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ORIGINAL ARTICLE

Bone health and body composition in paediatric patients with idiopathic nephrotic syndrome managed with glucocorticoids

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ABSTRACT

Introduction: Prolonged administration of glucocorticoids (GCs) is known to have deleterious effects on growth and bone integrity. This study aimed to assess the effects of GC therapy on bone health and body composition in South African children with primary nephrotic syndrome (NS).
Methods: A retrospective review was performed of idiopathic NS in patients attending the Paediatric Renal Unit at Chris Hani Baragwanath Academic Hospital (CHBAH) between 1 January 2010 and 31 December 2019. Demographics, dual-energy X-ray absorptiometry (DXA) scans, biochemistry results and treatment history were analysed.
Results: NS was diagnosed in 346 patients; 145 met inclusion criteria. Histology showed 90 (62.1%) minimal change NS (MCNS). One hundred and twenty-four (85.5%) had steroid-sensitive NS and 21 (14.5%) demonstrated steroid resistance. Sixty-two (42.7%) had at least one relapse with a median (IQR) time to relapse of 356 (179, 453) days. Thirty-three (22.8%) patients had DXA scans performed. Lumbar spine bone mineral density (BMD) z-score was –1.10 (–1.70, –0.30) and whole body less head BMD z-score was –0.81 (–1.86, –0.10). Four (12.1%) DXA patients had documented fractures. Ten (6.9%) patients had hypothyroidism treated with thyroxine; they were relatively younger, stunted, had lower albumin, higher cholesterol and lower bone metabolism markers at diagnosis and on last clinic visit.
Conclusions: In paediatric patients with NS who had DXA performed, the fracture prevalence was 12.1% with predominantly incidental vertebral fractures despite normal BMD measurements in those receiving GC therapy. We recommend screening these high-risk NS patients on prolonged GC therapy for hypothyroidism, low BMD and vertebral or non-vertebral fractures.

Keywords: glucocorticoids; nephrotic syndrome; fractures; children; bone mineral density; South Africa.

INTRODUCTION

Nephrotic syndrome (NS) is the most common kidney disease of childhood with normal renal function [1]. The condition usually responds to high-dose glucocorticoid (GC) therapy (2 mg/kg/day) [1]. Childhood NS typically follows a relapsing and remitting course, often requiring recurrent courses of GC [2]. Prednisone is the first-line treatment of the condition to induce remission. Prolonged administration of prednisone is known to interfere with growth and bone mineralisation and has deleterious effects on bone integrity [2]. Glucocorticoid treatment results in reduction in bone formation because of decreased osteoblast differentiation and activity as well as increased osteoblast and osteocyte apoptosis [3]. Skeletal development in childhood is characterised by increases in bone mineral density (BMD) [1]. The growing skeleton may be especially susceptible to the reduced bone formation and bone resorption effects of GCs. The risk of fracture is increased in children with a history of frequent use of oral corticosteroids [4].

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Urinary losses of albumin and low molecular weight proteins that are necessary for the transport of metals, drugs and hormones like thyroid binding globulin (TBG) and vitamin D binding globulin (VDBG), are a major complication in patients with NS [5]. The loss of TBG contributes to the resultant hypothyroidism seen in the condition [6]. Hypothyroidism in childhood causes delayed skeletal development, growth retardation and short stature with impaired bone maturation due to defective endochondral ossification [7]. A Ugandan study reports hypothyroidism in 23% of NS patients, 81.2% of whom had subclinical hypothyroidism [8]. The patients with hypothyroidism were found to have hypoalbuminaemia [8]. Children with nephrotic syndrome have been found to have a reduction in free 25-hydroxyvitamin D (25(OH)D) and serum calcium values, presumably related to a urinary loss of VDBG [5].

Urinary loss of proteins also results in intensified hepatic synthesis in an attempt to replace lost plasma proteins, generating a catabolic state [9]. As muscle is the main source of amino acids, the catabolic state existing in NS is manifested by a reduction in lean mass as measured by dual energy X-ray absorptiometry (DXA) [9,10]. Growth and bone health in NS is influenced by multiple factors related to the urinary protein loss of VDBG and TBG but is also due to the effects of GC therapy.

