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Bone mass and vertebral fractures in South African children on prolonged oral glucocorticoids for chronic non-malignant illnesses

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ABSTRACT

Introduction: We hypothesized that the prevalence of vertebral fractures would be low and that bone mineral density (BMD) would be less severely affected in a black South African (SA) population treated with glucocorticoids (GCs) than that reported in mainly white populations.

Methods: All children aged 5–17.9 years with chronic non-malignant illnesses who were on GCs (intravenous or oral) for greater than 3 months duration were evaluated. DXA scans were performed using a Hologic Discovery machine (Software version Apex 4.0.2) and the Hologic paediatric reference database. Whole body less head (WBLH) and lumbar spine (LS) bone mineral content (BMC) and density (BMD) Z-scores unadjusted and adjusted for height were calculated using the Zemel equation calculator.

Results: Seventy-two patients (49% with renal, 24% with rheumatic, 14% with neurological, 11% with hepatic and 3% with respiratory conditions; mean age 11.6 ± 3.3 years, 57% boys, 92% SA black) were enrolled. The mean duration of GC treatment was 34.1 (±25.1) months. Mean WBLH and LS height adjusted BMD Z-scores were −1.2 ± 1.5 and −0.9 ± 1.0 respectively. Eleven percent of patients had a LS height adjusted BMD Z-score ≤ −2. The prevalence of vertebral fractures on lateral vertebral fracture assessment (VFA) was 15% (11 of 72 patients).

Conclusion: The prevalence of vertebral fractures (15%) in predominantly black children on GCs with chronic non-malignant illnesses is similar to that reported from North America suggesting that routine yearly DXA scans including VFA are warranted in this highly at-risk population.

1. Introduction

Glucocorticoid-induced complications are common in adult chronic illnesses and are associated with significant morbidity and increased fracture risk (Canalis et al., 2004; Van Staa et al., 2005). Children treated with glucocorticoids (GCs) have lower spine bone mineral density (BMD) and higher rates of fractures compared to healthy children (Hansen et al., 2014). However, there have been few studies conducted outside of well-resourced countries and as far as the authors are aware, none conducted in low- or middle-income countries (LMIC), such as those in sub-Saharan Africa. Further prospective studies are required to establish the effects of glucocorticoid therapy on bone mass and fractures in South African children, who have a high prevalence of nutritional stunting (Said-Mohamed et al., 2015).

Systemic glucocorticoid therapy is frequently used in many chronic childhood illnesses such as Duchenne muscular dystrophy, nephrotic syndrome, autoimmune hepatitis, inflammatory bowel diseases and rheumatological disorders.

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The mechanisms of bone loss in GC treated diseases are varied, the underlying disease often playing a major role. Chronic inflammatory conditions such as rheumatoid arthritis produce pro-inflammatory cytokines, mainly interleukin (IL) 6, IL-1 and tumour-necrosis factor alpha that have an osteoimmunological effect similar to the direct effects of glucocorticoids on bone resulting in diffuse bone loss and osteoporosis (McInnes and Schett, 2007). In addition to the inflammatory cytokines, other risk factors associated with bone loss in chronic inflammatory illnesses may include a decrease in physical activity, lack of sun exposure with resultant vitamin D deficiency, growth faltering together with delayed puberty, poor nutrition, muscle deficits and co-morbidities (Alsufyani et al., 2005; Larson and Henderson, 2000).

The effects of GCs on vertebral fracture incidence (varying between 6%–100%) and bone mineral density in children with non-malignant chronic illnesses have been reported mainly in Caucasian children (Mayo et al., 2012; Rodd et al., 2012; Singh et al., 2018). Consequently, there are no good comparative studies on its effects on mainly black children living in LMICs.

We have previously shown that fracture rates in healthy South African children and adolescents differ markedly depending on race and sex, with black males and females having fracture rates approximately half those of their white peers (Thandrayen et al., 2009). The aims of this study are thus to determine the prevalence of fractures and the association of bone mass with the prevalence of fractures in non-oncological South African children treated on GCs for chronic diseases. This is a novel study as we investigate the association of bone mass on the prevalence of vertebral fractures in South African children (predominantly black) with non-malignant chronic illnesses, who have received GCs for more than three months and are being treated at a tertiary hospital in Johannesburg. We hypothesize that the prevalence of vertebral fractures would be low and that bone mineral density would be less severely affected in this population on glucocorticoids due to possible genetic protective factors in healthy black South African children who typically have greater bone mineral content at the femoral neck, total hip and mid-radius than healthy white South African children (Vidulich et al., 2006).

2. Methods

All children between the ages of 5 and 17.9 years with chronic non-malignant illnesses who were on GCs (intravenous or oral) for greater than 3 months duration at a dose of 5 mg/day or greater were enrolled after obtaining parental informed consent and assent from the children. Study participants were children attending the paediatric sub-specialty clinics at Chris Hani Baragwanath Academic hospital (CHBAH) in Soweto, Johannesburg between 21 January 2016 and 12 June 2019. Sample size was calculated based on a previously reported incidence of 6–10% of morphometric vertebral fractures in children less than 18 years of age on systemic glucocorticoid therapy (Hansen et al., 2014). A sample size of at least 59 patients was needed with a confidence level of 80% to detect an incidence of 10% of vertebral fractures.

