## ORIGINAL ARTICLE

# Skeletal findings in children recently initiating glucocorticoids for the treatment of nephrotic syndrome

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**Abstract**

*Summary* Eighty children with nephrotic syndrome underwent lumbar spine densitometry and vertebral morphometry soon after glucocorticoid initiation. We found an inverse relationship between glucocorticoid exposure and spine areal bone mineral density (BMD) Z-score and a low rate of vertebral deformities (8%).

*Introduction* Vertebral fractures are an under-recognized complication of childhood glucocorticoid-treated illnesses.

Our goal was to study the relationships among glucocorticoid exposure, lumbar spine areal BMD (LS BMD), and vertebral shape in glucocorticoid-treated children with new-onset nephrotic syndrome.

*Methods* Lateral thoracolumbar spine radiography and LS BMD were performed in 80 children with nephrotic syndrome (median age 4.4 years; 46 boys) within the first 37 days of glucocorticoid therapy. Genant semiquantitative grading was used as the primary method for vertebral

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morphometry; the algorithm-based qualitative (ABQ) method was used for secondary vertebral deformity analysis.

*Results* Six of the 78 children with usable radiographs (8%; 95% confidence interval 4 to 16%) manifested a single Genant grade 1 deformity each. All deformities were mild anterior wedging (two at each of T6, T7, and T8). Four of the 78 children (5%; 95% confidence interval 2 to 13%) showed one ABQ sign of fracture each (loss of endplate parallelism; two children at T6 and two at T8). Two of the children with ABQ signs also had a Genant grade 1 deformity in the same vertebral body. None of the children with a Genant or ABQ deformity reported back pain. An inverse relationship was identified between LS BMD Z-score and glucocorticoid exposure.

*Conclusions* Although we identified an inverse relationship between steroid exposure and LS BMD soon after glucocorticoid initiation for childhood nephrotic syndrome, there was only a low rate of vertebral deformities. The clinical significance of these findings requires further study.

**Keywords** Bone mineral density · Children · Glucocorticoids · Nephrotic syndrome · Vertebral deformities

**Abbreviations**

| | |
|---|---|
| ABQ | Algorithm-based qualitative |
| BMI | Body Mass Index |
| BMD | Bone mineral density |
| CI | Confidence interval |
| GC | Glucocorticoid |
| LS | Lumbar spine |
| NS | Nephrotic syndrome |

## Introduction

Childhood nephrotic syndrome (NS) is characterized by proteinuria, edema, and hyperlipidemia. The annual incidence of NS varies from 1:15,000 to 1:50,000 [1]. Children with their first episode of idiopathic NS are treated with a widely accepted high-dose glucocorticoid (GC) regimen for 4 to 6 weeks (typically prednisone 60 mg/m$^2$/day) followed by a reduced but still supra-physiological dose over a similar time interval (prednisone 40 mg/m$^2$ every other day) [2]. With this initial regimen, one third of patients will enter into permanent remission; another third will require re-initiation of GC therapy for up to 6 weeks duration at infrequent intervals, and the final third will either require frequent courses of pulse GC therapy or chronic daily immunosuppressive therapy [3].

GCs are known for their adverse effects on skeletal health, highlighted in a large, epidemiological study describing increased extremity fracture rates among children treated with GCs for a variety of underlying conditions [4]. Studies in adults

treated with GCs for systemic disorders suggest that GC therapy impairs trabecular bone metabolism [5, 6], with estimates that up to 50% of adults receiving GCs for more than 1 year will develop osteoporotic (including vertebral) fractures [7, 8]. In adults with systemic disorders, vertebral fractures can occur early in the course of GC treatment, attributed to the rapid loss of bone mass in the first few months of therapy [6].