DXA is a technique used to assess BMD, which is the amount of mineral mass per area or bone volume [2]. Other techniques are also available, but it is the gold standard method due to short scan times, easy set-up of patients for scanning, low radiation dose and good measurement precision [4]. There is evidence of a positive correlation between body mass index (BMI) and body composition as shown in a Chinese study assessing obesity and bone turnover [9]. This investigation further emphasised an inverse in this correlation once children displayed BMIs of greater than the 97th percentile [9]. While there is a paucity of data on this correlation in children with NS on GC therapy, a London study in children with Crohn's disease managed with long-term steroids reported a positive correlation between BMI and BMD [10]. DXA analysis provides the opportunity to assess BMD and body composition in children with NS with presumably elevated BMI secondary to long-term steroid use, which is known to have deleterious effects on BMD.

In children with nephrotic syndrome treated with glucocorticoids, monitoring height for age z-scores (HFAZ) is essential for evaluating the impact of GC therapy on growth. An HFAZ score, or a standard deviation score, expresses a child's height relative to a reference population of the same age and sex. This anthropometric assessment allows for early detection of growth faltering through a standardised method across time points. Similarly, with growth velocity, the rate that height increases over time, is a sensitive indicator of early growth suppression. Growth velocity is an individualised measure of assessing a child's growth and also varies depending on stages of growth; for example, infantile is on average 26 cm/year in the first year of life, and prepubertal is 5–6 cm/year and must be assessed over a one-year period for accuracy or a more precise interpretation [11].

The purpose of the study reported here was to determine the effects of disease-modifying GC therapy on BMD and body composition in South African children with NS, who are managed in the Paediatric Renal Unit of the Chris Hani Baragwanath Academic Hospital (CHBAH).

METHODS

We reviewed the records of patients younger than 18 years of age diagnosed with idiopathic NS at the CHBAH's Paediatric Renal Unit, which serves a predominantly Black population [12].

The study included patients seen from 1 January 2010 to 31 December 2019. They were identified using the renal unit's monthly admission lists. A total of 346 patients were diagnosed with NS during the study period and 145 (41.9%) met the inclusion criteria. These criteria included children between the ages of two and 17.9 years attending the paediatric renal clinic and diagnosed with NS. Exclusion criteria were conditions other than the disease, infantile or secondary NS such as in systemic lupus erythematosus and HIV-associated nephropathy, and underlying bone disease such as rickets, or a history of an oncological condition. A total of 201 patients were excluded: 137 (68.2%) had secondary NS, 58 (28.9%) were under two years of age, five (2.5%) were excluded due to missing clinical data, and one patient was detected as a duplicate. Of the 145 patients recruited into the study population, 136 (93.8%) presented to the last clinic visit during the study period. Thus, a total of 9 (6.2%) were either lost to follow-up, transferred out of the province or died. A sub-analysis was further conducted on 33 (22.8%) patients who had records of DXA scans (Figure 1).

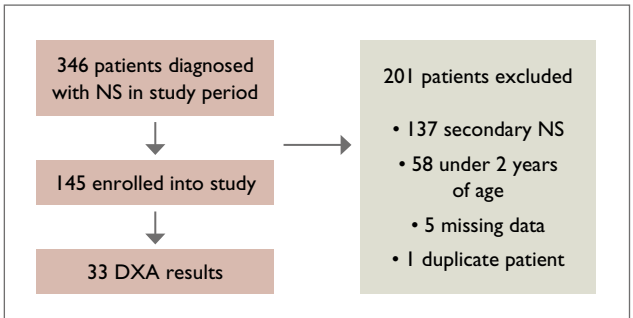


Figure 1. Process of study population determination.

Anthropometric calculations of patients' weight for age z-scores (WFAZ), HFAZ and body mass index z-scores (BMIZ) were performed using measurements documented at diagnosis, from DXA scan and at last clinic visit. These z-scores were calculated using WHO Anthroplus software.

Biochemical results such as creatinine, electrolytes, calcium, phosphate, alkaline phosphatase (ALP), 25(OH)D, parathyroid hormone (PTH), thyroid function tests (TFTs), cholesterol and albumin were obtained from files at diagnosis, at the time of DXA scan visit, and at the last clinic visit, which was defined as the patients' last presentation at the unit within the study period. The estimated glomerular filtration rate was calculated using the Schwartz formula [13].

Histopathological diagnosis was collected from biopsy results documented in patient files as well as sourced through results captured by the National Health Laboratory Service. Steroid sensitivity was classified according to the guidelines derived from the International Paediatric Nephrology Association (IPNA) [14]:

Steroid-sensitive nephrotic syndrome (SSNS): Complete remission within 4 weeks of GC (prednisone) at standard dose (60 mg/m^2/day or 2 mg/kg/day, maximum 60 mg/day).

Steroid-resistant nephrotic syndrome (SRNS): Lack of complete remission within 4 weeks of treatment with GC at standard dose.