2.1. Inclusion criteria

1. Children between the ages 5 years and 17.9 years of age attending the paediatric sub-speciality clinics at CHBAH.
2. Children with chronic non-malignant illnesses who were currently being treated with oral GCs for more than 3 months duration. Chronic non-malignant illnesses included Duchenne muscular dystrophy (DMD), myasthenia gravis, nephrotic syndrome and other renal conditions, autoimmune hepatitis, inflammatory bowel disease, pulmonary haemosiderosis and all rheumatological conditions.

2.2. Exclusion criteria

1. Any prior use of bisphosphonates or long-acting progestogen injectable contraceptives such as depot medroxyprogesterone acetate and norethisterone enanthate.
2. Any endocrine abnormality likely to be associated with disturbances in mineral homeostasis.
3. History of previous malignancies or oncologic conditions such as leukaemia and lymphoma.
4. The presence of primary bone diseases such as osteogenesis imperfecta, idiopathic juvenile osteoporosis and rickets.

Information on the primary diagnosis, anthropometric measurements, physical activity (questionnaire on formal and informal activities) and medications prescribed and their dosages were recorded at time of evaluation. Height for age (HAZ), weight for age (WAZ) and body mass index for age (BAZ) z-scores were determined using WHO AnthroPlus. Dual energy x-ray absorptiometry (DXA) scans of the whole body less head (WBLH), LS and lateral VFA were performed using a Hologic Discovery machine (Software version Apex 4.0.2) at the time of enrolment into the study.

Vertebral fractures on VFA were defined as deformations of the vertebrae at the posterior (crush), mid (biconcave) or anterior (wedge) vertebral positions and were graded according to the method described by Genant et al. (1993); as grade 0 (normal), grade 0.5 (indeterminate), grade 1 (mildly deformed with 20–25% reduction in height), grade 2 (moderately deformed with 25–40% reduction of height) and grade 3 (severely deformed with greater than 40% reduction of height). The positioning of the vertebral points generated by the DXA machine for VFA were reviewed and adjusted by the DXA technician prior to completing the analyses. The VFA report was reviewed by the principal investigator (KT). WBLH and LS BMC and BMD measurements were derived from the Hologic Discovery machine that utilises the age and sex specific white reference population (United States), whose LS BMD measurements are similar to those of our black South African population (Micklesfield et al., 2011). We also measured LS and WBLH BMC and BMD Z-scores, unadjusted and adjusted for height, using the Zemel equation calculator (https://zscore.research.chop.edu/bmdCalculator.php) (Zemel et al., 2011). The Hologic Discovery machine LS BMD Z-scores were compared to the height adjusted LS BMD Z-scores that were calculated using the Zemel equation calculator.

The weight and height of the patients were used to determine body surface area and the dose of systemic GCs/m^2 were calculated based on the GC dose received in the last 28 days or month prior to the DXA scan. The average GC dose in the last month was defined as the cumulative dose in prednisone equivalents (mg/m^2) divided by 28 days.

Serum calcium, inorganic phosphate, alkaline phosphatase (ALP) were measured by standard laboratory methods, while serum 25-hydroxyvitamin D (25(OH)D) were assayed using DiaSorin Liaison. At the same visit as that for the DXA scan, additional information was collected on physical activity, back pain and fracture/s.

2.3. Statistical analyses

Data were entered into excel spreadsheets and then imported into Statistica (USA Statsoft version 13.5) and Stata (USA StataCorp version 15.1) for data analysis. Categorical data are presented as numbers and percentages and continuous data as means with standard deviations or medians with interquartile ranges depending on the distribution of the data. Chi-square and Fischer exact analyses were performed to compare categorical data. Comparisons of continuous data between those with and without vertebral fractures were done using the Student's *t*-test or Mann Whitney *U* test depending on whether the data were normally distributed or not. ANOVA was used to compare data between the different types of chronic illnesses. Pubertal status was classified according to Tanner staging (1–5) for genital and pubic hair development

(Tanner, 1969), which was subdivided into absent (Tanner 1) or present (Tanner 2–5) for logistic regression analyses. Logistic regression analyses were performed to assess for factors associated with vertebral fractures and factors with univariate p values <0.2 were thereafter added into the model for multivariable logistic regression analyses.

2.4. Ethics

Human Research Ethics Committee of the University of the Witwatersrand (approval number M151153) and the CEO of Chris Hani Baragwanath Academic hospital approved the study. Assent was obtained from children between 8 and 17.9 years of age and informed consent from the parents or guardians of the children enrolled in the study. None of the procedures that were performed was outside of routine practice. All study participants were allocated a study number and the data anonymized by excluding names and hospital numbers.

3. Results

3.1. The demographics of the cohort

Seventy two patients (49% with renal, 24% with rheumatological, 14% with neurological, 11% with gastrointestinal/hepatic and 3% with respiratory conditions; mean age 11.6 ± 3.3 years, 57% boys, 92% SA black) were enrolled in the study. A total number of 85 patients were screened to enter the study but four did need meet the inclusion criterion of GC for >3 months, two did not consent and seven did not get DXA scans completed due to technical or logistical reasons. The different diagnoses of the patients enrolled are listed in Table 1. The most common renal condition treated with GCs was nephrotic syndrome (66%) followed by systemic lupus erythematosus (SLE) nephritis (17%). Juvenile arthritis and dermatomyositis (both 35% each) were the common rheumatological conditions on steroids followed by SLE without renal involvement (18%) and DMD (80%) was the commonest neurological condition.