Similarly, reductions in lumbar spine areal bone mineral density (LS BMD) have been documented during the initial high-dose GC treatment phase in children with NS [9, 10], and modest deficits in LS bone mineral content have been shown following years of intermittent GC therapy for steroid-sensitive disease [11]. Overt bone fragility manifesting as vertebral fractures has also been reported in children with NS following the initial GC treatment phase in the context of a treatment study [10], and later in the disease course [12]. However, the frequency and characteristics of vertebral deformities in pediatric NS as well as their relationship to clinical factors have not been well studied. Therefore, we sought to determine the prevalence and characteristics of vertebral deformities around the time of GC initiation in an inception cohort of children with GC-treated NS. Other goals of the study were to describe the relationship between vertebral deformities and relevant clinical indices such as LS BMD, back pain, GC exposure, and calcium and vitamin D intake.

## Subjects and methods

### Patients and study design

Patients were recruited through the Canadian STeroid-Associated Osteoporosis in the Pediatric Population (STOPP) research program, a national research initiative that studies bone morbidity in children with steroid-treated illnesses. The decision to initiate GC therapy was made clinically prior to consideration for study enrolment.

Patients from 1 month to 17 years of age were enrolled between January 1, 2005 and December 31, 2007 in 10 participating tertiary care children's hospitals. All patients were targeted for evaluation within the first month of GC initiation. Children were included in the study if they met the clinical criteria for NS, including edema, proteinuria >960 mg/m$^2$/day or urine protein/creatinine >0.2 g/mmol, and serum albumin <25 g/L. Idiopathic NS was diagnosed either clinically (following an appropriate response to GC treatment in the first month of therapy, presumed minimal change disease) or confirmed by renal biopsy (biopsy-confirmed minimal change disease). NS due to focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis was also confirmed on renal biopsy. The

diagnosis of Henoch–Schoenlein purpura was made on clinical grounds.

Children were excluded if GCs had previously been used at any time for treatment of the underlying disease. Patients were also excluded if they had received intravenous or oral GCs for more than 14 consecutive days in the 12 months preceding study enrolment to treat any other medical condition (e.g., asthma), if they had received prior medication for osteoporosis or if they had received calcium or vitamin D supplementation that exceeded the Dietary Reference Intake for age [13].

The study was approved by the research ethics board in each participating institution, and informed consent/assent was obtained prior to study enrolment, as appropriate.

Clinical evaluation

Demographic and anthropometric data were recorded. Raw values for height, weight, and body mass index [BMI; weight (kilograms) divided by height squared (square meters)] were transformed into age- and gender-matched Z-scores according to the United States Center for Disease Control National Center for Health Statistics normative database [14] except for children under 2 years of age, for whom BMI Z-scores were calculated according to the World Health Organization child growth standards [15]. Pubertal staging was carried out according to the methods of Marshall and Tanner [16, 17]. The presence or absence of reported back pain in the 3 months preceeding enrolment was recorded.

Calcium and vitamin D intake were assessed by a validated food frequency questionnaire [18]. Intake for each nutrient was expressed as the percent of the adequate intake value based on the nutrient's Dietary Reference Intake [13]. Calcium and vitamin D intake by supplementation was added to the dietary intake to arrive at a total daily intake for both nutrients. For descriptive purposes the percentage of adequate intake scores were then classified as <50% of the age-related Dietary Reference Intake, $\geq 50$ and <100% of the Dietary Reference Intake, or $\geq 100\%$ of the Dietary Reference Intake. Calcium and vitamin D supplementation (yes/no) variables were chosen as clinically relevant covariates to include in the regression modeling. Physical activity was assessed according to the Habitual Activity Estimation Scale as previously described [19]. For descriptive purposes, the number of very active weekend hours was compared to Canada's recommended guidelines for daily physical activity for children [20]. Tertiles of very active weekend hours were included in the regression models.

Glucocorticoid exposure

The dose of systemic GC therapy (oral and intravenous) was converted into prednisone equivalents, and results were expressed in three ways, as previously described [21–23]:

(1) cumulative GC dose, defined as the amount of GC in prednisone equivalents (milligrams per square meters) received during a given observation period; (2) GC dose intensity, defined as the cumulative dose in prednisone equivalents (milligrams per square meters), divided by the number of days actually taking GCs; and (3) average GC dose, defined as the cumulative dose in prednisone equivalents (milligrams per square meters) divided by the total number of days during the observation period.