Steroid-dependent nephrotic syndrome (SDNS): A patient with SSNS who experiences two consecutive relapses during recommended GC therapy for first presentation or relapse or within 14 days of its discontinuation.

Relapse: Urine protein excretion was measured by urine dipstick and considered a relapse if the dipstick ≥3+ (≥300 mg/dL) or urine protein creatinine ratio (UPrCr) ≥ 200 mg/mmol on a spot urine sample on three consecutive days, with or without reappearance of oedema in a child who had previously achieved complete remission.

Frequently relapsing nephrotic syndrome (FRNS): ≥2 relapses in the first 6 months following remission of the initial episode or ≥3 relapses in any 12 months.

Infrequently relapsing nephrotic syndrome: <2 relapses in the 6 months following remission of the initial episode or fewer than 3 relapses in any subsequent 12-month period.

A sub-analysis of patients with DXA scans was conducted. This subgroup consisted of 33 patients, of whom 23 were enrolled in a cross-sectional study where patients scanned had at least 3 months' exposure to GC [15]. Of the 23 patients from the cross-sectional study that had DXA scans, 15 had data collected for quantifiable 28-day cumulative GC doses in the months preceding the imaging. The weight and height measurements of the patients were used to determine body surface area, thus the dose of systemic GC/m^2 were calculated based on the GC dose received in the last 28 days or month prior to the DXA scan. In that case the average GC dose in the last month was defined as the cumulative dose in prednisone equivalents (in mg/m^2) divided by 28.

The remaining 10 patients had DXA scans performed at the discretion of the clinicians at the clinic. Documented histories of fractures, BMD measurements, and lateral vertebral fracture assessments (VFA) of DXA scans performed during GC therapy were obtained from files. Vertebral fractures were defined as deformations of the vertebrae at the anterior (wedge) or mid- (biconcave) and posterior (crush) vertebral positions. Vertebral fractures were graded according to the method described by Genant et al. [16] 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 in 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 by the DXA technician and adjusted if warranted prior to completing the analyses. The VFA report was reviewed by KT. The potential limitations of VFA compared with standard radiography include inferior image resolution and poor visualisation of thoracic spine levels above T7, thus misclassification of fractures or non-evaluable vertebrae can lead to an inaccurate or underestimation of fracture risk [17].

DXA uses a dual-energy beam of radiation that passes through the soft tissue and bone, and is then captured by an opposing sensor array to measure energy attenuation [3]. Therefore, it depicts the bone in two-dimensional form. The limitations of DXA are the inability to assess bone geometry, distinguishing trabecular bone from cortical bone, and requiring comparison with healthy individuals of the same age, sex, and ethnicity, analysed by similar equipment and software in paediatric assessments. DXA measurements of the whole body less head (WBLH), lumbar spine (LS), lateral vertebral assessments, fat mass (FM) and lean mass (LM) were obtained from scans using a Hologic Discovery machine (Software version Apex 4.0.2). Measurements were performed for LS and WBLH BMD z-scores, adjusted for height, using the Zemel equation calculator [18].

DXA is one of the most common body composition assessment techniques, providing acceptable accuracy in measuring body composition of children. The masses derived from DXA were then used to calculate fat mass index (FMI) and lean mass index (LMI), reported in kg/m^2.

Biochemical results obtained at the time of DXA scan for patients with confirmed fractures were analysed to assess for any potential associations with DXA measurements. Serum calcium, inorganic phosphate, and alkaline phosphatase (ALP) were measured by standard laboratory methods, whereas serum 25(OH)D was assayed using DiaSorin LIAISON.

Patients with low or normal T4 and normal or slightly decreased TSH without any documented history of eltroxin treatment were classified as the sick euthyroid group. Subclinical hypothyroidism (SH), a mild form of thyroid failure, was defined biochemically by elevated TSH levels with normal free T4. Primary hypothyroidism was confirmed by elevated TSH and low fT4, while central hypothyroidism was characterised by low fT4 with a low, normal, or minimally elevated TSH [19,20].

Data analysis

Anonymised patient data were collected from patient files and entered into an Excel spreadsheet, then imported into Statistica version 14.0.0.15 (TIBCO Software Inc., Palo Alto, CA, USA) and Stata version 15.1 (StataCorp LLC, College Station, TX, USA) for analysis. Categorical data were analysed as frequencies and percentages, whereas continuous data were recorded as means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on the distribution of the data. The comparison between those with and without fractures was compared using the Mann–Whitney U test for skewed data and continuous variables. Fisher exact or Chi-Squared tests were performed for comparisons of categorical data. The paired Student's t-test for dependent samples was used to compare variables from diagnosis until last clinic visit. Partial correlations and 2D scatterplots were recorded to correlate BMD with LMI and FMI.