3.2. Anthropometric measurements, sex, GC treatment and DXA measurements

The mean duration of GC treatment for all the patients was 34.1 (±25.1) months with a minimum duration of 3 months. The mean or median age, HAZ, WAZ, BAZ, duration of GC use in months, recent cumulative GC dose in the last 28 days (mg/m^2/d), height adjusted WBLH and LS BMC and BMD Z-scores are shown for the different diagnostic categories in Table 2 and between those with and without vertebral fractures in Table 3. The renal group was younger than the neurological group ($p < 0.05$). There were a higher number of males in the renal and neurological group compared to the rheumatological group ($p < 0.05$). WAZ and BAZ were significantly lower in the rheumatological compared to the renal and neurological groups ($p < 0.05$). The renal group had a higher recent cumulative GC dose compared to the rheumatological and hepatic groups ($p < 0.01$).

Mean WBLH height adjusted BMD Z-score was −1.2 ± 1.5 and LS height adjusted BMD Z-score was −0.9 ± 1.0. WBLH BMC and BMD Z-scores (unadjusted and adjusted for height) were lower in the neurological group compared to the renal and rheumatological groups (Table 2). Comparing the frequency of low (≤−2) unadjusted LS BMD Z scores for age to height adjusted LS BMD Z scores, 44% of patients (n = 31/72) had an unadjusted LS BMD Z-score ≤ −2 and 11% (n = 8/72) had a height adjusted LS BMD Z-score ≤ −2 (31/72 vs 8/72; $p < 0.001$). The percentage of children with WBLH height adjusted BMD Z-scores ≤ −2 was higher (26%) than that at the LS (11%).

Table 1
The diagnoses of the 72 participants at entry into the study.

	Diagnosis	Number of patients (n)
Nephrology (N = 35)	Nephrotic syndrome	23
	Systemic lupus erythematosus (SLE) nephritis	6
	Takayasu arteritis	4
	IgA nephropathy	1
	Vasculitis	1
Rheumatology (N = 17)	Juvenile arthritis or sera positive polyarthritis	6
	Juvenile dermatomyositis	6
	Systemic lupus erythematosus	3
	Sarcoidosis	1
	Scleroderma	1
Neurology (N = 10)	Duchene muscular dystrophy	8
	Myasthenia gravis	1
	Myasthenia gravis and type 1 diabetes	1
Gastroenterology (N = 8)	Autoimmune hepatitis	7
	Crohn's disease	1
Pulmonology (N = 2)	Pulmonary haemosiderosis	2

3.3. The prevalence of vertebral fractures and its' association with bone mass measurements

The prevalence of patients with vertebral fractures on VFA was 15% (11 of 72 patients) of whom 5/11 (45%) had a LS BMD Z-score ≤ −2 (p = 0.89) but when the Z-score was adjusted for height only 3/11 (27%) had a Z-score of ≤−2 (p = 0.09); however these numbers are small to show a meaningful comparison. Of those 11 patients with vertebral fractures, two had sustained multiple fractures (5 and 3 fractures). In Fig. 1, a bimodal distribution of vertebral fractures is apparent with fractures being grouped around T4–6 (upper-mid thoracic region) and T9-L3 (lower thoraco-lumbar region). The upper-mid thoracic fractures were all mild (100%) and the lower thoraco-lumbar fractures were mainly of moderate grade (73%). The morphology of the vertebral fractures is shown in Fig. 2, all the upper-mid thoracic fractures being anterior wedge fractures.

When comparing those with and without vertebral fractures (Table 3), height adjusted WBLH BMC and BMD were significantly lower in those with fractures than in those without. In addition, the percentage of patients with a height adjusted WBLH BMD ≤ −2 was significantly greater in those with fractures compared to those without fractures (60% vs 20%; $p < 0.05$). These significant differences between those with and without fractures were not seen at the lumbar spine.

3.4. The association between GCs and bone mass measurements

There was no correlation between WBLH or LS height adjusted Z-scores and the duration of steroid therapy (WBLH BMC: $r = 0.08$; p = 0.52; WBLH BMD: $r = -0.02$; p = 0.89; LS BMC: $r = 0.09$; $p = 0.46$; LS BMD: $r = 0.07$; $p = 0.57$) or recent GC exposure (WBLH BMC: $r = 0.10$; p = 0.39; WBLH BMD: $r = 0.22$; $p = 0.06$; LS BMC: $r = 0.05$; $p = 0.67$; LS BMD: $r = 0.14$; $p = 0.23$).

3.5. Factors associated with vertebral fractures

There was no statistical difference in the prevalence of vertebral fractures between any of the diagnostic categories of patients, but the numbers of patients in each category were small (Table 2). Of the 11 patients with vertebral fractures, two had a history of previous long bone fractures; three (27%) had complained of back pain since commencing glucocorticoids and one was vitamin D insufficient (25 (OH)D = 36.1 nmol/L). Of the two patients with a previous history of long bone fracture, one had a right tibial fracture after falling out of a wheelchair while on GCs. The second patient had a radial fracture after minor trauma, a month prior to starting GCs. None of the vertebral fractures were known to be associated with trauma. The mean duration

Table 2
Demographics, anthropometric measurements, months on GCs, vertebral fractures and DXA measurements in the different diagnostic categories.

