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BRIEF REPORT

Vertebral fractures despite normal spine bone mineral density in a boy with nephrotic syndrome

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Abstract Glucocorticoids (GCs) are associated with fragility fractures in children with various chronic illnesses. The impact of GCs on bone health in children with nephrotic syndrome (NS) is less well understood. Here we report skeletal findings in a 10-year-old boy with steroid-sensitive NS who presented with back pain due to vertebral fractures 5 years after NS diagnosis. Spine radiographs showed a Genant grade 2 fracture at T7 and a grade 1 fracture at T8. Dual-energy X-ray absorptiometry (DXA) revealed a lumbar spine areal bone mineral density (BMD) Z-score of −0.5 and a total body areal BMD Z-score of −0.4. Quantitative transiliac bone histomorphometry revealed low trabecular bone volume and cortical width but no osteomalacia. Our findings show the potential for significant bone morbidity due to osteoporosis in steroid-sensitive NS treated with intermittent GC therapy and emphasize that vertebral fractures may be an underrecognized complication. Furthermore, our report highlights that vertebral fractures can be associated with normal spine areal BMD in this context, suggesting that DXA-based, anteroposterior areal BMD should not be relied upon exclusively for assessing bone health and disease in children with steroid-sensitive NS.

Keywords Clinical/pediatrics · Corticosteroid osteoporosis · Bone histomorphometry · Bone densitometry · Vertebral fractures

Abbreviations

AP	anteroposterior
BMD	bone mineral density
BMC	bone mineral content
Cr	creatinine
DXA	dual-energy X-ray absorptiometry
GC	glucocorticoid
NS	nephrotic syndrome
SS	steroid-sensitive
N	normal

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Introduction

The initial therapy for childhood idiopathic nephrotic syndrome (NS) consists of high-dose daily prednisone for 4–6 weeks followed by alternate-day prednisone for another 4–6 weeks. Intermittent glucocorticoid (GC) therapy is further required upon NS relapse for steroid-sensitive (SSNS) disease [1], resulting in the potential for significant cumulative GC load. GCs are associated with fragility fractures in children with various chronic illnesses [2, 3], but the effect of GCs on bone health in childhood SSNS remains less-well understood. Studies in the first year of

GC therapy have shown significant reductions in spine bone mineral density (BMD) parameters [4, 5], whereas a large, cross-sectional study after 4.4 years of intermittent GC therapy showed similar spine and total body bone mineral content (BMC) as controls [6]. Here we describe the skeletal findings of a boy who presented with painful vertebral fractures during a GC-treated relapse for SSNS. The study was approved by the ethics committee at the Children's Hospital of Eastern Ontario.

Case report

A previously healthy 5-year-old boy was diagnosed with NS, presumed secondary to minimal change disease, upon presentation with progressive periorbital, scrotal, and lower-extremity swelling associated with the following results: 3+ protein on urinalysis, with urine protein concentration 18.03 g/l and urine protein/creatinine (Cr) 1.18 g/mmol Cr; normal serum Cr 0.5 mg/dl (41 μmol/L), normal (N) 0.1–0.7 mg/dl (10–60 μmol/L); decreased serum albumin 1.7 g/dl (17 g/L), N 3.6–5.5 g/dl (36–55 g/L); elevated fasting total cholesterol 480 mg/dl (12.4 mmol/L), N 128–224 mg/dl (3.3–5.8 mmol/L), and elevated triglycerides 159 mg/dl (1.80 mmol/L), N 75–150 mg/dl (0.85–1.70 mmol/L). Complement levels were normal; antinuclear antibodies, anti-DNase B, and antistreptolysin titers were negative. He was treated with oral daily prednisone (60 mg/m^2 daily) for 6 weeks, followed by alternate-day prednisone (40 mg/m^2 every second day) for another 6 weeks. Although he initially responded to GC therapy, he subsequently had multiple relapses (n=8) over the next 5 years. Cyclophosphamide therapy was offered, but this was declined because of concerns regarding potential side effects. Therefore, he received repeated intermittent courses of prednisone as the mainstay of immunosuppressive therapy, resulting in a cumulative dose of 10,146 mg/m^2 over 5 years. At 10.9 years of age, he presented with his ninth relapse. He also complained of new-onset back pain limiting participation in physical activities. There was no history of extremity fractures. A chest radiograph revealed an incidental finding of vertebral fractures at T7 and T8. A lateral thoraco-lumbar spine radiograph confirmed Genant grade 2 and grade 1 anterior wedge vertebral fractures [7] with loss of endplate parallelism at T7 and T8 [8] (Fig. 1).