Radiological assessment

BMD was measured in the anterior–posterior direction at the LS (L1–L4) by dual-energy X-ray absorptiometry using either Hologic machines (QDR 4500, three centers; Discovery, two centers; Delphi, one center) or Lunar Prodigy (four centers). Machines were cross-calibrated using a Hologic spine phantom (serial number 2603). The phantom was scanned 10 times on each machine without repositioning, and the mean value was used to derive cross-calibration factors. Data were converted to Hologic units, and Z-scores were generated using the Hologic 12.4 normative database.

Bone age and second metacarpal morphometry on a left hand radiograph were also carried out as described in a previous publication by the Canadian STOPP Consortium [19].

Vertebral deformity assessment was carried out independently by two radiologists (NS, MM) from T4 to L4 [19, 24]. Discrepancies between the first two readers were resolved by a third expert radiologist (BL) who was blinded to the results of the other two, as previously described [19].

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

As a secondary and exploratory assessment of vertebral deformities, lateral spine radiographs were also reviewed for radiological signs of fracture according to the algorithm-based qualitative (ABQ) method [26], including loss of

endplate parallelism, endplate depression, and anterior cortical buckling.

Statistical analyses

All analyses were conducted using SPSS 16.0 (SPSS Inc., Chicago, IL). Categorical variables were summarized using frequency and percentage. Normally distributed continuous variables were summarized using mean and standard deviation. Non-normally distributed continuous variables were summarized using median and minimum, maximum. The 95% confidence intervals (CI) for the proportion of patients with vertebral deformities were calculated using the Wilson score method [27]. Z-score variables were compared to the healthy average (Z-score=0) using a one-sample Student's $t$ test to assess whether the patient population significantly differed from the normal reference values. In addition, children with vertebral deformities were compared to those without using Wilcoxon Mann–Whitney and Fisher exact tests. Presented $p$ values are two sided. A $p$ value $\leq 0.05$ was considered significant.

Scatter plots were generated in order to visually explore relationships between clinical covariates and LS BMD Z-score, and to identify potential outliers. Multiple linear regressions were carried out to identify clinical parameters associated with LS BMD Z-score. Height and weight Z-scores were included in all linear regression models to adjust for bone size. GC exposure (in prednisone equivalents) was also included in the models since this was the clinical parameter of primary interest. The following covariates (in addition to the three mentioned above) were chosen *a priori* based on clinical relevance: age, gender, physical activity (very active weekend hours divided into tertiles), vitamin D and calcium supplementation, and underlying NS diagnosis (minimal change disease versus other diagnoses).

## Results

### Patient characteristics

Eighty children (46 boys, 58%) were enrolled in the study at a mean of 18.6 days (range 0 to 37 days) following GC initiation (Table 1). Fifty-four percent of the children were White; the remainder was Aboriginal (10%), South Asian (10%), Black (1%), and mixed or other ethnicity (25%). Height Z-scores were significantly above the normal average ($p=0.028$), as were weight ($p<0.001$) and BMI ($p<0.001$) Z-scores.

### Vertebral deformity and second metacarpal morphometry

Six of the 78 children with spine radiographs (8%; 95% CI 4 to 16%) manifested a single, Genant grade 1 deformity

**Table 1** Description of an inception cohort of children recently initiating glucocorticoids for the treatment of nephrotic syndrome