Ethical approval for the study was granted by the University's Human Research Ethics Committee (clearance number M210668; MED21-04-115).

RESULTS

Demographics and clinical characteristics

The median (IQR) age of the study population was 6.5 (3.8, 9.4) years (Table 1). Males accounted for 97 (66.9%) patients. Percutaneous kidney biopsy was performed in 140 (96.6%) patients after clinical diagnosis to attain a histopathological diagnosis. The commonest histological diagnosis was minimal change nephrotic syndrome (MCNS) in 90 (62.1%), and focal segmental glomerulosclerosis (FSGS) in 43 (29.7%). SSNS was seen in 124 (85.5%) of whom 20 (16.1%) were SDNS. Sixty-two (42.7%) patients had at least one relapse during the study period. The median (IQR) time to relapse was 356 (179, 453) days. Four (6.5%) patients with initial SRNS responded to methylprednisolone and monthly intravenous cyclophosphamide and relapsed once during the study period.

Table 1. Clinical characteristics of patients with childhood nephrotic syndrome on GC therapy at CHBAH paediatric renal unit.

Characteristics	Patients (N = 145)
Age (years), median (IQR)	6.5 (3.8, 9.4)
Sex n (%)	
M	97 (66.9)
F	48 (33.1)
Histology n (%)	
MCNS	90 (62.1)
FSGS	43 (29.7)
MPGN	4 (2.8)
Primary membranous	3 (2.1)
Presumed MCNS	5 (3.4)
Days to renal biopsy, median (IQR)	6.0 (2.0, 11.0)
Steroid sensitivity n (%)	
SSNS	124 (85.5)
SDNS	20/124 (16.1)
SRNS	21 (14.5)

Abbreviations: MCNS, minimal change nephrotic syndrome; FSGS, focal segmental glomerulosclerosis; MPGN, membrano-proliferative glomerulonephritis; SSNS, steroid-sensitive nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome

Anthropometric and biochemical results

Table 2 shows the anthropometric and serum biochemical results for the study population at diagnosis and at last clinic visit. The WFAZ and HFAZ scores were normal at diagnosis and at last visit with no significant increase in WFAZ ($P = 0.19$), and similarly in HFAZ ($P = 0.56$). The BMIZ score showed a significant decrease from diagnosis to last clinic visit but remained normal ($P = 0.01$).

The mean corrected calcium level at diagnosis was low and improved ($P < 0.01$) but remained marginally low at last clinic visit. Similarly, serum albumin increased but remained low ($P < 0.01$) and urine protein creatinine ratio decreased ($P = 0.04$). PTH was high in response to hypocalcaemia and 25(OH)D, but PTH and 25(OH)D were not routinely tested.

Bone mineral density and body composition

A total of 33 (22.8%) patients had DXA scans performed. Their median (IQR) age at the time of scanning was 9 (7, 11) years. Analysis of steroid sensitivity within the subgroup showed 32 (96.9%) had SSNS, of whom 11 (33.3%) were steroid dependent, with a single patient (3.0%) with SRNS. Twenty-five (75.8%) patients in the subgroup had experienced at least one relapse. The number of days from

Table 2. Anthropometric and biochemical measurements at diagnosis and last clinic visit.

	n	Diagnosis (Mean ± SD)	Last clinic visit (Mean ± SD)	P value
WFAZ	136	0.07 ± 1.26	–0.05 ± 1.37	0.19
HFAZ	136	–0.70 ± 1.41	–0.62 ± 1.92	0.56
BMIZ	136	0.72 ± 1.46	0.35 ± 1.38	0.01
Corrected calcium (2.19–2.64 mmol/L)	68	1.98 ± 0.27	2.19 ± 0.34	<0.01
Phosphate (0.90–2.10 mmol/L)	67	1.67 ± 0.40	1.67 ± 0.61	0.96
ALP (93–345 U/L)	28	161.8 ± 68.7	189.7 ± 113.7	0.15
PTH (1.2–6.9 pmol/L)	5	22.17 ± 36.9	40.8 ± 50.7	0.13
cGFR (mL/min/1.73 m^2)	91	153.23 ± 68.7	125.66 ± 56.6	<0.01
Albumin (29–42 g/L)	58	16.0 ± 5.9	28.8 ± 12.8	<0.01
Cholesterol (<4.4 mmol/L)	47	11.57 ± 3.5	8.3 ± 4.4	<0.01
UPrCr (<0.2 g/mmol)	23	0.75 ± 0.66	0.44 ± 0.55	0.04