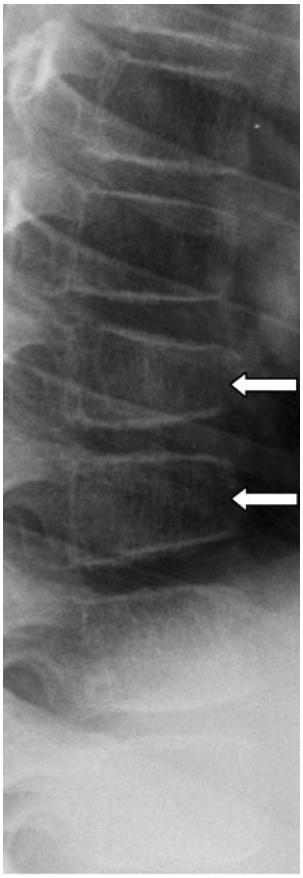

Fig. 1 Vertebral compression fractures. The *upper arrow* points to a grade 2 (moderate) anterior wedge fracture at T7, and the *lower arrow* points to a grade 1 (mild) anterior wedge fracture at T8. Both fractures have loss of endplate parallelism

The patient's height was 145.5 cm (Z-score +0.3, compared with +1.54 at diagnosis), weight 48.4 kg (Z-score +1.4), and body mass index 22.9 kg/m^2 (Z-score +1.6). Z-scores were calculated using reference data provided by the National Center for Health Statistics [9]. His bone age was 10 years, and his hand radiograph showed no evidence of rickets. Pubertal development was Tanner stage 1. Lumbar spine (vertebrae L2 to L4) and total body areal BMD were measured by dual energy absorptiometry (DXA) in the anteroposterior (AP) direction (Lunar Prodigy; General Electric; Madison, WI, USA). Results were transformed to age- and gender-specific Z-scores using reference data supplied by the manufacturer. Total body BMC Z-scores were calculated using published reference data [10]. DXA revealed the following: Lumbar spine areal BMD Z-score −0.5, total body BMD Z-score −0.4, and total body BMC Z-score −0.6. He was no longer edematous at the time of testing. A prior DXA following his first three relapses also revealed normal BMD Z-scores: spine −0.2, total body −0.4, and total body BMC −1.2. His 25-hydroxyvitamin D level was low at 8 ng/ml (21 nmol/L), whereas biochemical parameters of bone and mineral ion metabolism were otherwise unperturbed: ionized calcium 4.4 mg/dl (1.10 mmol/L), N 4.4–5.2 mg/dl (1.10–1.30 mmol/L); phosphate 3.1 mg/dl (1.0 mmol/L), N 3.1–5.3 mg/dl (1.0–1.7 mmol/L); alkaline phosphatase (ALP) 125 IU/L, N 120–488 IU/L; and parathyroid hormone (PTH) 50 pg/ml (5.3 pmol/L), N 10 – 65 pg/ml (1.1–6.8 pmol/L).

Given the multiple relapses and vertebral fractures, renal and bone biopsies were carried out 14 days following resumption of GC therapy. A transiliac bone biopsy was performed 2 cm posterior to the superior anterior iliac spine. Bone biopsy preparation and histomorphometric analyses were performed as described previously [11], with

the exception that dual tetracycline labelling was not completed because of insufficient time to complete the labelling protocol. Measurements were performed using a digitizing table with Osteomeasure software (Osteometrics Inc., Atlanta, GA, USA). Results were compared with reference data and expressed as percentages of the healthy average values [11].