	All patients $n = 72$ Mean (±SD)	Renal n = 35 Mean (±SD)	Rheumatological n = 17 Mean (±SD)	Neurological n = 10 Mean (±SD)	Hepatic n = 8 Mean (±SD)	Respiratory n = 2 Mean (±SD)	ANOVA p value
Demographics and anthropometry							
Age (years)	11.6 (±3.3)	**10.7$^{\#}$ (±3.3)**	12.5 (±3.4)	13.5 (±2.8)	12 (±3.1)	9.1 (±3.9)	0.077
Males n (%)	41 (57)	**24$^{\#}$ (69)**	6 (35)	**8$^{\#}$ (80)**	3 (37.5)	0 (0)	
HAZ	−1.3 (±1.3)	−1.0 (±1.1)	−1.5 (±1.2)	−1.7 (±1.3)	−1.3 (±1.4)	−4.0 (±1.0)	0.19
WAZ	−0.3 (±1.4)	0.04 (±1.3)	**−0.9$^{\#}$ (±1.1)**	0.06 (±1.0)	−0.3 (±1.6)	−2.1 (±0.3)	0.067
BAZ	0.7 (±1.4)	0.9 (±1.4)	**−0.04$^{\#}$ (±1.5)**	1.3 (±0.8)	0.5 (±1.7)	0.6 (±0.5)	0.057
Months on GCs and vertebral fractures							
Months on GCs	34.1 (±25.1)	28.9 (±20.0)	38.9 (±28.2)	42.5 (±35.9)	36.0 (±22.8)	33.1 (±31.7)	0.36
GC dose in last 28 days ($mg/m^2/d$)	15.5 (±11.8)	**19.5* (±14.3)**	10.1 (±6.8)	17.0 (±4.3)	6.8 (±5.7)	17.8 (±4.5)	**0.005**
Patients with vertebral fractures n (%) (number of fractures/patient)	11 (15) (0–5)	4 (11) (0–1)	4 (23.5) (0–5)	2 (20) (0–3)	1 (12.5) (0–1)	0	
WBLH DXA measurements							
WBLH BMC Z-score	−2.1 (±1.6)	−1.7 (±1.4)	−2.2 (±0.75)	**−3.7$^{\#}$* (±2.7)**	−2.1 (±1.4)	−3.4 (±1.6)	**0.012**
Height adjusted WBLH BMC Z-score	−0.92 (±1.3)	−0.7 (±0.9)	−0.7 (±1.0)	**−1.9$^{\#}$* (±2.3)**	−1.2 (±0.9)	−0.22 (±1.9)	**0.036**
Height adjusted WBLH BMC Z-score ≤ −2 n (%)	10 (14.5)	4 (11)	1 (6)	4 (44)	1 (12.5)	0	
WBLH BMD Z-score	−2.0 (±1.2)	−1.8 (±1.5)	−2.2 (±1.0)	**−3.8$^{\#}$* (±2.8)**	−2.3 (±1.2)	−2.6 (±1.2)	**0.012**
Height adjusted WBLH BMD Z-score	−1.2 (±1.5)	−0.9 (±1.2)	−1.0 (±1.2)	**−2.7* (±2.5)**	−1.6 (±1.1)	0.1 (±2.1)	**0.013**
Height adjusted WBLH BMD Z-score ≤ −2 n (%)	18 (26)	6 (17)	3 (20)	5 (56)	4 (50)	0	
LS DXA measurements							
LS BMC Z-score	−1.9 (±1.4)	−1.9 (±1.2)	−1.9 (±1.2)	−1.9 (±2.2)	−1.7 (±1.2)	–	0.96
Height adjusted LS BMC Z-score	−0.8 (±1.1)	0.9 (±0.9)	−0.6 (±1.1)	−0.3 (±1.6)	−0.9 (±0.7)	–	0.32
Height adjusted LS BMC Z-score ≤ −2 n (%)	9 (13)	5 (14)	1 (6)	2 (22)	1 (12.5)	0	
LS BMD Z-score	−1.7 (±1.1)	−1.8 (±1.1)	−1.7 (±1.1)	−1.4 (±1.2)	−1.4 (±1.0)	−1.4 (±1.4)	0.64
Height adjusted LS BMD Z-score	−0.9 (±1.0)	**−1.1$^{\#}$ (±0.9)**	−0.8 (±1.2)	−0.4 (±1.0)	−0.9 (±0.8)	0.6 (±2.1)	0.23
LS BMD (machine derived) Z-score ≤ −2 n (%)	31 (44)	15 (43)	9 (53)	3 (33.3)	3 (37.5)	1 (50)	
Height adjusted LS BMD Z-score ≤ −2 n (%)	8 (11)	6 (17)	1 (6)	0	1 (12.5)	0	

HAZ = height for age z-score; WAZ = weight for age z-score; BAZ = body mass index for age z-score; WBLH = whole body less head; LS = Lumbar spine; BMD = bone mineral density; BMC = bone mineral content.
HAZ, WAZ and BAZ z-scores were calculated using WHO AnthroPlus.
LS and WBLH BMC and BMD Z-scores (unadjusted and adjusted for height) were calculated using the Zemel equation calculator.
ANOVA excluded the respiratory group from comparison as numbers are small and within group comparisons are reported:
$^{\#}p < 0.05$ Renal group younger than neurological group; more males in the renal compared to rheumatological group and in the neurological compared to rheumatological group; WAZ and BAZ lower in rheumatological group compared to renal and neurological groups.
$^{*}p < 0.01$ renal group had higher GC dose compared to the rheumatological and hepatic group.
$^{\#}p < 0.05$ $^{*}p < 0.01$ WBLH BMC Z-score lower in the neurological group compared to the renal*, rheumatological$^{\#}$ and hepatic$^{\#}$ group; WBLH height adjusted BMC Z-score lower in neurological group compared to renal* and rheumatological$^{\#}$ groups.
$^{\#}p < 0.05$ $^{*}p < 0.01$ WBLH BMD Z-score lower in the neurological group compared to the renal* and rheumatological$^{\#}$ groups.
$^{*}p < 0.01$ Height adjusted WBLH BMD Z-score lower in the neurological group compared to the renal* and rheumatological* groups.
$^{\#}p < 0.05$ Height adjusted LS BMD lower in renal group compared to neurological group.
Bold numbers denotes significant values.