Abbreviations: WFAZ, weight for age z-score; HFAZ, height for age z-score; BMIZ, BMI for age z-score; ALP, alkaline phosphatase; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; cGFR, calculated glomerular filtration rate; TSH, thyroid stimulating hormone; T4, thyroxine; UPrCr, urine protein creatinine ratio.

diagnosis of nephrotic syndrome to DXA scans was a median (IQR) of 564 (192, 1053). Four (12.1%) of the DXA-scanned patients were identified as having fractures post initiation of GC therapy for NS. Fifteen (45.5%) of the scanned patients had data collected for quantifiable 28-day cumulative GC doses and, of these subjects, three belonged to the fracture group. The months on GC prior to DXA scanning for the fracture and non-fracture groups were 20 (5.0, 24.0) and 23.5 (13.0, 40.5) (P = 0.29), respectively, showing no significant difference between the two groups. Paradoxically, the fracture group in this small population had a lower cumulative GC dose (in mg/m^2/day) prior to the DXA scan than the non-fracture group, 24.34 (12.66, 38.05) vs 15.49 (10.23, 18.80) (P = 0.20); however, this was not a statistically significant difference. Seven out of 32 patients (21.9%) had WBLH BMD z-scores < –2 and 6 out of 33 (18.2%) had LS BMD z-scores < –2, of whom none fractured. There were no significant differences in anthropometry, DXA measurements or biochemistry between those with and without fractures, but the numbers were too small to permit a meaningful comparison (Table 3). Except for one patient being vitamin D insufficient at the DXA scan, all four fracture patients had normal anthropometry, BMD measurements and biochemistry results (Tables 3 and 4).

All four patients with fractures had MCNS and three were steroid dependent, of whom two had frequently relapsing NS (Table 4). Three patients had incidental anterior wedge vertebral fractures of mild or Genant grade 1 detected on lateral VFA on DXA scan. One patient sustained an ulna–radial fracture after a fall as documented in the patient file, post GC exposure.

FMI and LMI were within normal reported ranges and interpreted according to National Health and Nutrition Examination Survey (NHANES) [21] and LEAD (Lung, hEart, sociAl, boDy) cohort [22] published percentile charts. We found a positive correlation between WBLH BMD and LMI (r = 0.59; P < 0.01) and FMI (r = 0.46; P = 0.02) as shown in Figures 2 and 3, respectively.

Ten (6.9%) patients in this study were treated with thyroxine for either sub-clinical or overt hypothyroidism. Thirty-three (22.8%) patients had normal TFTs. The remaining 102 (70.3%) subjects with abnormal TFTs were either euthyroid sick or had indeterminate results but were monitored and not started on treatment. The hypothyroid group was marginally younger than the euthyroid group at diagnosis [3.64 (2.95, 5.39) vs 7.41 (3.84, 10.92) years (P = 0.06)] and at last clinic visit [5.93 (4.89, 11.05) vs 9.78 (7.82, 12.59) years (P = 0.06)]. The thyroxine group was stunted with HFAZ –2.17 (–2.88; –1.49) at diagnosis and –3.23 (–3.45; –1.55) at last visit, showing poor linear growth. The hypothyroid group also showed significantly lower corrected calcium and marginally lower ALP levels at diagnosis compared to the euthyroid group (P = 0.03 and 0.06, respectively). In the hypothyroid group, albumin remained low, whereas the euthyroid group showed normalising from a median albumin of 16.0 g/L (13.0; 18.0) to 42.0 g/L (32.5; 46.0) (P = 0.01), from diagnosis to last clinic visit. The hypothyroid group also had considerably higher cholesterol levels at diagnosis compared to last clinic visit [16.86 mmol/L (11.2, 17.4) vs 8.25 mmol/L (6.29, 10.21) (P = 0.07)].