| Clinical characteristics ($n=80$) | Results |
|---|---|
| **Demographic data** | |
| Chronological age, median (min, max) in years | 4.4 (1.3, 16.9) |
| Male, $n$ (%) | 46 (58) |
| **Anthropometry and pubertal staging** | |
| Height Z-score, mean (SD) | 0.24 (0.96)[a] |
| Weight Z-score, mean (SD) | 0.68 (1.06)[a] |
| BMI Z-score, mean (SD) | 0.81 (1.15)[a] |
| Pubertal stage, $n$ (%) | |
| Stage 1 | 67 (84) |
| Stage 2–5 | 13 (16) |
| Bone age ($n=77$), median (min, max) in years | 4.5 (1.8, 17.5) |
| Chronological age to bone age difference, years mean (SD) | 0.05 (0.73) |
| **Diagnosis, $n$ (%)** | |
| Idiopathic NS without renal biopsy histology, presumed minimal change disease | 40 (50) |
| Minimal change disease, confirmed on renal biopsy | 20 (25) |
| Focal segmental glomerulosclerosis | 13 (16) |
| Nephrotic syndrome due to Henoch–Schoenlein purpura | 6 (8) |
| Other, membranoproliferative glomerulonephritis type 1 | 1 (1) |
| **Glucocorticoid treatment[b]** | |
| Number of days between GC initiation and LS BMD, mean (SD) | 18.6 (9.9) |
| Cumulative GC dose (mg/m²) between GC initiation and LS BMD, median (min, max) | 974 (0, 3,909) |
| GC dose intensity (mg/m²/day) between GC initiation and LS BMD, median (min, max) | 57 (0, 458) |
| Average GC dose (mg/m²/day) between GC initiation and LS BMD, median (min, max) | 55 (0, 458) |
| **Physical activity level ($n=74$)** | |
| Very active weekend hours, $n$ (%) of patients in each category[c] | |
| <30 min | 23 (31) |
| ≥30 min | 51 (69) |
| **Total vitamin D ($n=78$) and calcium intake ($n=77$)** | |
| Total vitamin D daily intake (% of DRI), $n$ (%) of patients in each category | |
| <50% | 19 (24) |
| 50–<100% | 19 (24) |
| ≥100% | 40 (52) |
| Vitamin D supplementation—yes, $n$ (%) | 26 (33) |
| Total calcium daily intake (% of DRI), $n$ (%) of patients in each category | |
| <50% | 2 (3) |
| 50–<100% | 5 (6) |
| ≥100% | 70 (91) |
| Calcium supplementation—yes, $n$ (%) | 19 (24) |
| **Second metacarpal morphometry, mean (SD)** | |
| Metacarpal length Z-score ($n=65$) | 0.44 (0.92)[a] |
| Combined cortical thickness Z-score ($n=65$) | 0.30 (0.84)[a] |

**Table 1** (continued)

| Clinical characteristics ($n$=80) | Results |
|---|---|
| Percent cortical area Z-score ($n$=76) | 0.28 (0.81)[a] |
| **Lumbar spine (LS) BMD, mean (SD)** | |
| LS BMD Z-score for chronological age | −0.54 (1.08)[a] |
| LS BMD Z-score for bone age ($n$=77) | −0.58 (1.07)[a] |

*SD* standard deviation, *BMI* Body Mass Index, *LS BMD* lumbar spine bone mineral density, *GC* glucocorticoids, *MCD* minimal change disease

[a] Z-score results significantly different compared to the healthy average

[b] GC dose is reported in prednisone equivalents

[c] Thirty minutes is the amount of vigorous activity per day recommended in Canada's Physical Activity Guide for Children

each. All of these deformities were mild anterior wedging in the mid-thoracic region (two each at T6, T7, and T8). Exploratory analyses of ABQ vertebral deformity signs found that 4 of 78 children (5%; 95% CI 2 to 13%) manifested ABQ signs of vertebral fracture (one radiological sign each due to loss of endplate parallelism in all cases; two at T6, and two at T8), with the 2 children having a Genant grade 1 deformity at T8 also manifesting an ABQ sign of fracture in the same vertebral body. A total of eight children (10%; 95% CI 5 to 19%) showed evidence of vertebral deformity by one or both methods; none of these reported back pain. Examples representative of the vertebral deformities detected in this cohort are presented in Fig. 1a–c. Table 2 describes children with vertebral deformities and those without, as defined by the Genant method (our primary method for characterization of vertebral deformity).