Histomorphometric analysis of bone structure did not reveal a mineralization defect despite the hypovitaminosis D, as osteoid thickness was not elevated (2.7 μm; 46% of age- and gender-matched mean). However, signs of osteoporosis were present, with marked thinning of the cortices (557 μm; 57% of mean) and decreased trabecular bone volume (17.6%; 79% of mean). Static parameters revealed a paucity of osteoblasts (2.2% of bone surface; 27% of mean) and an increased osteoclast number (0.8/mm of bone perimeter; 213% of mean). Cortical porosity was below average (6.3%; 90% of the healthy mean). Renal biopsy showed immunoglobulin M (IgM) immune complex-mediated mesangioproliferative glomerulonephritis. Consequently, mycophenolate mofetil was started in addition to prednisone.

Discussion

This case highlights the potential for significant bone morbidity in childhood NS treated with intermittent GC therapy, given the presence of moderately severe and symptomatic vertebral fractures despite minimally reduced AP BMD parameters. Although this boy's fractures were detected 5 years after SSNS diagnosis, it is possible that more subtle, asymptomatic fractures may have been present in the preceding years. The comprehensive characterization of this boy's skeletal phenotype furnishes insight into the mechanism of the bone fragility. Despite a low 25-hydroxyvitamin D, serum mineral ion metabolism was unperturbed. Furthermore, there was no radiographic evidence of rickets, and osteomalacia (accumulation of unmineralized osteoid) was not present in the bone sample. On the other hand, transiliac histomorphometry was consistent with the hallmarks of osteoporosis: a reduction in trabecular bone volume and thinning of the cortices. In addition, the amount of bone covered by osteoblasts was reduced, and the osteoclast number was markedly elevated. The boy's biopsy findings are in line with reports in adults and animals describing the effects of GCs on iliac histomorphometry [12] and suggest that GC therapy was the main culprit giving rise to his vertebral fractures. Interestingly, cortical porosity was below average in our patient, a finding that is in line with the study by Wetzsteon et al. [13], who showed that tibial cortical density (by peripheral quantitative computed tomography) was increased in children with GC-treated NS. Together, these findings suggest that the rate of intracortical remodelling is reduced in GC-treated NS.

The effect of GC treatment on bone health in children with NS is a matter of ongoing debate. Leonard et al. recently reported that intermittent GC therapy resulted in similar spine and total-body BMC in children with SSNS compared with controls [6], suggesting that bone mass is relatively preserved. However, Acott et al. [14] reported vertebral fractures among NS children within 3 months of receiving GCs. Our report further supports the observation that vertebral body strength can indeed be compromised with intermittent GC therapy for NS.

The International Society for Clinical Densitometry (ISCD) states that a diagnosis of pediatric osteoporosis is reserved for children with a clinically significant fracture history (including vertebral fractures) and a spine BMD Z-score worse than −2.0 [15]. In our patient, lumbar spine areal BMD was normal, but he nevertheless had bone fragility and clear evidence of osteoporosis on transiliac histomorphometry. This resembles findings in postmenopausal women with GC-treated rheumatic disorders, where lumbar spine BMD was similar between patients with and without fractures [16]. A possible explanation is that the standard AP areal BMD measure is not sensitive in detecting GC-induced changes at the spine. Indeed, Wetzsteon et al. showed that children with GC-treated NS have decreased lateral spine BMD Z-scores [13]. The lateral view captures the trabecular-rich vertebral body and is less affected by the dense, cortical posterior spinous processes than the AP view. As such, lateral spine BMD may be more sensitive in detecting GC-induced changes than standard AP DXA methods. Furthermore, quantification of thoracic in addition to lumbar spine BMD may be more informative, as the thoracic spine appears particularly vulnerable to bone-health threats [3].

In conclusion, our comprehensive description of the skeletal phenotype in a boy with SSNS and vertebral fractures demonstrates that intermittent GC therapy can be associated with clinically significant bone morbidity due to osteoporosis. This report provides evidence that standard AP lumbar spine densitometry may not be sufficient for identifying children with NS who are at risk for fracture in the context of intermittent GC treatment. Longitudinal studies to determine the incidence and evolution of vertebral fractures in this context are warranted.

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Conflicts of interest None

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