


# Bone densitometry in children with idiopathic nephrotic syndrome on prolonged steroid therapy

## A tertiary multicenter study

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### Abstract

Long-term glucocorticoids administration inhibits bone mineralization and has a negative impact on basic cellular mechanisms that are critical in the development and maintenance of bone strength. Steroids can cause osteoporosis in children and have a negative impact on bone mineral content (BMC) and bone mineral density (BMD).

We aim to determine the BMD of children with idiopathic nephrotic syndrome (INS) who are on corticosteroids therapy.

This cross-sectional study included 90 patients on corticosteroids therapy and 50 apparently healthy age and sex-matched children served as a control group. Renal functions, bone biochemistry, and parathyroid hormone (PTH) were measured in patients and controls. BMD was measured at the lumbar spinal region (L2–L4) using Dual-energy X-ray absorptiometry (DEXA) scan in both patients and controls groups.

Serum PTH, phosphorous, and alkaline phosphatase levels were significantly higher in patients than in controls. There was a statistically significant reduction in blood calcium levels in patients compared to controls. Osteopenia was diagnosed by DEXA scan in 24 patients (26.7%) and osteoporosis in 12 patients (13.3%). There was a statistically significant decline in BMD-z score, BMD, and BMC in patients compared to the healthy group.

Patients with INS on corticosteroids treatment have a lower BMD than their peers. Pediatric INS patients had a high prevalence of osteopenia and osteoporosis as measured by DEXA. Steroid therapy has a deleterious impact on bone mineralization in children with INS.

**Abbreviations:** ALP = Alkaline phosphatase, BMC = Bone mineral content, BMD = Bone mineral density, Ca = Serum Calcium, DEXA = Dual-energy X-ray absorptiometry, FRNS = Frequently relapsing nephrotic syndrome, GCs = Glucocorticoids, INS = Idiopathic nephrotic syndrome, NS = Nephrotic syndrome, P = Phosphorous, PTH = Parathyroid hormone, SDNS = Steroid dependent nephrotic syndrome, SRNS = Steroid resistant nephrotic syndrome.

**Keywords:** bone mineral density, children, idiopathic nephrotic syndrome.

## 1. Introduction

Nephrotic syndrome (NS) in childhood is characterized by nephrotic-range proteinuria, widespread edema, hypoalbuminemia, and hyperlipidemia in the presence of normal renal function. The etiology of NS can be classified into primary and secondary. The primary nephrotic syndrome often called idiopathic nephrotic syndrome (INS), is a group of illnesses affecting

the glomeruli of the kidney that are unrelated to systemic causes. Nephrotic syndrome is typically a relapsing illness in children in two-thirds of cases that require repeated courses of glucocorticoids (GCs).<sup>[1]</sup> All children presenting with their first episode of NS should be admitted to the hospital for diagnostic assessment, nursing, and medical management, and parental education.<sup>[2]</sup>

Osteoporosis is defined as “a systemic skeletal disorder characterized by a low bone mass and microstructural degradation

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*Competing interests:* All authors declare no competing interests related to the study.

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of bone tissue, resulting in an increase in bone fragility and fracture susceptibility".<sup>[3]</sup> A deficit of bone minerals produces metabolic bone disease, which changes skeletal mineralization because of a lack of bone mineral content (BMC). Detrimental GCs effects on bone development and peak bone mass may be more pronounced in children. GCs cause apoptosis in the cells that detect bone tissue strain (osteocytes) and hence limits osteoblastogenesis and thus bone growth. Additionally, GCs prolongs the lifetime of osteoclasts, leading to increased skeletal resorption. That followed by osteoclast genesis inhibition, leading to a low bone turnover state.<sup>[4]</sup> Dual-energy X-ray absorptiometry (DEXA) is a method for imaging the skeleton in 2 dimensions, and it focuses on areas where fractures are.<sup>[5]</sup> The primary goals of management of osteoporosis are prevention of fractures particularly vertebral fractures and scoliosis with improvement in function, mobility, pain, and rapid rehabilitation.<sup>[6]</sup>

The study objective is to evaluate bone mineral density among pediatric patients with idiopathic nephrotic syndrome receiving corticosteroids therapy.