Metacarpal morphometry

Analysis of second metacarpal morphometry revealed above average metacarpal length Z-score (0.44, 95% CI 0.21 to 0.66, $p<0.001$), combined cortical thickness Z-score (0.30, 95% CI 0.09 to 0.51, $p=0.005$), and percent cortical area Z-score (0.28, 95% CI 0.09 to 0.46, $p=0.004$; Table 1).

Bone densitometry

The mean LS BMD Z-score was significantly below the healthy average for the entire cohort (−0.54, 95% CI −0.78 to −0.30, $p<0.001$). LS BMD Z-scores were similar between patients with and without vertebral deformities (Table 2).

The relationship between LS BMD Z-score and clinical parameters was assessed by multiple regression analysis (Table 3). Cumulative GC dose was inversely related to LS BMD Z-score after adjusting for the clinical covariates

chosen *a priori* as being the most clinically relevant. For every additional gram of cumulative GC dose per body surface area (square meters), LS BMD Z-score was lower by 0.37 SD (95% CI, −0.69 to −0.04). Similar relationships were found for GC dose intensity ($p=0.007$), and average GC dose ($p=0.006$). One patient was identified as having an extreme outlying value (i.e., value exceeding the third quartile+3×IQR) for GC dose intensity (458 mg/m$^2$/day) and average GC dose (458 mg/m$^2$/day); therefore, this outlying value was excluded from models 2 and 3 (but not from model 1). When the outlying value was included (models not shown), there was no association between GC exposure and LS BMD Z-score for GC dose intensity ($\beta$ −0.003, 95% CI −0.008 to 0.002, $p=0.19$) or for average GC dose ($\beta$ −0.003, 95% CI −0.008 to 0.001, $p=0.17$).

## Discussion

One of the key findings in this study was the observed inverse relationship between short-term GC exposure and LS spine BMD among children who recently initiated GCs
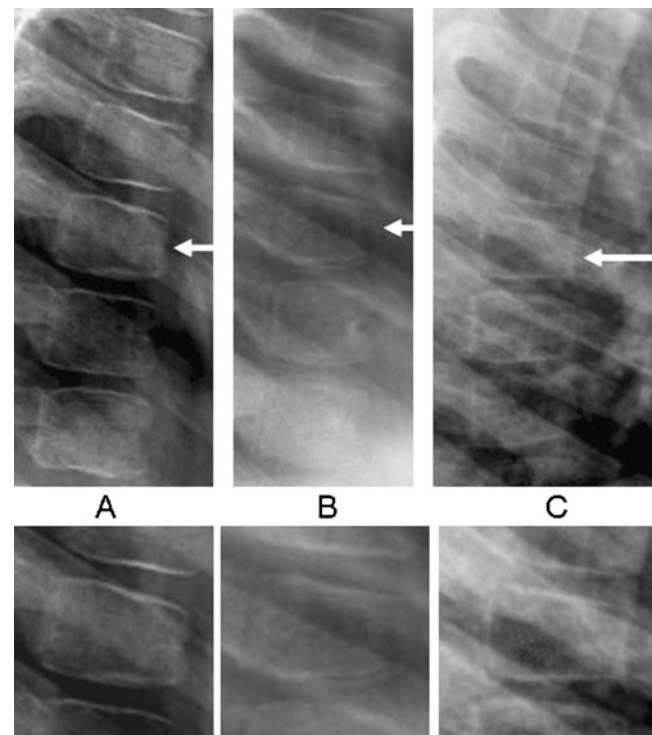


**Fig. 1 a–c** Vertebral deformities that were representative of the spine changes observed in this cohort. **a** A 5-year-old girl with membranoproliferative glomerulonephritis and a grade 1 anterior wedge deformity at T7, **b** A 4-year-old girl with minimal change NS and a grade 1 anterior wedge deformity with loss of endplate parallelism at T8, **c** An 8-year-old boy with minimal change NS and a grade 1 anterior wedge deformity at T6