Table 3
Demographics, anthropometric measurements, months on GCs and dosage, and DXA measurements in those patients with and without vertebral fractures.

	Vertebral fractures $n = 11$	No vertebral fractures $n = 61$	p values
Demographics and anthropometry			
Age (years)			
Mean (±SD)	12.9 (±3.6)	11.4 (±3.3)	0.18
Median (IQR)	13.7 (8.9–16.4)	11.2 (9.0–14.0)	0.20
HAZ			
Mean (±SD)	−1.3 (±1.1)	−1.3 (±1.3)	0.71
Median (IQR)	−1.3 (−2.0 to −0.5)	−1.2 (−1.9 to −0.5)	0.68
WAZ			
Mean (±SD)	0.2 (±1.2)	−0.4 (±1.3)	0.18
Median (IQR)	0.4 (−0.6–1.1)	−0.4 (−1.4–0.7)	0.18
BAZ			
Mean (±SD)	1.2 (±1.5)	0.6 (1.4)	0.23
Median (IQR)	1.4 (−0.3–2.2)	0.7 (−0.3–1.6)	0.25
Months on GCs and dosage			
Months on GCs			
Mean (±SD)	33.7 (±24.9)	34.2 (±25.3)	0.95
Median (IQR)	37.0 (10.3–41.7)	28.7 (14.9–45.4)	0.94
GC dose last 28 days (mg/m^2/d)			
Mean (±SD)	11.2 (±6.2)	16.3 (±12.4)	0.19
Median (IQR)	10.8 (4.9–15.2)	15.9 (6.0–21.0)	0.34
WBLH DXA measurements			
WBLH BMC Z-score			
Mean (±SD)	−3.1 (±2.2)	−1.9 (±1.5)	0.051
Median (IQR)	−3.4 (−4.7 to −1.2)	−1.64 (−2.7–1.0)	0.14
Height adjusted WBLH BMC Z-score			
Mean (±SD)	**−1.7 (±1.6)**	**−0.8 (±1.2)**	**0.042**
Median (IQR)	−1.6 (−2.2 to −0.53)	−0.8 (−1.5–0.1)	0.061
Height adjusted WBLH BMC Z-score ≤ −2 n (%)	3 (30)	7 (12)	0.15
WBLH BMD Z-score			
Mean (±SD)	**−3.7 (±2.4)**	**−2.0 (±1.5)**	**0.003**
Median (IQR)	**−3.5 (−6.2 to −1.7)**	**−1.85 (−2.8 to −0.84)**	**0.028**
Height adjusted WBLH BMD Z-score			
Mean (±SD)	**−2.7 (±1.5)**	**−1.0 (±1.3)**	**0.001**
Median (IQR)	**−2.3 (−4.5 to −1.2)**	**−1.05 (−1.8–0.1)**	**0.007**
Height adjusted WBLH BMD Z-score ≤ −2 n (%)	**6 (60)**	**12 (20)**	**0.008**
LS DXA measurements			
LS BMC Z-score			
Mean (±SD)	−2.4 (±1.4)	−1.8 (±1.3)	0.19
Median (IQR)	−2.2 (−3.3 to −1.4)	−2.0 (−2.6 to −1.0)	0.33
Height adjusted LS BMC Z-score			
Mean (±SD)	−1.1 (±0.8)	−0.7 (±1.1)	0.29
Median (IQR)	−0.8 (−1.2 to −0.6)	-0.0.8 (−1.4–0.0)	0.47
Height adjusted LS BMC Z-score ≤ −2 n (%)	2 (20)	7 (12)	0.61
LS BMD Z-score			
Mean (±SD)	−2.0 (±1.4)	−1.6 (±1.0)	0.24
Median (IQR)	−1.6 (−3.5 to −1.4)	−1.7 (−2.3 to −0.9)	0.53
Height adjusted LS BMD Z-score			
Mean (±SD)	−1.2 (±1.2)	−0.8 (±1.0)	0.26
Median (IQR)			0.52
	−1.1 (−2.4 to −0.1)	−0.9 (−1.5 to −0.33)	
LS BMD (Machine derived) Z-score ≤ −2 n (%)	5 (45)	26 (43)	0.90
Height adjusted LS BMD Z-score ≤ −2 n (%)	3 (27)	5 (8)	0.10

HAZ = height for age z-score; WAZ = weight for age z-score; BAZ = body mass index for age z-score; WBLH = whole body less head; LS = lumbar spine; BMD = bone mineral density; BMC = bone mineral content.
HAZ, WAZ and BAZ z-scores were calculated using WHO AnthroPlus.
LS and WBLH BMC and BMD Z-scores (unadjusted and adjusted for height) were calculated using the Zemel equation calculator.
Bold numbers denotes significant values.