Table 3. Demographics, anthropometry and DXA measurements of patients that had DXA scans with and without fractures.

	n	Total (n = 33) Median (IQR)	n	Fractures (n=4) Median (IQR)	n	No fractures (n= 29) Median (IQR)	P value
Demographics							
Age (years)	33	9.00 (7.00, 11.00)	4	11.00 (10.00, 11.00)	29	9.0 (6.0, 10.0)	0.03
Anthropometry							
WFAZ	32	0.57 (–0.56, 0.95)	4	0.1 (–0.64, 1.16)	28	0.69 (–0.56, 1.03)	0.33
HFAZ	32	–0.34 (–1.60, 0.34)	4	–0.05 (–0.18, 0.54)	28	–0.46 (–1.63, 0.34)	0.21
BMIZ	32	0.72 (–0.07, 1.72)	4	0.3 (–0.88, 1.27)	28	0.79 (0.19, 2.02)	0.11
DXA measurements							
WBLH BMD z-score	32	–0.81 (–1.86, –0.10)	4	–1.05 (–1.50, –0.26)	28	–0.67 (–2.01, –0.10)	0.89
LS BMD z-score	33	–1.10 (–1.70, –0.30)	4	–0.9 (–1.25, –0.51)	29	–1.10 (–1.50, –0.20)	0.73
FMI (kg/m^2)	28	5.28 (3.98, 7.10)	3	5.34 (3.21, 9.62)	25	5.23 (3.99, 6.94)	0.94
LMI (kg/m^2)	28	12.25 (11.51, 13.82)	3	13.47 (12.23, 14.50)	25	12.25 (11.40, 13.65)	0.35
Biochemistry							
Corrected calcium (2.19–2.64 mmol/L)	30	2.27 (2.00, 2.37)	4	2.33 (2.16, 2.41)	26	2.26 (2.00, 2.37)	0.43
Phosphate (0.90–2.10 mmol/L)	29	1.60 (1.37, 1.94)	4	1.70 (1.45, 1.87)	25	1.60 (1.37, 2.00)	1.00
ALP (93–345 U/L)	24	189 (143, 281)	4	230 (165, 262)	20	175.50 (143.50, 281.0)	0.97
PTH (1.2–6.9 pmol/L)	19	2.00 (1.80, 4.10)	4	2.95 (2.10, 4.45)	15	1.90 (1.5, 4.10)	0.26
25(OH)D (deficient <30; insufficient 30–50 sufficient > 50 nmol/L)	17	69.75 (26.25, 105.23)	4	78.43 (40.75, 121.69)	13	69.75 (26.25, 105.23)	0.65
Albumin (29–42 g/L)	9	31 (14.00, 40.00)	0	–	9	31 (14.0, 40.0)	–
cGFR (mL/min/1.73 m^2)	18	125.20 (106.5, 159.9)	3	117.60 (106.50, 154.30)	15	127.34 (104.40, 164.00)	0.65

Abbreviations: WFAZ, weight for age z-score; HFAZ, height for age z-score; BMIZ, BMI for age z-score; WBLH BMD, whole body less head bone mineral density; LS BMD, lumbar spine bone mineral density; FMI, fat mass index; LMI, lean mass index; ALP, alkaline phosphatase; PTH, parathyroid hormone; 25(OH)D, 25 hydroxyvitamin D; cGFR, calculated glomerular filtration rate.

Table 4. Summary of clinical, anthropometric and DXA-derived BMD data of 4 NS patients diagnosed with fractures during GC therapy.

	Age (years)	Histology	Steroid sensitivity	Relapses prior to fracture	WFAZ	HFAZ	BMIZ	Fracture site	WBLH BMD z-score	LS BMD z-score
1	11	MCNS	SDNS	4	1.74	1.07	1.65	T5 mild wedge	–0.5	0.51
2	9	MCNS	SDNS	3	–0.38	–0.34	–0.29	T5 mild wedge	–1.7	–1.4
3	8	MCNS	SDNS	1	–0.9	–0.02	–1.46	T5 mild wedge	–1.3	–0.31
4	8	MCNS	SSNS	1	0.58	0.01	0.89	Ulna/ Radius	0.3	–0.7

Abbreviations: MCNS, minimal change nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome; WFAZ, weight for age z-score; HFAZ, height for age z-score; BMIZ, BMI for age z-score; WBLH BMD, whole body less head bone mineral density; LS BMD, lumbar spine bone mineral density.

An analysis of steroid sensitivity in the group of 10 patients managed for hypothyroidism showed that three manifested SRNS and seven had SSNS. The predominant histological diagnosis in this group was FSGS found in eight patients (80.0%) with only two patients with MCNS. Similarly, the euthyroid group was also predominantly steroid-sensitive (93.9%) but in contrast MCNS was seen in 24 (72.7%) of the euthyroid patients. A clinical overview of these ten patients showed several variables potentially responsible for the stunting in this group. Eight patients had a concurrent diagnosis of pulmonary tuberculosis (PTB), one of whom had multidrug-resistant PTB (MDR PTB). Three patients were on prolonged steroid therapy, defined as more than eight weeks of treatment, three received intravenous methylprednisolone, and five patients received monthly cycles of intravenous cyclophosphamide, an immunomodulatory agent known for its deleterious effects on growth [23]. Three patients had repeat TFT at the last visit, one normalised and two remained abnormal. The remaining seven patients had no documented evidence of repeat TFT, four of whom were lost to follow-up.