**Table 2** Comparison of children with and without vertebral deformity according to the Genant semiquantitative method

| Clinical characteristics | Children without vertebral deformity $n=72$ | Children with vertebral deformity $n=6$ | $p$ |
|---|---|---|---|
| **Demographic data** | | | |
| Chronological age, median (min, max) in years | 4.4 (1.3, 16.9) | 6.0 (3.2, 9.2) | 0.574 |
| Male, $n$ (%) | 44 (61) | 1 (17) | 0.078 |
| **Diagnosis, $n$ (%)** | | | |
| Minimal change NS | 53 (74) | 5 (83) | 1.000 |
| **Glucocorticoid treatment**[a] | | | |
| Cumulative GC dose (mg/m$^2$) between GC initiation and LS BMD, median (min, max) | 943 (0, 3,909) | 1,737 (288, 2,052) | 0.129 |
| GC dose intensity (mg/m$^2$/day) between GC initiation and LS BMD, median (min, max) | 57 (0, 458) | 59 (41, 71) | 0.680 |
| Average GC dose (mg/m$^2$/day) between GC initiation and LS BMD, median (min, max) | 55 (0, 458) | 58 (41, 70) | 0.793 |
| **Total vitamin D ($n=76$) and calcium intake ($n=75$)** | | | |
| Total vitamin D daily intake (% of DRI), $n$ (%) of patients in each category | | | |
| <50% | 15 (21) | 4 (67) | |
| 50–<100% | 17 (24) | 2 (33) | **0.012** |
| ≥100% | 38 (54) | 0 (0) | |
| Vitamin D supplementation—yes, $n$ (%) | 25 (35) | 0 (0) | 0.169 |
| Total calcium daily intake (% of DRI), $n$ (%) of patients in each category | | | |
| <50% | 1 (2) | 0 (0) | |
| 50–<100% | 3 (4) | 2 (33) | 0.070 |
| ≥100% | 65 (94) | 4 (67) | |
| Calcium supplementation—yes, $n$ (%) | 17 (24) | 1 (17) | 1.000 |
| **Lumbar spine (LS) BMD** | | | |
| LS BMD Z-score, mean (SD) | −0.52 (1.1) | −0.58 (1.4) | 0.851 |

*SD* standard deviation, *LS BMD* lumbar spine bone mineral density, *GC* glucocorticoids

[a] GC dose is reported in prednisone equivalents

for the treatment of NS. This relationship was consistent for all three methods used to quantify GC exposure, including cumulative GC dose, GC dose intensity, and average GC dose. The possibility that even short-term, high-dose GC therapy can have a deleterious effect on spine BMD in pediatric NS is not inconceivable, given a number of supporting observations in the literature. First, it is well known that GCs have a predilection for interference with trabecular bone architecture, both in humans [6] and in animal models [5]. Furthermore, bone resorption markers increase acutely in adults with NS following administration of GCs [28], and are associated with a significant decline in spine BMD after a few weeks of therapy in both adults [28] and children with NS [9]. In addition, spine BMD has been shown to decline rapidly in adults following GC initiation for organ transplantation [29]. These reports and our study attest to the potential for insult to spine BMD after short-term GC use, with the effects of longer-term administration highlighted in a large cross-sectional case-control study which showed after 4 years of GC exposure that spine bone

mineral content in children with steroid-sensitive NS was reduced compared to controls [11].

In a recent study using peripheral quantitative computed tomography (pQCT) at the tibia, GC-treated children with NS showed greater cortical volumetric BMD and cortical area, and lower trabecular volumetric BMD compared to controls [30]. Similar results were reported by Hegarty et al., who found by pQCT a significant reduction in distal radial trabecular volumetric BMD, but no reduction in total volumetric BMD in young adults who had NS during childhood [31]. We did not use pQCT to assess the effects of GCs on the trabecular and cortical compartments separately. However, we did observe a decrease in BMD at the spine (a trabecular-rich site) but increased cortical thickness at the second metacarpal. Our results are therefore in line with previous reports [30, 31] suggesting disparate effects of GCs on cortical and trabecular sites.