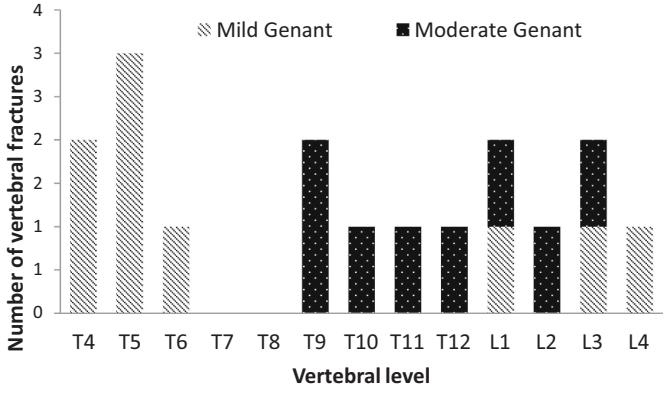

Fig. 1. The Genant grading and distribution of vertebral fractures at the different vertebral levels.

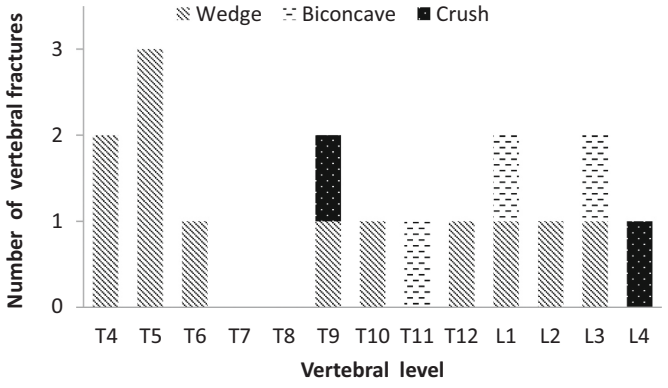

Fig. 2. The morphology of vertebral fractures at the different vertebral levels.

of GC exposure in those with vertebral fractures was 33.7 (±24.9) months and the range of GC exposure was 5.2–77 months.

In logistic regression analyses, the only factor associated with vertebral fractures was WBLH height adjusted BMD Z-scores ($p = 0.005$). Months on GCs, recent cumulative GC dose, WBLH height adjusted BMC, LS height adjusted BMC or BMD, sex, anthropometric measurements (WAZ, HAZ and BAZ), puberty and 25(OH)D levels were not associated with fractures (results not shown). There was a 50% reduction in the odds of fracture (OR = 0.5; 95% CI 0.31–0.81; p = 0.005) for every SD increase in WBLH height adjusted BMD Z-score. Multivariable logistic

regression analyses, that included WBLH height adjusted BMD and BMC Z-scores, WAZ and recent cumulative GC dose ($p < 0.2$), showed a decrease in fracture odds of 88% for every SD increase in WBLH height adjusted BMD Z-score (OR = 0.12 95% CI 0.02–0.62; $p = 0.012$).

Median serum calcium, phosphate, PTH and ALP levels were normal and similar in those with and without vertebral fractures (Table 4). The majority of patients (49/55) had 25(OH)D levels >30 nmol/L. Only one of the six patients with vitamin D deficiency had a LS height adjusted BMD Z-score ≤ -2 and two of the six patients had a WBLH height adjusted BMD Z-score ≤ -2. No patients with vitamin D deficiency had vertebral fractures.

4. Discussion

Glucocorticoids (GCs) have been considered a major factor in poor skeletal health in children with chronic non-malignant illnesses. This cross-sectional study in a predominantly black South African population of children on GCs with chronic non-malignant illnesses has shown a high prevalence of vertebral fractures (15%) as assessed by DXA lateral vertebral fracture assessment. The prevalence of vertebral fractures is similar to that reported in the literature for Caucasian children on GCs with chronic non-malignant illnesses (LeBlanc et al., 2015; Nakhla et al., 2009; Valta et al., 2007). This finding suggests that black children in South Africa are not protected from GC related fractures despite having lower fracture rates in healthy children compared to their white peers (Thandrayen et al., 2009). The lower fracture rate in black South African children (Thandrayen et al., 2009) was postulated to be due to genetic protective factors against low bone mass in this population (Thandrayen et al., 2011; Vidulich et al., 2006).

The International Society of Clinical Densitometry's (ISCD) official position supports the use of the DXA VFA as a substitute for spine radiography in the identification of vertebral fractures if the evaluator has experience in the assessment of paediatric vertebral fractures. The ISCD official position also provides the following advantages of DXA VFA compared to radiography: the entire spine can be visualised, parallax is eliminated and there is a 3–5 fold lower radiation exposure. The disadvantage of VFA is that the upper thoracic area can be a site of unevaluable vertebrae and high-risk patients should be reimaged with conventional radiography or MRI.

The vertebral fractures in our study patients showed a bimodal distribution, similar to other studies performed in predominantly Caucasian children with chronic non-malignant conditions on long-term GCs and were of either mild or moderate grades (Feber et al., 2012; Huber et al., 2010; LeBlanc et al., 2015; Phan et al., 2014; Rodd et al., 2012). There are reasons for an increased susceptibility to fracture at the upper-mid-thoracic and thoraco-lumbar regions. The thoracic kyphosis is more pronounced at the mid-thoracic region so the loading forces applied in flexion on this area are accentuated (Halton et al., 2009). At the thoraco-lumbar junction, the spine transitions from being more rigidly fixed by ribs to being freely mobile and maximal compression stresses will easily cause fractures (Halton et al., 2009).