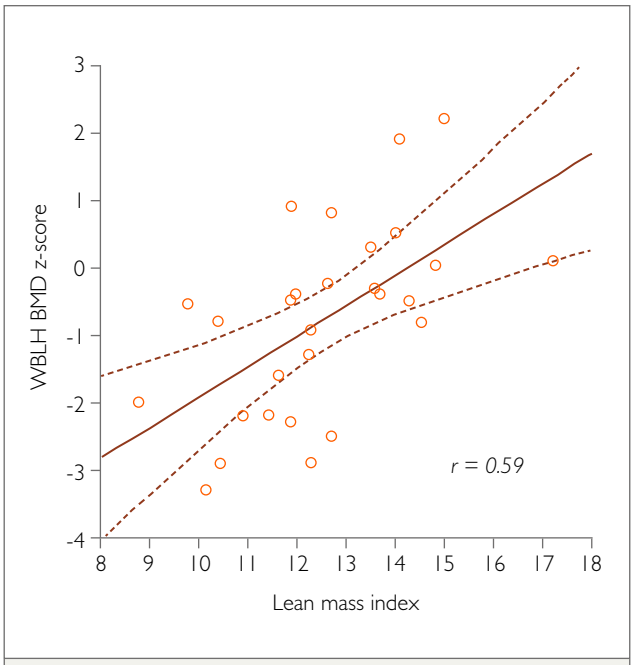


Figure 2. Correlation between WBLH BMD z-score and lean mass index (n = 28).
Abbreviations: WBLH, whole body less head; BMD, bone mineral density.

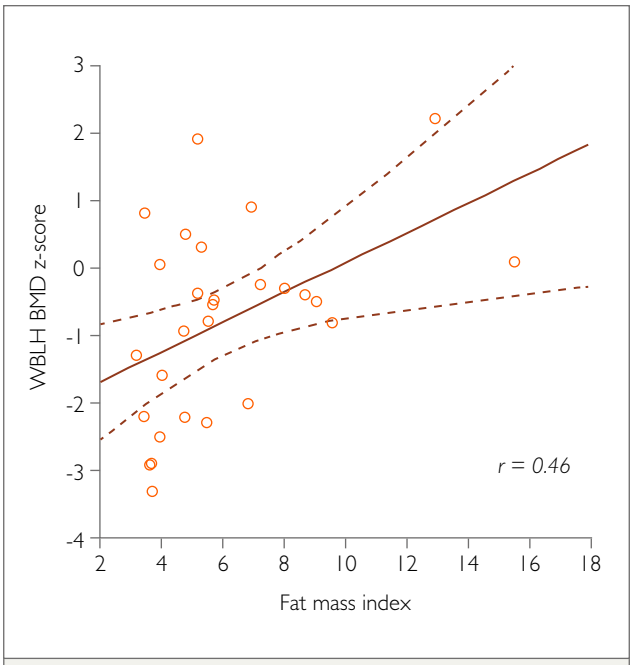


Figure 3. Correlation between WBLH BMD z-score and fat mass index (n = 28).
Abbreviations: WBLH, whole body less head; BMD, bone mineral density.

DISCUSSION

This South African study of paediatric patients with predominantly SSNS and low relapse recurrence, treated with GC therapy, demonstrated normal BMD measurements and body composition.

A fracture prevalence of 12.1% among the scanned patients in our study mirrored findings in both a Canadian and our South African study assessing fracture prevalence in children managed with oral GCs [15,24]. The Canadian investigation further emphasised the need for detection of incidental vertebral fractures in children on prolonged oral GCs and proposed ways to allow for early detection by risk assessment and symptom review. Although a small study population, our fracture group also consisted predominantly of patients with incidental vertebral fractures.

The most common histopathological diagnosis in our study was MCNS, drawing similarity to findings in a previous Johannesburg report while contrasting the historical findings of FSGS predominance in Black African patients, perhaps because we excluded secondary causes of nephrotic syndrome [25]. The proportion of FSGS is similar to another report from an international study [26].