At the same time, we found the prevalence of vertebral deformities early in the course of GC treatment to be low, with the vast majority of patients in this cohort treated

**Table 3** LS BMD Z-score multiple linear regression analysis

| Clinical parameters | Model 1, cumulative GC dose[a] | | Model 2, GC dose intensity[b] | | Model 3, average GC dose[c] | |
|---|---|---|---|---|---|---|
| | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ |
| Height Z-score | 0.161 (−0.154, 0.476) | 0.311 | 0.240 (−0.076, 0.555) | 0.134 | 0.208 (−0.103, 0.519) | 0.186 |
| Weight Z-score | 0.323 (0.038, 0.607) | **0.027** | 0.266 (−0.021, 0.554) | 0.069 | 0.283 (−0.002, 0.567) | 0.052 |
| Age | 0.022 (−0.039, 0.083) | 0.472 | 0.015 (−0.047, 0.076) | 0.634 | 0.018 (−0.042, 0.079) | 0.548 |
| Gender (female vs. male) | 0.449 (−0.016, 0.914) | 0.058 | 0.458 (−0.001, 0.918) | 0.051 | 0.434 (−0.023, 0.890) | 0.062 |
| Physical activity[d] | 0.360 (−0.131, 0.851) | 0.148 | 0.363 (−0.126, 0.851) | 0.143 | 0.386 (−0.102, 0.874) | 0.119 |
| Vitamin D supplementation | −0.058 (−0.747, 0.632) | 0.867 | −0.064 (−0.752, 0.624) | 0.853 | -0.091 (−0.778, 0.595) | 0.791 |
| Calcium supplementation | 0.188 (−0.559, 0.935) | 0.616 | 0.188 (−0.546, 0.922) | 0.610 | 0.235 (−0.491, 0.962) | 0.519 |
| MCD vs. other diagnosis | 0.065 (−0.479, 0.610) | 0.812 | 0.049 (−0.489, 0.588) | 0.856 | 0.037 (−0.501, 0.575) | 0.891 |
| GC exposure | −0.367 (−0.692, −0.041) | **0.028** | −0.017 (−0.029, −0.005) | **0.007** | −0.016 (−0.028, −0.005) | **0.006** |
| Model $R^2$ | 0.303 | | 0.332 | | 0.336 | |

One patient identified as having an extreme outlier value for GC dose intensity (458 mg/m$^2$/day) and average GC dose (458 mg/m$^2$/day) was excluded from models 2 and 3, as described in the results

[a] Total amount of GC received during the observation period relative to body surface area (grams per square meters)

[b] Ratio between the total amount of GC received during the observation period and the number of days when GC treatment was received. This ratio was expressed relative to body surface area

[c] Ratio between the total amount of GC received during the observation period and the number of days since the first GC was taken. This ratio was expressed relative to body surface area

[d] As measured by the Habitual Activity Estimation Scale. Highest tertile of very active weekend hours vs. tertiles 1 and 2

according to the standardized international protocol (prednisone 60 mg/m$^2$/day for 4 to 6 weeks). Specifically, we have demonstrated a vertebral deformity prevalence rate of 8% (95% CI 4 to 16%) according to the Genant protocol, our primary vertebral assessment method. Indeed, we would not expect a high rate of vertebral deformity early in the course of GC exposure, since the path to fractured bone begins with alterations in bone architecture and density, with loss in bone strength observed following acute declines in LS BMD [6, 29].

The clinical significance of the observed vertebral deformities remains unclear and merits discussion, particularly since this is an inaugural study in its assessment of vertebral body height ratios early in the course of pediatric GC-treated NS. First of all, it is possible that these changes represent normal variants, especially given that none of the children with vertebral deformities reported back pain. At the same time, the lack of back pain does not negate the possibility that these deformities represent fractured bone, since vertebral fractures have been described without back pain in postmenopausal osteoporosis [32], in children with long-standing histories of rheumatic conditions [33], and in childhood acute lymphoblastic leukemia [19]. Furthermore, a recent pediatric study by Gaca et al. [34] showed 95% of healthy children had anterior wedging (the same deformity reported in our cohort) at the thoracolumbar junction that was represented by less than an 11% reduction in the anterior to posterior height ratio. The authors suggested that