## 2. Patients And Methods

### 2.1. Patients

We carried out a cross-sectional study on 90 patients with INS on corticosteroids treatment (Group 1) recruited from the nephrology clinics of 2 tertiary centers (Benha University Specialized Children Hospital, Benha, Egypt, and Alhada Armed Forces Hospital, Taif, Saudi Arabia) during the period from January 2021 till June 2021. Fifty apparently healthy age and sex-matched children served as a control group (Group 2).

Written informed consents were obtained from the legal guardians of all patients and controls for contribution in the study and for publication of the study data. The study was approved by the local ethical committees of Benha University and Alhada Armed Forces Hospital.

### 2.2. Inclusion criteria

1. INS pediatric patients defined as nephrotic range proteinuria  $>50\text{mg/kg/day}$  & hypoalbuminemia  $<30\text{g/l}$  at initial diagnosis before starting corticosteroids therapy.
2. INS fulfilling criteria 1 who were subsequently treated with corticosteroids for more than 6 months.
3. Both sexes were included.
4. Age  $<14$  years.

### 2.3. Exclusion criteria

1. Children suffering from any bone disease before being diagnosed as INS.
2. Children with secondary NS.

### 2.4. Definitions

1. Steroid-dependent nephrotic syndrome (SDNS) is defined as nephrotic syndrome with 2 consecutive relapses during alternate day prednisolone or within 2 weeks of its discontinuation.<sup>[7]</sup>
2. Steroid-resistant nephrotic syndrome (SRNS) is defined as the persistence of edema and proteinuria after 4 weeks of initial standard prednisolone therapy or after 4 weeks of daily prednisolone for relapse.<sup>[7]</sup>
3. Frequently relapsing nephrotic syndrome (FRNS) is 2 or more relapses within 6 months of the original response,

or 4 or more relapses during a 12-month period following the initial steroid-responsive episode.<sup>[7]</sup>

## 2.6. Methods

All patients and controls underwent all the following:

1. Full history taking includes sex, age, age of onset, duration, residence, family history of NS, type of treatment, its duration, and dates, and the total number of relapses in SDNS, SRNS & FRNS.
2. Thorough clinical examination with special focus on anthropometric measures, vital signs, edema, & ascites.
3. Radiological work up by DEXA Scan. Challenger Envision osteodensitometer, DMS, England, was used for the assessment of bone mineral density (BMD). DEXA scan is frequently used to diagnose or assess a person's risk of osteoporosis. The scan generally takes 10 to 20 minutes. It is painless, and the amount of radiation used is low. The patient lies on an open X-ray table and tries to stay still as the scanner passes over his body. The machine produces 2 X-ray beams (high and low) and tracks the amount of X-ray energy that passes through the bone for each type of the 2 beams. The thickness of bone and the quantity of energy lost owing to scattering affect this amount utilizing DEXA. The lumbar spinal area (L2–L4) was assessed for BMD.

BMD was classified on the basis of the BMD Z-score.<sup>[8]</sup> Scores were calculated from the following equation:  $Z\text{-score} = (\text{BMD} [\text{gram/cm}^3] \text{ of the patient} - \text{BMD predicted for age and sex/SD for BMD} [\text{age, sex, and height matched}])$ . A patient will be considered osteopenia if the Z-score was  $<-1.0$ . If the Z-score was  $\leq -2.5$ , the patient was classified as having severe osteopenia (osteoporosis).<sup>[6]</sup>

4. Laboratory investigations for serum levels of creatinine, urea, phosphorous (P), total calcium (Ca), and alkaline phosphatase (ALP) using the Biochemistry analyzer (Biosystem) A15 autoanalyzer.

Serum intact parathyroid hormone (PTH) was measured using a direct label, 2 sites ELISA assay intended for the quantitative determination of PTH in serum (Biomerica, USA; normal range: 10–65 pg/ml) lot no (2329), company name (Diasorin), and instrument name (Diasorin Liaison) PTH 4-2016/W0886200.2.6.

## 3. Statistical Analysis

SPSS version 22 was used to tabulate and analyze the gathered data (SPSS Inc, Chicago, IL). Percentages and numbers were calculated for categorical data. Chi-square test ( $\chi^2$ ), or Fisher exact test were used to analyze categorical variables. Quantitative data were tested for normality using the Kolmogorov Smirnov test assuming normality at  $P > 0.05$ .

