	393 days (343–3408) (median+ range)	−0.8±1.2 (aBMD) (p <0 .001)	NA
Lim (2012)	68 (11–14.3)[a]	84, 16	SLE	64 days (15–109[a]) (median + IQR[a])	−0.42±1.18 (aBMD)	872 days (median)	−1.11±1.07 (p<0.001)	Cumulative GC exposure (100 mgkg^{-1} [b] would reduce LS BMD by 0.12 *z*-score per year, adjusted for all other predictors) Pubertal at diagnosis Reduced weight *z*-score
Stagi (2010)	89 (followed longitudinal ly, n=219 with at least one DXA at recruitment)	71, 29	JIA	3.5 years±3.0 (mean ± SD, n=219)	−0.78±1.00 for all JIA xsubtypes −1.42±0.7 for systemic JIA (BMAD)	8.3 years ±3.4 (mean ± SD, n=89)	Unchanged for all JIA subtypes −1.11±0.8 for systemic JIA (BMAD)	NA

GC, glucocorticoid; JDM, juvenile dermatomyositis; SLE, systemic lupus erythematosus; SV, systemic vasculitis; JS, juvenile scleroderma; OS, overlap syndrome; MCTD, mixed connective tissue disease; F, female; M, male; aBMD, areal bone mineral density; BMAD, apparent bone mineral density; BMD, bone mineral density

[a] Interquartile range

[b] Prednisone equivalent

with age at onset, and BMAD was significantly lower for patients with the systemic subtype of JIA [12•]. Over time, BMAD did not significantly improve in JIA patients, with the exception of those with systemic JIA (p<0.05).

More recently, Lim et al. [25•] prospectively followed 68 children with SLE for a median of 872 days. They found a significant proportion of patients with a low lumbar spine areal BMD measured within six months of diagnosis, with 9 % having a BMD *z*-score≤−2.0. This number more than doubled over time, with 19 % having a BMD *z*-score≤−2.0 at the time of last follow-up. Predictors for this decrease included cumulative GC dose, being pubertal at diagnosis of SLE, and decreased weight *z*-score.

Lower mean BMD compared with population reference data was also found for 134 STOPP study subjects with GC-treated rheumatic diseases who were assessed by use of DXA within 30 days of enrolment [23]. At one year follow-up there was a modest decrease in BMD for the entire cohort (p<0.001 compared with study entry and also with the healthy average) (Table 2). No predictors were identified for this decrement [29•]. A lumbar spine aBMD *z*-score<−2.0 was found for 19 % of patients at 12 months and for 67 % of patients who developed incident VF at 12 months. It is important to recognize that these longitudinal studies are limited by a number of possible selection biases, including limited numbers of children, willingness to consent, and dropout rates of the sickest patients, and the less frequent follow-up required for those with mild disease. Nevertheless, these recent studies suggest there is reduced lumbar spine BMD in both GC-treated and non-GC treated children with rheumatic diseases. As health-care providers increasingly use biological agents, particularly anti-TNF alpha therapy, there is the suggestion that use of these potent, steroid-sparing, anti-inflammatory agents contributes to increased BMD within 12 months of initiating therapy [32]. Further studies will be needed to confirm these findings.

Vitamin D Status

Increasingly, vitamin D deficiency is being recognized not only in the general population [36] but also in children with rheumatic diseases [25•, 37]. By use of liquid chromatography–quadrupole mass spectrometry, Pelajo et al. [37] recently measured 25(OH)D in 169 children with rheumatological autoimmune disorders and in 85 patients with nonautoimmune conditions. The first group included patients with SLE, JIA, JDM, MCTD, scleroderma, and vasculitis, whereas the second group was composed of children with non-inflammatory conditions (infectious diseases or pain amplification syndrome). Twenty-three percent of children in the

rheumatic group were found to have potential 25(OH)D inadequacy (<50 nmolL^{-1}) vs. 14 % in the control group. After adjustment for supplement use, ethnicity, BMI, and season, vitamin D deficiency was more prevalent in patients with autoimmune conditions (OR=2.3, $p<0.04$).

Not surprisingly, risk factors for vitamin D deficiency in the rheumatic disease group included lack of supplements, increased BMI, and reduced cutaneous synthesis during winter [37]. Children with MCTD and SLE had lower 25 (OH)D concentrations than other children with rheumatic conditions, possibly because of photosensitivity and more rigid sun avoidance behavior. Several other papers have highlighted vitamin D insufficiency in pediatric rheumatic conditions [17•, 25•, 38]. The previously described cohort of 68 children with SLE followed for over two years experienced a decrease in vitamin D deficiency from 57 % to 21 % with screening for 25(OH)D concentrations [25•].

Vitamin D sufficiency and a minimum intake of the recommended dietary allowance of calcium may help to reduce bone loss and even enable small gains in BMD [39]. Despite a lack of universal definition of optimum 25 (OH)D concentrations (50 nmolL^{-1} vs. 75 nmolL^{-1}) [40–42], screening high-risk children to detect vitamin D deficiency is recommended. The objective is to correct existing deficiencies. Additional benefits to musculoskeletal health or immune function are possible, but still poorly defined [40]. We advocate routine screening, particularly in the non-synthesizing seasons.

Conclusions

Children with rheumatic diseases have significant risks which threaten normal bone health. Notwithstanding recent therapeutic advances, GC are important therapeutic agents. However, they are associated with fragility fractures and reduced BMD in at least some of these children. Diseases with more systemic involvement and more severe inflammation (e.g. SLE, MCTD, JDM) seem to be at somewhat higher risk, although additional studies are warranted. The risk to bone health in this population may change with increased use of potent biological agents and treatment protocols that reduce GC exposure. What is clear from review of these recent papers is that fragility fractures occur, and that neither BMD nor GC dose are ideal markers for risk of fractures. Moreover, as we progress and harmonize our approaches to these children (for example, applying the same radiographic methods and scoring tools for VF) we will probably obtain more substantive results. Published studies are, typically, those with significant findings (publication bias) and the children studied are often those with more severe diseases. There are also other bone health outcomes, for example avascular necrosis, that have been poorly evaluated. We believe that screening these children for bone health issues is warranted, using methods including spine palpation for pain as a potential marker of VF, DXA, or other measures of bone mass, measurement of 25(OH)D, and dietary evaluation to improve vitamin D and calcium intake. Promotion of weight-bearing physical activity, to promote muscle mass, coordination, and balance, is equally important. Agents to prevent bone loss, for example bisphosphonates, are not routinely advocated. Currently these agents are primarily used as rescue medication for painful VF, although their efficacy and safety in this setting are still unproved. Clearly, more studies are justified.

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