A meta-analysis of mainly rheumatological conditions, indicated that the prevalence of morphometric vertebral fractures was as high as 29–45% (Hansen et al., 2014) while in a renal study (nephrotic patients) the prevalence was lower at 6% after 1 year of GCs (Phan et al., 2014). The prevalence of fractures in neurological patients with DMD was 16% (Mayo et al., 2012) but a more recent study (Singh et al., 2018), reviewing 49 DMD patients on long term deflazacort treatment, found a prevalence ranging from 19%–100% within a period of 3–9 years on treatment. Our study also confirms the reported trend toward a higher prevalence of vertebral fractures in rheumatological and neurological patients compared to renal patients but confirmatory statistical analyses was not possible due to the small sample sizes in each diagnostic group.

The mean duration of GC treatment in our patients was greater than 2 years with no significant difference between the diagnostic groups. The recent cumulative GC dose was higher in the renal group compared to the rheumatological and hepatic groups which is an interesting finding as the trend was that of lower vertebral fractures in the renal group which warrants further investigation. Both the recent cumulative GC dose and the duration of GC therapy had no influence on vertebral fracture risk and showed no association with BMC or BMD measurements. Rodd et al. (2012) had shown a positive association between vertebral fractures and higher cumulative doses of GCs received within a year of treatment while Markula-Patjas et al. (2012) found an association between vertebral fractures and GC use in the past 3 years but not for the total duration of GC exposure (median 7.1 years) which was supported by Valta et al. (2007).

The neurological group had a lower WBLH BMD height adjusted Z-score (mean WBLH Z score = −2.7) than the renal and rheumatological patients whose height adjusted BMD Z-scores for WBLH and LS were greater than −2.0. This difference could be due to the greater risk factors in DMD patients such as the degree of immobility. Nevertheless it has been reported that fracture risk increases while on GCs regardless of the changes in BMD (Markula-Patjas et al., 2012), which can be normal in children presenting with fractures due to both primary and secondary osteoporosis (Ward et al., 2020). Our study confirmed lower height adjusted WBLH BMC and BMD Z scores in those that fractured but the WBLH BMC Z score was not below −2. The odds of fracture was significantly reduced by 88% for every unit increase in the WBLH height adjusted BMD Z-score.

The prevalence of low bone mass (BMD Z-score ≤ -2) in those patients with vertebral compression fractures was high (45% when Hologic derived Z-scores were used and 27% when using height adjusted Z-scores). Two studies performed on rheumatological patients confirmed a high percentage (67% and 79%) of LS BMD Z-scores (machine-derived) being less than −2 (LeBlanc et al., 2015; Rodd et al., 2012). Despite the association of GCs with reduced BMD, the median Z-score of children with vertebral fractures was >−2. Furthermore, when the fractures occurred they were frequently asymptomatic, thus making it difficult to select out those children with possible vertebral fractures (Huber et al., 2010; Markula-Patjas et al., 2012; Valta et al., 2007). Valta et al. (2007) and Markula-Patjas et al. (2012) also have shown no correlation between fracture risk and LS aBMD measurement or disease characteristics. A meta-analysis showed that there was an inconsistent reduction in spine BMD or Z-score in relation to GC therapy (Hansen et al., 2014). In view of the majority of vertebral fractures being asymptomatic (73%) in our study and similarly in other studies (43% and 67% in rheumatological patients (LeBlanc et al., 2015; Rodd et al., 2012)) and 100% in renal or nephrotic patients (Feber et al., 2012; Phan et al., 2014), routine

Table 4
Serum biochemical measurements in patients with and without vertebral fractures.

	n	Patients with vertebral fractures Median (IQR)	n	Patients without vertebral fractures Median (IQR)	p values
Calcium (2.19–2.64 mmol/L)	10	2.3 (2.3–2.4)	53	2.3 (2.2–2.5)	1.00
Phosphate (1.45–1.80 mmol/L)	10	1.4 (1.2–1.9)	52	1.4 (1.2–1.6)	0.69
ALP (93–345 U/L)	10	151 (98–283)	53	166 (119–251)	0.62
PTH (1.2–6.9 pmol/L)	8	1.85 (1.3–2.9)	47	2.4 (1.5–3.5)	0.52
25 (OH) D (deficient < 30 nmol/L; insufficient 30–50 nmol/L)	7	67.4 (50.4–101.6)	48	75.6 (52.1–104.6)	0.80

No significant differences between those with and without fractures.

vertebral fracture surveillance in children on GCs should be undertaken. In addition, due to the long bone and vertebral fracture rates being very high in GC-treated DMD patients, there are more recent recommendations to monitor for signs of vertebral fractures with annual spine radiographs starting at the time of GC initiation and to start osteoporosis intervention at the first sign of a single low-trauma long-bone or vertebral fracture (Birnkrant et al., 2018). Ma et al. studied 400 children at risk for prevalent vertebral fractures and showed that either a low BMD (Z-score < -1.6) or back pain history had high sensitivities to identify those children with the highest risk of prevalent vertebral fractures so that radiography can be used judiciously (Ma et al., 2020). The importance of vertebral fracture identification in paediatric osteoporosis work-up has been identified by the Paediatric Task force of the ISCD, which has endorsed the use of DXA-based VFA in children in the 2019 Official Paediatric position report (Weber et al., 2019).