Variables such as mean, standard deviations, and ranges were used for quantitative data. Mann-Whitney U test was used for nonparametric variables and the Student "t" test was used to evaluate regularly distributed variables between 2 independent groups. Pearson correlation was utilized to assess the correlation between nonparametric variables. The accepted level of significance was 0.05 ( $P < 0.05$  was considered significant).

## 4. Results

This study was carried out on 90 cases with INS on corticosteroids treatment and 50 healthy age and sex-matched children who served as a control group. In the current study, the age of studied children of NS ranged from 3 to 14 years, mean  $\pm$  SD was  $9.06 \pm 3.9$  years with male predominance (60%).

Eighty-three% of patients received corticosteroids alone, the remaining received both corticosteroids and immunosuppressive. FRNS patients were 46.6% and SDNS patients were 36.6% while SRNS patients were 16.7%.

The commonest presenting symptom was eyelids puffiness (93.3%) while the commonest sign was edema of both lower limbs (66.6%). There was a significant decrease in height in patients versus healthy controls while there was a significant increase in both body weight and body mass index (BMI) ( $30.25 \pm 2.95$ ) in cases versus controls (Table 1).

Serum PTH, P, and ALP were significantly increased while Ca was significantly decreased among patients as compared to controls (Table 2).

There was a statistically significant decrease in BMD, BMD Z-score, and BMC among patients as compared to controls (Table 3). Regarding BMD categories, 24 patients (26.7%) had osteopenia and 12 patients (13.3%) had osteoporosis while none of the controls had either (Table 4).

There were statistically significant negative correlations between BMD/BMD Z-score and age of onset of disease, weight, BMI, duration and dose of steroid therapy, serum levels of ALP, PTH, urea, creatinine, systolic, and diastolic blood pressure (Table 5).

## 5. Discussion

GCs are the cornerstone of management of a variety of immunological illnesses, including INS, and their toxicity is one of the most

common causes of iatrogenic sickness linked with their long-term usage. Among these iatrogenic effects is a high risk of bone loss during the first few months of usage with a high risk of fractures.<sup>[3]</sup>

The current study demonstrated unequivocally the influence of GCs on BMC and its clinical effects. The age of the studied children of NS ranged from 3.5-14 years, mean  $\pm$  SD was  $9.06 \pm 3.9$  years. This agrees with Moon et al,<sup>[9]</sup> who investigated the effects of glucocorticoids on BMD and bone geometry in children with NS and they found the mean age was  $10.7 \pm 3.1$  years.

During the study of the sex distribution in our patients, we found male predominance (60%). Rhuma et al,<sup>[10]</sup> and Ephraim et al,<sup>[11]</sup> similarly reported that INS affected males more than females.

Regarding the presenting symptoms and signs among the studied patients, the most common presenting symptom was puffiness of the eyelids (93.3%) while the most presenting sign was lower-limb edema (66.6 %). This is in line with the findings of Ray et al,<sup>[12]</sup> who found that edema is the most common presentation in INS patients. In the study done by Sahana,<sup>[13]</sup> he reported that ascites was there in 63%, genital edema in 31%, pleural effusion in 15%, and hypertension in 12% in children with nephrotic syndrome. This was contrary to our study, and this can be explained by the fact that most of our cohort were FRNS (46.6%) who were on regular follow up with clear instructions for patients to seek medical advice with early signs of relapse that is why they were picked up early before more generalized or severe edema happens.

**Table 1**  
Demographic and anthropometric data of patients and controls.

		Patients (N = 90)	Controls (N = 50)	Statistical test	P value
Age (yr)	Range	3–14	3–14	t test	0.878
	Mean $\pm$ SD	9.0 $\pm$ 3.9	8.8 $\pm$ 2.5	0.154	
Male (%)		54 (60%)	25 (50%)	Chi-square	0.124
Height (cm)	Range	50–165	80–156	t test	0.005*
	Mean $\pm$ SD	98.77 $\pm$ 42.31	130.20 $\pm$ 26.58	2.33 2.951	
Weight (kg)	Range	12–105	22–105	t test	0.016*
	Mean $\pm$ SD	55.17 $\pm$ 24.05	43.60 $\pm$ 22.29	1.398	
Body mass index (kg/m <sup>2</sup> )	Range	16.00–38.39	17.71–31.19	t test	0.019*
	Mean $\pm$ SD	30.25 $\pm$ 2.95	25.039 $\pm$ 1.51	2.427	

\*Statistically significant.