This review found no significant differences in WFAZ and BMIZ scores from diagnosis to last clinic visit for the study population, as well as no growth parameter faltering as per WHO classifications. Instead BMIZ decreased likely due to resolution of oedema in patients in remission at last clinic visit. Assessments of FMI and LMI also proved to be within normal published reference ranges; however, the DXA study population was small. We found a positive correlation between WBLH BMD and LMI as well as FMI. Despite this chronic illness, these findings were similar to those of a meta-analysis in healthy children that supported a positive association between BMD and LMI [27]. A possible explanation for the normal findings of bone health and body composition in our study population could be the higher rates of SSNS and lower overall relapse rates compared to the Iran study [26].

The DXA sub-analysis group had normal BMD, metabolism markers and anthropometry. These findings may be due to our small sample size, but they were also supported by similar findings of another study in the United Kingdom [4]. In contrast, an Indian study showed a decrease in BMD with GC treatment and the beneficial role of calcium and vitamin D supplementation, even during the first episode of NS [28]. The reason for this difference is unclear as this Indian study was conducted in New Delhi, with those patients experiencing similar sun exposure to South Africans. Differences in diet and/or nutrition are postulated but were not assessed in both studies. Adequate nutrition and regular vigorous physical activity are essential for optimal bone health [29]. Bone mass and accrual is genetically determined but these modifiable lifestyle factors determine bone mass attainment in childhood and adolescence as well as bone loss in the elderly [30]. Assessment of nutritional status and physical activity were beyond the scope of

our study, but the effects of these environmental or genetic factors could mitigate or downplay the influences of GC on bone health that warrants further investigations in NS patients.

In our study population, the hypothyroid patients were stunted despite thyroxine treatment compared to euthyroid patients. However, this group of subjects had exposure to confounders as they had prolonged steroid exposure, concurrent PTB and received cycles of cyclophosphamide all affecting final height [23]. Furthermore, many patients were lost to follow-up and/or had no TFT results from their last clinic visit, limiting assessment of progression or resolution of hypothyroidism over time. In addition, albumin levels remained low in the hypothyroid group.

We recommend routine yearly DXA scans including VFA in high-risk populations on prolonged GCs. The risk of vertebral fractures can be assessed by enquiring about backache on GCs and other potential risk factors such as lack of sun exposure and physical activity or sedentary behaviour on history taking. Screening at initial presentation for hypothyroidism should be part of routine practice and thereafter at follow-up visits (3–4 monthly), especially if patients are not in remission and albumin remains low. If abnormalities are then detected, physicians need to consult paediatric endocrinologists for further advice on treatment. Serial assessments of height (6–12 monthly) and growth velocity are important to detect growth faltering and also to alert the treating paediatrician to monitor for potential causes of poor growth or factors influencing bone growth and health.

This study is limited by the retrospective collection of data and missing data and biochemical tests not performed for the purpose of the investigation. The lack of adequate data and the differing lengths of GC therapy in patients are a potential bias to the interpretation of the effects of GC on DXA measurements; however, the calculated cumulative doses could have mitigated this influence and there was no difference noted between the fracture and non-fracture groups. DXA scans were not routinely performed in patients with NS and limited the sample size of the DXA scan group. In view of the small sample size and the retrospective design of the study, multiple regression analyses could not be performed to account for confounding factors affecting BMD and body composition. In addition, serum 25(OH)D and parathyroid hormone levels were not routinely tested at clinic visits. This limited the detection of vitamin D deficiency and hyperparathyroidism as possible causes of growth faltering and poor bone health in this study of patients with NS.

The strength of the study is that it reviewed a 10-year period, and documents bone health in an African paediatric population treated with GC for primary nephrotic syndrome. Secondary causes of the condition were excluded to limit confounding factors due to the underlying disease.

CONCLUSIONS

Bone health and body composition in NS can be affected by the complex interplay of the effects of the syndrome as a disease and in conjunction with treatment. No significant abnormalities of bone health or body composition were identified in this study, possibly due to the predominant histological type of MCNS with sensitivity to GC therapy and the low frequency of relapses. NS patients with hypothyroidism displayed significant growth stunting and persistent hypoalbuminaemia despite receiving treatment, but many factors contributing to growth faltering were also identified in this group, including lack of remission. We recommend screening all patients with NS for hypothyroidism and assessment of growth faltering with appropriate referral to endocrinologists. DXA scanning should be considered in NS patients treated with prolonged GC. Enquiring about symptoms of backache suggestive of vertebral fractures and a history of fractures should be routine clinical practice. The early detection or prevention of vitamin D deficiency and thus of the role of vitamin D could be explored in future studies.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Use of AI in manuscript preparation

No AI tools were used in the preparation of this manuscript.

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