reductions in excess of 11% should raise the suspicion of vertebral injury. In our study, a reduction in height ratio of 20% or more was considered a vertebral deformity. At the same time, we note that the study by Gaca et al. [34] was carried out using a different imaging approach (computed tomography) and from T10 to L3 exclusively. Whether a normal cutoff around 11% would apply to the mid-thoracic region, the site of vertebral deformities in our cohort and also the site where minimal physiological rounding of vertebral bodies is frequently seen in children [35], remains to be determined. To date, there are no available normative data for vertebral morphometry by lateral radiograph among healthy children, a fact which renders interpretation of the clinical significance of our vertebral findings difficult.

Interestingly, the mid-thoracic region (T6–T8) is the most frequent site for both mild and more severe vertebral fractures in adults [36–39], as well as in children with acute lymphoblastic leukemia [19] and rheumatic conditions [40]. This distribution is suggested to result from the relatively increased mechanical stresses on vertebrae at these sites imposed by the shape of the spine [41]. Furthermore, studies in adults have shown that grade 1 deformities are clinically important, since they are associated with an increased risk for future (incident) vertebral fracture [42]. Whether the grade 1 deformities in our report will be associated with increased risk for incident vertebral fractures in the face of ongoing bone health threats remains

to be determined through further longitudinal assessment of our cohort.

We sought to explore the clinical significance of these findings by describing children with vertebral deformities compared to those without; however, the small number of children with vertebral deformities limited our power to detect differences. While the lack of statistical association between LS BMD, a key clinical parameter, and vertebral deformities could be a function of limited power, it is also possible that the time course following GC initiation was simply too short for vertebral fractures to manifest clinically, as previously mentioned. On the other hand, it should be noted that an absence of association between spine BMD and vertebral fractures has also been reported in postmenopausal women with GC-treated rheumatic disorders, where those with vertebral fractures had similar LS BMD results compared to those without [43]. The absence of a relationship between spine BMD and vertebral fractures among GC-treated patients has been postulated to result from alterations in bone mass or architecture that are not readily discernable by BMD testing in the anterior–posterior direction compared to the more sensitive width-adjusted approach which removes the dense posterior spinous processes from the projected scan [30, 44].

Limitations to our study merit consideration. While our overall research program is predicated upon within-subject change during longitudinal follow-up in key parameters such as vertebral morphometry and spine BMD, the description of this inception cohort at the time of study enrolment is based on uncontrolled, cross-sectional evaluation of spine status in relation to relevant clinical parameters. Another limitation is that to optimally assess the impact of GCs on skeletal health in the short term, it would have been ideal to obtain the first study visit prior to GC initiation, as opposed to shortly thereafter. For logistical reasons this was not possible, as NS treatment would then have been delayed. In addition, we were unable to measure 25-hydroxyvitamin D levels in this study; beyond vitamin D intake (which we found to be frequently reduced in children with spine deformities compared to those without), the impact of circulating levels of 25-hydroxyvitamin D on bone strength in steroid-treated children with NS deserves further study. Finally, while this is the first study to assess vertebral morphometry in pediatric GC-treated NS with only six patients harboring deformities, it is possible that some of the clinical variables were in fact related to the vertebral deformities but that these relationships went undetected due to insufficient power. Nevertheless, this study provides a novel description of vertebral morphometry in GC-treated NS and the basis for further longitudinal comparison.

In conclusion, we observed an inverse relationship between GC exposure and LS BMD Z-score in children following short-term GC treatment for NS and a low rate of vertebral deformity at this time point. Additional studies are required before more definitive conclusions can be drawn about the clinical significance of the observed vertebral deformities and the impact of short-term steroids on spine health in children with NS. Further light will be shed through documentation of the clinical outcomes in these children with early deformities and through assessment of the incident vertebral deformity rate in the face of further GC exposure.

## The Canadian STeroid-Associated Osteoporosis in the Pediatric Population (STOPP) Consortium (a pan-Canadian pediatric bone health working group)

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**Conflicts of Interest**   None.

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