**Table 2**  
Biochemical data of patients and controls.

		Patients (N = 90)	Controls (N = 50)	t test	P value
Phosphorus (mg/dl)	Range	3-6	2.5-3.5	4.847	0.000*
	Mean $\pm$ SD	4.77 $\pm$ 0.88	2.91 $\pm$ 0.27		
Corrected calcium for albumin level (mg/dl)	Range	6–11	9–11	2.879	0.006*
	Mean $\pm$ SD	9.02 $\pm$ 1.50	10.03 $\pm$ 0.55		
Parathyroid Hormone (pg/ml)	Range	12–96	5–51	1.439	0.015*
	Mean $\pm$ SD	47.71 $\pm$ 27.64	38.25 $\pm$ 11.81		
Alkaline phosphatase (U/L)	Range	55–152	42 – 110	4.611	0.000*
	Mean $\pm$ SD	109.20 $\pm$ 26.74	76.80 $\pm$ 20.13		

\*Statistically significant.

**Table 3**  
Bone mineral density, bone mineral density Z-score & bone mineral content in patients and controls.

		Patients (N = 90)	Controls (N = 50)	t test	P value
BMD(g/cm <sup>3</sup> )	Range	0.32–0.87	0.58–1.29	5.718	0.000*
	Mean ± SD	0.56 ± 0.17	0.87 ± 0.22		
BMD Z-score	Range	(–3.3) to (–4)	(–0.9) to (–3.1)	3.015	0.004*
	Mean	–1.77 ± 0.56	–0.78 ± 0.34		
BMC (g)	Range	7.36–80.61	23.34–80.61	4.392	0.000*
	Mean ± SD	25.07 ± 18.18	48.52 ± 18.97		

\*Statistically significant.

BMC = bone mineral content, BMD = bone mineral density.

**Table 4**  
Bone mineral density categories in patients and controls.

		Patients (N = 90)	Controls (N = 50)	χ <sup>2</sup>	P value
Bone mineral density categories	Average	No. 54	50	10.526	0.005*
		% 63%	100.0%		
	Osteopenia	No. 24	0		
		% 26.7%	0.0%		
	Osteoporosis	No. 12	0		
		% 13.3	0.0%		

\*Statistically significant.

**Table 5**  
Correlation between patients' bone mineral density and other study parameters.

Bone mineral density	Pearson correlation	P value
Age (yr)	–0.799	0.000*
Age of onset of disease	–0.728	0.000*
Duration of corticosteroids therapy	–0.654	0.005*
Corticosteroids dose/year	–0.661	0.005*
Weight (kg)	–0.611	0.000*
SBP (mmHg)	–0.708	0.000*
DBP (mmHg)	–0.745	0.000*
Creatinine (mg/dl)	–0.163	0.039*
Urea (mg/dl)	–0.198	0.041*
PTH (pg/dl)	–0.244	0.020*
ALP (U/L)	–0.137	0.047*

\*Statistically significant.

ALP = alkaline phosphatase, DBP = diastolic blood pressure, PTH = parathyroid hormone, SBP = systolic blood pressure.

Most of the study cohort were on solo GCs therapy (83.3%) while 16.7% were on both GCs and GCs sparing agents. Most of our cohort (46.6%) were FRNS, 36.6% were SDNS, and 16.7% were SRNS. The frequent relapses in INS patients were explained by Al-Fakeeh et al,<sup>[14]</sup> who found that children with INS have altered cellular and humoral immunity, predisposing them to infection mostly upper respiratory tract infections resulting in repeated relapses. Additionally, immunosuppressive medications can dramatically exacerbate infections. Alwadhdi and his colleagues<sup>[15]</sup> reported that relapses of nephrotic syndrome are often temporally associated with the occurrence of infection.

GCs also caused significant increase in weight and BMI in our patients which was also reported by Lestari et al.<sup>[16]</sup> and Ribeiro et al.<sup>[17]</sup> High-dose and long-term GCs use increase food intake and decrease energy expenditure by stimulating neuropeptide-Y and inhibiting the release of corticotrophin hormone. This leads to weight gain. Obesity is the result of the anabolic process that is triggered because of steroids prolonged use.