The other significant finding in our study was the difference in Z-score measurements calculated using the Hologic reference database and those that were calculated using the Zemel equation (Zemel et al., 2011) to adjust for height, besides age and sex. WBLH and LS Z-scores that were adjusted for height were greater than those that were calculated using the Hologic database. This finding suggests that the interpretation of DXA machine bone mass measurements should be adjusted for height especially in chronic illnesses to correct for the falsely low results associated with stunting. Mayo et al. (2012) highlights the technical difficulties in interpreting DXA scans in DMD patients because of the short stature that requires height adjustments to be made, the difficulty in positioning of patients and the increased body fat that may artificially elevate the BMD results.

Vitamin D status is important to evaluate in children with chronic illness, as they may have multiple risk factors for vitamin D deficiency such as immobility, lack of sun-exposure, concomitant use of medication interfering with vitamin D metabolism and use of sunscreen in diseases such as SLE. Eleven percent of our patients had vitamin D deficiency (<30 nmol/L) but none of these patients had vertebral compression fractures. Poopedi et al. (2011) found that 7% of healthy 10 year old South African children residing mainly in Soweto and the greater Johannesburg area had vitamin D deficiency suggesting that the prevalence of vitamin D deficiency in this study population from CHBAH in Soweto is not different from the general healthy population. In patients with juvenile idiopathic arthritis on GCs in Finland, 10% of whom had asymptomatic vertebral compression fractures, the prevalence of vitamin D deficiency was found to be similar to the general population (Valta et al., 2007). However, DMD patients on long-term GCs but not on vitamin D supplementation, had a high prevalence of vitamin D deficiency (43.3% < 30 nmol/L) (Barzegar et al., 2018). In our cohort, 64% ($n = 46$) of the patients were prescribed vitamin D supplements. As children with chronic illnesses are at-risk patients for vitamin D deficiency, all patients should be prescribed vitamin D.

This study also highlights some contrasting characteristics of vertebral fracture prevalence and BMD measurements in the different diagnostic categories. Renal patients including those with nephrotic syndrome had a trend toward lower vertebral fracture prevalence despite receiving higher cumulative GC doses than the other groups and studies confirm that the majority of these fractures are asymptomatic (Feber et al., 2012; Phan et al., 2014). DMD patients had a high prevalence of vertebral fractures and lower WBLH height adjusted Z-scores, probably due to a combination of multiple risk factors such as severe skeletal muscle weakness and loss of ambulation. The DMD patients in our study participated in less informal activities compared to patients in other diagnostic categories ($p < 0.001$, data not shown). A postulated reason for the differences in fracture prevalence between rheumatological and nephrotic patients is as a result of persistent elevations in osteotoxic inflammatory cytokines in rheumatological patients despite treatment as opposed to nephrotic patients who respond to GC therapy and enter quiescence (Burnham, 2012). Thus, future disease-specific studies especially in black South African children to investigate the effects of GC therapy on their skeletal health are needed.

The limitations of this study include that this was a cross-sectional study with no controls. Other limitations included the lack of radiological confirmation of the vertebral compression fractures and missing biochemical tests as phlebotomy was not mandatory for this study and the bloods were taken when routine tests were done at the clinic visits. The study numbers are small particularly in some of the disease categories and thus meaningful comparisons and detailed statistical analyses to identify independent risk factors for fractures could not be made.

5. Conclusion

Despite the lower prevalence of fractures in healthy black children compared to white children in South Africa, the prevalence of vertebral fractures in predominantly SA black children on GCs with chronic non-malignant illnesses is similar to that reported in other studies internationally, suggesting that black children are not protected from fractures when treated on GCs and that routine yearly DXA scans including VFA are warranted in this highly at risk population.

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CRediT authorship contribution statement

Kebashni Thandrayen: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Udai Keshav Kala:** Methodology, Data curation, Writing – review & editing. **Nilesh Lala:** Methodology, Data curation, Writing – review & editing. **Grace Okudo:** Methodology, Data curation, Writing – review & editing. **Kiran Bhagoo Parbhoo:** Methodology, Data curation, Writing – review & editing. **Fatima Yakoub Moosa:** Methodology, Data curation, Writing – review & editing. **Charl Verwey:** Methodology, Data curation, Writing – review & editing. **Marc Hauptfleisch:** Methodology, Data curation, Writing – review & editing. **Christina Hajinicolaou:** Methodology, Data curation, Writing – review & editing. **Priya Ramanlal Ambaram:** Methodology, Data curation, Writing – review & editing. **Bhadrish Jayantkumar Mistry:** Methodology, Data curation, Writing – review & editing. **Karen Lavinia Petersen:** Methodology, Data curation, Writing – review & editing. **John Morley Pettifor:** Conceptualization, Methodology, Investigation, Writing – review & editing.

Declaration of competing interest

Kebashni Thandrayen, Udai Kala, Nilesh Lala, Grace Okudo, Kiran Parbhoo, Fatima Moosa, Charl Verwey, Marc Hauptfleisch, Christina Hajinicolaou, Priya Ambaram, Bhadrish Mistry, Karen Petersen and John Pettifor declare that they have no conflict of interest.

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Ethics approval

Human Research Ethics Committee of the University of the Witwatersrand (approval number M151153) and the CEO of Chris Hani Baragwanath Academic hospital approved the study.

Informed consent

Assent was obtained from children between 8 and 17.9 years of age and informed consent from the parent or guardian of all the children enrolled in the study.

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