There was also a statistically significant drop in Ca levels in patients when compared to controls. This was in agreement with Koşan et al.<sup>[18]</sup> who stated that hypocalcemia occurred in most individuals with nephrotic syndrome receiving corticosteroids. El-Mashad et al,<sup>[19]</sup> in their study to assess BMD in INS children with normal glomerular filtration rate found similar findings in their patients who had much lower levels of ionized Ca than controls. This could be explained by the fact that corticosteroids promote hypocalcemia by reducing Ca absorption from the gut and increasing its excretion through the kidney tubules.<sup>[17]</sup> This disagreed with Sinha et al,<sup>[20]</sup> who found no difference in Ca levels between their patients and controls. Paczyk-Tomaszewska<sup>[21]</sup> also reported normal Ca levels in his cohort and noted that their findings could be explained by a subsequent increase in PTH blood levels. The apparent discrepancies in blood ionized Ca readings may be explained by variations in patient demographics or in the conditions of measurement.

Serum P, ALP, and PTH levels were significantly increased in patients compared to controls throughout this study. Paczyk-Tomaszewska et al,<sup>[21]</sup> Esmaeili et al,<sup>[22]</sup> and Koşan et al<sup>[18]</sup> agreed with us. They hypothesized that corticosteroids indirectly influence bone through decreasing intestinal Ca absorption and increasing urinary Ca losses. The hyperparathyroidism observed in our study was most likely caused by corticosteroid-induced hypocalcemia; high levels of PTH are known to induce Ca reabsorption from bones, as stated by Aceto.<sup>[23]</sup>

One of the isoenzymes, bone-specific ALP, is produced by osteoblasts and is an excellent marker of bone development; in the current study, ALP was much higher in patients than in healthy children. Koşan et al also observed ALP increase in his NS cohort during corticosteroid therapy this rise may be due to enhanced bone turnover.<sup>[18]</sup> El-Mashad and coworkers<sup>[19]</sup> similarly found higher P, ALP, and PTH levels in their cases than in controls.

In children with NS, steroids therapy has detrimental effect on bone mineralization. We found that DEXA scans revealed osteoporosis in 24 patients (26.7%) and osteopenia in 12 patients (13.3%), indicating a highly statistically significant drop in BMD, BMD Z-score, and BMC in patients compared to controls. El-Mashad and coworkers<sup>[19]</sup> found similar findings as 11 patients (44%) had osteopenia and 2 (8%) had osteoporosis. This is also consistent with Basiratnia's<sup>[24]</sup> conclusions.



In some SDNS patients, particularly those with a greater cumulative steroids dose, bone loss can occur; larger cumulative doses were associated with increased steroids consumption and, subsequently, increased bone loss. Indeed, a linear relationship between the cumulative dose of GCs and BMD was observed. These findings agreed with those of Paczyk-Tomaszewska et al,<sup>[21]</sup> who found that children with NS who are treated with GCs are at risk of losing bone mass. Additionally, Aceto et al<sup>[23]</sup> demonstrated that GCs decreased the BMD Z-score in steroid-sensitive NS and that the BMD Z-score is substantially correlated with the total prednisone dosage. Children who need many doses of corticosteroids are at a higher risk of bone fractures.

The most often used approach for detecting bone loss is the DEXA assessment of BMD.<sup>[25]</sup> In children with INS who were just started on steroids therapy, an inverse relationship between steroid dose and BMD was discovered.<sup>[26]</sup> There is a link between low BMD and fractures in children.<sup>[27]</sup> As a result, BMD evaluated by DEXA appears to be an adequate technique for assessing the risk of bone loss in children receiving steroid therapy for renal diseases.<sup>[28]</sup>

## 6. Conclusions

Patients with INS have a lower BMD. DEXA detected that both osteopenia and osteoporosis are common in children with INS on corticosteroids therapy. Routine BMD evaluations are essential for follow up of those patients. Longitudinal studies with a larger sample size and a longer follow-up time are required for more characterization of this problem. Research on the effect of calcium and vitamin D supplementation on the prevention and treatment of this problem is warranted.

## Author contributions

WE, AS, ES: set the idea of the study and designed the study  
 NB, AE: critically analyzed the data  
 NK, MA, AS, OA: reviewed literature & drafted the manuscript  
 AS, WE, SA, AMA, AOA, MA, NB: collected patients' data  
 All authors reviewed and approved the manuscript for final publication

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